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Investigation of the Predictive Value of De Ritis Ratio and Inflammatory Markers in Prostate Cancer Patients Suitable for Active Surveillance

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ABSTRACT

Objective: To demonstrate the role of inflammatory markers and the De Ritis ratio (aspartate aminotransferase/alanine aminotransferase) in selecting patients with localized prostate cancer for active surveillance.

Methods: A total of 83 patients who met the criteria for active surveillance and underwent radical prostatectomy in our clinic between January 2010 and June 2017 were included in the study. Preoperative neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), platelet-to-hemoglobin (Plt/Hb) ratio, red cell distribution width (RDW), and De Ritis ratio were retrospectively evaluated with postoperative outcomes.

Results: NLR, PLR, RDW, and Plt/Hb ratios were not significantly associated with upgrade and upstage. Twenty-three patients (27.7%) underwent upgrade, 10 patients (12%) underwent upstage, and 29 patients (34.9%) were found unsuitable for active surveillance of radical prostatectomy results. A high De Ritis ratio was significantly associated with increased upgrade and unsuitability for active surveillance.

Conclusion: Preoperatively, a high De Ritis ratio is associated with poor pathological outcomes, and a high De Ritis ratio can be used as a cost-effective and accessible marker for selecting patients for active surveillance.

Keywords: Active surveillance, De Ritis ratio, inflammatory markers, prostate cancer, upgrade, upstage

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer in men (1). For patients with low-risk PCa [clinical category T1c-T2a, prostate specific antigen (PSA) level <10 ng/mL and Gleason 6], radical prostatectomy operation and radiotherapy are the preferred approaches for curative treatment (2). However, PCa treatment types have long-term side effects, such as urinary incontinence (20-21%) and erectile dysfunction (70-74%), which negatively affect patients' quality of life (3). This has led researchers to investigate conservative treatments. Active surveillances based on the principle that due to possible side effects in low-risk patients, curative treatment is applied when patients move to a higher risk group. Recent studies have shown that long-term overall survival (81-100%) and cancer-specific survival (98-100%) are achieved in active surveillance practices (4,5). Active surveillance has become routine practice PCa management and is recommended according to the criteria defined in international guidelines (6,7). Although various institutions have different criteria, most clinicians select patients for active surveillance by considering Gleason score 6, clinical stage T1c or T2a, PSA <10 ng/mL, PSA density (PSAD) <0.15 ng/mL/cc, and low tumor volume in biopsy (5,6). However, many issues such as optimal patient selection, long-term outcomes, disease-specific mortality, follow-up strategies, and the time to start active treatment. To overcome these uncertainties, additional clinical, radiological, tissue-level, and biochemical parameters are needed in addition to the existing criteria when selecting patients (8-10).

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The inflammatory response is well known to have an important role in the formation and progression of tumors, and inflammatory markers play predictive roles in some malignancies (11). The aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio (De Ritis) was first defined by De Ritis in 1959 for the evaluation of viral hepatitis and was subsequently demonstrated to be a useful marker for predicting prognosis in many types of cancer (12-15). Although AST and ALT are generally thought to be associated with liver function, AST is expressed in more common tissue types, whereas ALT is more liver-specific (16). A high degree of proliferation, high tumor cell turnover, and tissue damage may cause AST to increase more than ALT in cancer patients; therefore, the high De Ritis rate may be due to systemic changes related to possible tumor proliferation (17-19). In glucose metabolism, AST is activated more than ALT and plays an important role in aerobic glycolysis (16,20). This mechanism has also been demonstrated in bladder tumors (21). In previous studies, increased De Ritis rates were found to be associated with biochemical recurrence after radical prostatectomy in PCa, increased Gleason scores, and disease progression in castration-resistant cases (8,22).

In this study, we aimed to evaluate the use of inflammatory markers and the De Ritis ratio as criteria in patient selection for active surveillance.

METHODS

Patient Selection

Approval for the study was obtained from the University of Health Sciences Türkiye, Taksim Training and Research Hospital Clinical Research Ethics Committee under decision number 127 (date: 24.01.2018). A total of 245 patients who underwent radical prostatectomy for PCa between January 2010 and June 2017 were retrospectively evaluated. Among these patients, 103 low-risk patients were included in the study based on the following criteria: clinical stage ≤T2a, PSA ≤10 ng/mL, Gleason score ≤6, and ≤3 foci of PCa identified, accounting for ≤50% of the biopsy material. An additional 20 patients were excluded from the study due to exclusion criteria, such as chronic inflammatory and autoimmune diseases, rheumatologic pathology, hepatitis, and chronic liver disease. Consequently, the study was completed in 83 patients.

Evaluation

Demographic information (age, body mass index, comorbidities) of the patients was noted by compiling their electronic medical records, patient archive files, and outpatient clinic follow-up cards. Preoperative digital rectal examination, clinical stage, serum PSA levels, prostate volume, biopsy pathology results (tumor type, Gleason score, number of positive cores for PCa, tumor percentage), and type of surgery (open retropubic or laparoscopic) were evaluated. Postoperative pathological results (Gleason score, extraprostatic extension, seminal vesicle invasion) were recorded. Patients were staged according to the TNM (American Joint Committee on Cancer) staging system. Radical prostatectomy results were compared with biopsy pathology results to determine upgrades (Gleason ≥7) and upstaging.

Preoperative blood sample results (liver function tests and complete blood count tests) were noted. Hemoglobin (Hb), red cell distribution width (RDW), platelet count (Plt), lymphocyte count, neutrophil count, AST, ALT values were noted from the blood samples. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), platelet-to-hemoglobin (Plt/Hb) ratio, and De Ritis ratio were calculated based on these values. The correlation between biochemical parameters and upgrades, upstaging, and suitability for active surveillance in preoperative and postoperative pathology results was statistically investigated.

Statistical Analysis

Descriptive statistics, such as mean, standard deviation, median, minimum, maximum, frequency, and ratio, were used for data descriptions. The distribution of variables was measured using the Kolmogorov-Smirnov test. The independent sample t-test, Mann-Whitney U test were used in the analysis of quantitative independent variables. The significance level and cut-off value were determined using the receiver operating characteristic curve. SPSS 22.0 software was used for the analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 61.8±7 years. Open radical prostatectomy was performed in 70 (83.2%) patients, and laparoscopic radical prostatectomy was performed in 13 (15.7%) patients. Seven patients had various comorbidities. The mean preoperative prostate volume measured by transrectal ultrasonography was 48.7±17.9 mL. The mean pre-biopsy PSA was 6.6±2.1 ng/mL. The mean tumor length on biopsy was 4.6±2.9 mm, and the mean tumor percentage was 24.3±13. Seventy four (89.2%) patients were classified as T1 and 9 patients were classified as T2A (10.8%) (Table 1).

The mean Hb was 14.1±1.1 g/dL, neutrophil count was 4.4±1.4 10^3/μL, lymphocyte count was 2.1±0.7 10^3/μL, Plt was 232.7±62.6 10^3/μL, AST was 20.6±5.5 U/L, ALT was 19.5±8.3 U/L, RDW was 14.1±2.9%, NLR ratio was 2.2±0.8, PLR ratio was 118.5±42.6, Plt/Hb ratio was 16.6±4.8, De Ritis ratio was 1.2±0.3 (Table 2).

Sixty (72.3%) patients had a Gleason score of 6 (3+3), 22 (26.6%) patients had Gleason 7, and 1 (1.2%) patient had Gleason 8 (4+4). Seminal vesicle invasion was present in 2 (2.4%) patients. Ten (12%) patients underwent extraprostatic extension (T3), whereas 23 (27.7%) underwent upgrades. When patients with upgrades and/or upstaging were grouped as unsuitable for active surveillance, 54 (65.1%) patients were suitable for active surveillance, while 29 (34.9%) were unsuitable (Table 3).

The RDW, NLR, PLR, and Plt/Hb values were not significantly associated with upgrades, upstaging, or suitability for active surveillance ($p>0.05$) (Table 4).

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The De Ritis ratio was significantly higher in the upgrade group than in the non-upgrade group (p=0.001). There was no significant difference in the De Ritis ratio between the upstage group and the non-upstage group (p=0.812). The De Ritis ratio was statistically significant between patients suitable and those unsuitable for active surveillance (p=0.004) (Table 4).

The cut-off value of 1.08 for the De Ritis ratio showed significant efficacy [area under the curve 0.693 (0.575-0.810)] in distinguishing between these groups (p=0.004). The sensitivity was 79.3%, positive predictive value was 51.1%, specificity was 59.3%, and negative predictive value was 84.2% (Figure 1).

DISCUSSION

Active surveillance has been used worldwide over the past decade to reduce PCa overtreatment and to provide a reliable follow-up protocol for slow-progressing disease (23). Despite its widespread use, definite criteria for active surveillance have not been established. Thomsen et al. (24) included patients with clinical stage ≤T2a, PSA ≤10, Gleason 6, positive core number ≤3, and tumor percentage in the core ≤50% as inclusion criteria. Similarly, in our study, we included patients with clinical stage ≤T2a, PSA ≤10, Gleason ≤3+3, positive core number ≤3, and tumor percentage in the core ≤50%.

Table 1. Preoperative findings of the patients

		Min-max	Median	Mean ± SD/n-%
Age		**45-77**	**62**	**61.8±7.0**
BMI		17.9-31.2	25	24.6±3.4
Comorbidity	No			76 (91.6%)
	Yes			7 (8.4%)
	DM			2 (2.4%)
	HT			4 (4.8%)
	CAD			2 (2.4%)
Surgery type	Open			70 (84.3%)
	Laparoscopic			13 (15.7%)
PV (mL)		20-105	44	48.7±17.9
PSA (ng/mL)		2-9.9	6.5	6.6±2.1
Tumor length (mm)		0.1-15	4	4.6±2.9
Tumor percentage (%)		2-50	23	24.3±13.0
Preoperative clinical stage	T1			74 (89.2%)
	T2A			9 (10.8%)

DM: diabetes mellitus, HT: hypertension, CAD: coronary artery disease, PV: prostate volume, SD: standard deviation, PSA: prostate specific antigen, BMI: body mass index

Suitability for active surveillance	AUC	Cut-off	95% CI	p-value
AST/ALT	0.693	1.08	0.575-0.810	**0.004**
			Sensitivity	79.3%
			Positive prediction	51.1%
			Specificity	59.3%
			Negative prediction	84.2%

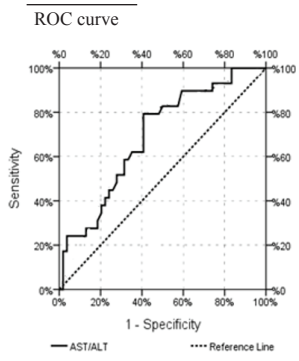

Figure 1. De Ritis cut-off value and confidence interval

AUC: area under the curve, CI: confidence interval, ROC: receiver operating characteristic, AST/ALT: aspartate aminotransferase/alanine aminotransferase

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Table 2. Preoperative laboratory values of the patients

	Min-max	Median	Mean ± SD
Hb	11.8-17.0	14.0	14.1±1.1
Neutrophil	1.8-10.7	4.2	4.4±1.4
Lymphocyte	1.0-4.8	2.0	2.1±0.7
Platelet	118.0-398.0	220.0	232.7±62.6
AST	11.0-39.0	19.2	20.6±5.5
ALT	8.0-46.0	17.0	19.5±8.3
RDW	10.8-36.0	13.9	14.1±2.9
NLR	0.8-4.6	2.1	2.2±0.8
PLR	50.8-252.2	111.3	118.5±42.6
Plt/Hb	7.9-32.1	15.8	16.6±4.8
AST/ALT	0.5-2.1	1.1	1.2±0.3

AST: aspartate aminotransferase, ALT: alanine aminotransferase, RDW: red cell distribution width, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, Plt/Hb: platelet-to-hemoglobin, SD: standard deviation, min-max: minimum-maximum

Table 3. Evaluation of patients after radical prostatectomy

		n-%
Gleason score	GS 6	60 (72.3%)
	GS 7	22 (26.6%)
	GS 8	1 (1.2%)
Seminal vesicle invasion	No	81 (97.6%)
	Yes	2 (2.4%)
Pathological stage	T2	73 (88%)
	T3	10 (12%)
Upgrade		23 (27.8%)
Upstage		10 (12%)
Suitability for active surveillance	Yes	54 (65.1%)
	No	29 (34.9%)

Although patients suitable for active surveillance are selected from low-risk PCa patients, some patients meeting the active surveillance criteria who undergo radical prostatectomy have been found to have more aggressive tumor characteristics. In our study, we found Gleason score 7 in 26.5% of patients, Gleason score 8 in 1.2%, seminal vesicle invasion in 2.4%, and extraprostatic extension (T3) in 12% of patients. One of the largest studies on patients suitable for active surveillance who underwent radical prostatectomy was conducted by Thaxton et al. (25). In this study, radical prostatectomy was performed in 4265 patients who were categorized according to three different active surveillance criteria, and their radical prostatectomy pathology results were evaluated. Gleason 8-10 was found in 3-4% of patients, extracapsular extension in 15-18%, and seminal vesicle invasion in 3-5%. These findings were consistent with our study, except for patients with Gleason 8. Thaxton al. (25) also included Gleason 7 patients in their study, which may explain this difference. Similarly, da Silva et al. (26) included 945 patients meeting the PRIAS criteria (clinical stage T1/T2, Gleason ≤6, PSA <10 ng/mL, ≤2 positive cores, and PSAD <0.2 ng/mL) in their study and found Gleason ≥7 in 38% of patients and extraprostatic extension (T3) in 10.3%, which was similar to our study.

Wang et al. (8) investigated the role of the De Ritis ratio in predicting pathological outcomes and prognosis in patients with localized PCa who underwent radical prostatectomy. According to this study, the median De Ritis ratio of the 438 patients was 1.33 (1.11-1.60), and the cut-off value was determined to be 1.325. When patients were grouped as high or low based on their De Ritis ratio, a high De Ritis ratio was found to be statistically significantly associated with high clinical and pathological stage, high Gleason score on biopsy and final pathology, high seminal vesicle invasion, and positive surgical margin. In our study, the mean De Ritis ratio was 1.2±0.3. A high De Ritis ratio was significantly associated with upgrades (p=0.001), which is consistent with the literature. In our study, the De Ritis ratio was statistically significant between patients suitable and those unsuitable for active surveillance (p=0.004). However, no significant difference was found in the De Ritis ratio for predicting extraprostatic extension in radical prostatectomy pathology (p=0.812). Taştemur et al. (22) investigated the role of the De Ritis ratio in predicting biochemical recurrence in 198 intermediate-high-risk patients who underwent radical prostatectomy. In this study, the cut-off value for De Ritis was 1.184, and the De Ritis ratio was found to be an independent risk factor for biochemical recurrence (22).

Inflammation plays a key role in the initiation and progression of many malignancies (27). NLR, which is used as a cancer-related inflammation marker, has been shown to be useful in predicting response to treatment and prognosis in some malignancies (28). High NLR indicates an increase in inflammation-dependent neutrophil count and decrease in lymphocyte count, which are associated with carcinogenic environments (29,30). One of the largest studies evaluating the NLR ratio in patients suitable for active surveillance who underwent radical prostatectomy was conducted by Kwon et al. (31). In this study, 217 patients with PSA <10 ng/mL, Gleason 6, clinical stage T2a, positive core number ≤3, and tumor in the core ≤50%, and 217 were included.

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Table 4. Evaluation of markers in terms of upgrade, upstage, and suitability for active surveillance

	Upgrade					Upstage					Suitability for active surveillance				
	Yes		No		p-value	Yes		No		p-value	Yes		No		p-value
	Mean	Median	Mean	Median		Mean	Median	Mean	Median		Mean	Median	Mean	Median	
RDW	14±2.1	13.1	14.1±3.2	14	0.623	14.7±2.1	14.6	14±3	13.5	0.122	14.1±3.3	13.9	14.1±2	13.6	0.836
NLR	2.1±0.58	2.06	2.29±0.87	2.23	0.452	2.16±0.65	2.01	2.25±0.83	2.14	0.845	2.31±0.89	2.23	2.1±0.6	2.06	0.385
PLR	106.1±34.9	98.3	123.3±44.5	113.2	0.200	128.3±38.7	120.7	117.2±43.2	108.8	0.218	122.1±44.3	113.2	111.9±39.1	104	0.528
Plt/Hb	15.8±4.8	14.8	16.9±4.7	16.1	0.46	17.8±5.1	16.1	16.4±4.7	15.8	0.334	16.7±4.6	16.1	16.4±5.1	14.8	0.774
De Ritis	1.36±0.32	1.25	1.08±0.31	1.05	**0.001***	1.18±0.29	1.14	1.15±0.07	1.11	0.812	1.08±0.32	1.05	1.3±0.32	1.21	**0.004***

RDW: red cell distribution width, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, Plt/Hb: platelet-to-hemoglobin

The rates of upgrade and upstaging in the postoperative pathology results were 26.7% and 8.3%, respectively, which were similar to our study. However, there was no significant difference in terms of upgrade, upstaging, or positive surgical margin between the groups categorized according to NLR (NLR ≥2.5 and NLR <2.6) (p>0.05). Our study also did not find a significant difference in upgrade, upstaging, or positive surgical margin concerning NLR. Maeda et al. (32) compared the preoperative and postoperative results of 73 patients who underwent radical prostatectomy and found no relationship between NLR and poor pathological outcomes. In a study by Sun et al. (9), which included 226 patients diagnosed with PCa and 100 healthy volunteers, the NLR, PLR, and RDW were found to be significantly higher in patients with PCa than in the control group, and increased NLR and PLR were associated with poor prognosis, high Gleason scores, and PSA. However, NLR, PLR, Plt/Hb, and RDW did not significantly differ in terms of upgrade and upstaging. This difference can be attributed to the inclusion of patients with high PSA and Gleason scores in the Sun et al. (9) study.

Study Limitations

The limitations of the study included its retrospective nature, a limited sample size, and its conduct at a single center.

CONCLUSION

Although active surveillance in localized PCa is a safe method, the patient selection criteria have not been clarified. Our findings suggest that the De Ritis ratio can be used to select suitable patients for active surveillance. However, further prospective studies with longer durations and larger sample sizes are needed to support these findings.

Ethics Committee Approval: Approval for the study was obtained from the University of Health Sciences Türkiye, Taksim Training and Research Hospital Clinical Research Ethics Committee under decision number 127 (date: 24.01.2018).

Informed Consent: Retrospective study.

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The Association of Blood Type Differences and Signal-noise Ratio in TEOAE and DPAOE in Individuals with Normal Hearing

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ABSTRACT

Objective: The aim of this study was to investigate whether ABO and Rhesus (Rh) blood type systems are associated with distortion product otoacoustic emission (DPOAE) and transient otoacoustic emission (TEOAE) amplitudes, with the hypothesis that blood types affect hearing thresholds.

Methods: Seventy participants with normal hearing, aged 18-26 years, with normal tympanometry and otoscopic examination findings, were included in the study. TEOAE and DPOAE tests were conducted on all participants.

Results: The Rh factor did not significantly affect the OAE results. It was found that the TEOAE amplitudes of blood type B at 1.4 kHz in the left ear were higher than those of blood types A and AB. The amplitude of AB blood was lower than that of O, A, and B blood types at 2 kHz.

Conclusion: Our study results did not indicate a consistent pattern for a specific blood type, in contrast to previous findings. Additional research is required to investigate the potential correlation between hearing function and ABO and Rh blood types.

Keywords: Otoacoustic emissions, distortion product otoacoustic emissions, transient evoked otoacoustic emissions, blood type, signal to noise ratio, normal hearing

Clinical Trials ID: NCT06326866.

INTRODUCTION

Blood is a body-specific fluid consisting of plasma, red blood cells, white blood cells, and thrombocytes (1). Blood type is defined by the presence of specific antibodies and antigens. Over three-hundred antigens on erythrocytes have been described in the literature, and the International Blood Transfusion Association lists more than 30 blood type systems (2). Among them, the ABO and Rhesus (Rh) systems were the most significant. The ABO system, discovered by Karl Landsteiner in 1900, categorizes blood types according to A and B antigens (3,4). The Rh system further classifies blood based on the presence or absence of the D antigen, resulting in Rh-positive or Rh-negative blood types (5). The distribution of blood types varies according to region, country, and ethnicity (6). In the USA, O+ is the most common blood type, whereas AB is rarer (7). Additionally, a study in Türkiye found that A+ is the most common blood type, whereas AB is the least common (8).

ABO antigens appear in many cell types and tissues, making certain blood types more susceptible to specific conditions because of their different genetic expression (9). For example, blood type O has been linked to a lower risk of otitis media due to higher antibodies against infectious agents, whereas blood type A has been associated with an increased risk of ischemic heart disease in patients with type 1 diabetes and a higher likelihood of developing oral cancer (10-12). Studies have also explored the association between blood types and coronavirus disease-2019, indicating that type A individuals may have a higher risk of infection than type O (13).

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Research into the relationship between blood type and hearing found no significant differences in hearing thresholds among blood types (14). However, other studies have shown that individuals with blood type O are more susceptible to noise-induced hearing loss (NIHL) (15-17). Continuous or sudden loud noise primarily damages the outer hair cells (OHC), and the otoacoustic emission (OAE) test serves as an objective measure of OHC function. Tracking changes in OAE amplitude can detect noise-induced damage more effectively than pure-tone hearing tests, and abnormal OAE responses can indicate increased NIHL risk (18). OAE tests are classified as spontaneous and evoked emissions. Spontaneous emissions occur without audible stimulation, whereas evoked emissions require an external signal. Among evoked emissions, transient-evoked otoacoustic emission (TEOAE) and distortion product otoacoustic emission (DPOAE) are commonly used for screening and diagnostic purposes (19). Factors such as race, age, and gender can influence OAE measurements although gender does not significantly affect responses (19-21).

Studies have shown that blood type and related antigens affect intercellular recognition during development, and this has potential implications for auditory function. Although some studies suggest blood types O and Rh+ may exhibit poorer responses to OAE, further extensive research is needed to confirm these findings (15,22). Given the demonstrated association between blood type and OAE responses, our research aimed to investigate the relationship between blood type (ABO) and Rh factors and TEOAE and DPOAE amplitudes. We aim to contribute to the limited literature on hearing loss susceptibility and blood types, hypothesizing that different blood types may be associated with varying hearing thresholds.

METHODS

Participants

This study was approved by the Local Ethics Committee of İstanbul University-Cerrahpaşa Non-invasive Clinical Research Ethics Committee under protocol 10.04.2018-134269 (decision no: 2024/42, date: 25.01.2024) and was carried out in accordance with the Declaration of Helsinki. Written informed consent to participate was obtained from all participants.

Individuals with normal otoscopic findings and middle ear function, with a hearing threshold of 15 dB and better at all frequencies between 125 Hz and 8 kHz, without a history of exposure to noise, and whose blood type was confirmed by a blood test before the study were prospectively included in the study. Participants who met the inclusion criteria were grouped according to the respective blood group. The demographic data and hearing thresholds of the patients are presented in Table 1.

Following a detailed otologic history including noise exposure, audiometric tests were performed to evaluate the range of 125-8 kHz. Patients with high-frequency hearing loss and those with NIHL configuration (4 kHz Notch) were excluded from the study.

Procedure

Otoscopic examination, acoustic immittance evaluation, and pure tone hearing tests were performed in all participants. Tympanometry, acoustic reflex, and eustachian function tests were performed using an acoustic immitancemetry device (GSI Tympstar V2-Grason-Stadler Inc. Eden Prairie, MN) to verify normal middle ear function. Hearing thresholds were measured using a calibrated clinical audiometer device (GSI Audiostar; Gram-Stadler Inc. Eden Prairie, MN) in a quiet cabinet using TDH-39P headphones in the 125 Hz-8 kHz range. An Echoport ILO 288 OAE device (Otodynamics Ltd, Hatfield, UK) was used for TEOAE and DPOAE measurements by placing a suitable silicone probe into the ear canal of the individual using 80-84 dB peSPL click stimulus and two pure tone stimuli at 65/55 dB SPL (f2/f1=1.22), respectively. The TEOAE and DPOAE tests were performed at 1-4 kHz and 1-6 kHz frequencies, respectively, as the frequencies measured in OAE equipment in clinical routine use are often measured in the range of 1-4 kHz, which is the range of communication in daily life. Patients were grouped according to ABO blood type. The amplitudes of TEOAE and DPOAE were measured in both the left and right ears of each group (ABO).

Statistical Analysis

All data were analyzed using the Statistical Packages for Social Sciences (SPSS) software version 21.0 (IBM Corp.; Armonk, NY, USA). The Kruskal-Wallis test was used for multiple group comparisons that were not normally distributed, and Dunn-Bonferroni correction was used to identify pairs with significant differences. Findings with $p<0.05$ were considered statistically significant.

Table 1. Demographic characteristics of the individuals participating in the study

Number of participants (n)	70
Male	27
Female	43
Age (mean ± SD)	21.75±1.36
Blood types	**n**
A	
Rh+	10
Rh-	9
B	
Rh+	10
Rh-	9
AB	
Rh+	10
Rh-	10
O	
Rh+	10
Rh-	2

p>0.05 air and bone conduction thresholds. SD: standard deviation

RESULTS

The study included 70 participants (43 female, 27 male) with the following blood type distribution: 19 participants had blood type A (10 Rh+ and 9 Rh-), 19 participants had blood type B (10 Rh+ and 9 Rh-), 20 participants had blood type AB (10 Rh+ and 10 Rh-), and 12 participants had blood type O (10 Rh+ and 2 Rh-). The ages of the participants ranged from 18 to 26 years (average age: 21.75 years; standard deviation: 1.36 years). The average air-conduction hearing thresholds of the participants were 5.09±3.01 dB in the right ear and 5.14±3.19 dB in the left ear. The bone conduction hearing thresholds of the participants were 3.26±2.96 dB in the right ear and 3.41±2.74 dB in the left ear.

An initial analysis of mean ranks was conducted to determine whether Rh had a significant effect on the OAE results. No statistically significant differences were observed between the same blood types with different Rh factors ($p>0.05$). Due to the lack of significant differences and the small number of participants with AB Rh blood type, subsequent analyses were conducted without considering Rh.

The TEOAE and DPOAE test results were analyzed using the Kruskal-Wallis test, which revealed a statistically significant difference in the left ear TEOAE results at 1.4 and 2 kHz ($p<0.05$). Further pairwise analysis using the Dunn test with Bonferroni correction indicated that at 1.4 kHz, the B blood type had a higher TEOAE signal-to-noise ratio (SNR) than the A ($p=0.008$) and AB ($p=0.018$) blood types. At 2 kHz, the AB blood type had a lower SNR than the O ($p=0.042$), A ($p=0.043$), and B ($p=0.002$) blood types. The descriptive statistics and statistical analysis results for the TEOAE and DPOAE tests are presented in Table 2. The DPOAE and TEOAE test results are also visualized in Figure 1.

DISCUSSION

In this study, we focused on the differences in OAE responses among ABO and Rh blood groups. In contrast to previous studies, we investigated the impact of both ABO and Rh blood types on OAE amplitudes and obtained different results. Participants with AB blood type tended to exhibit lower TEOAE and DPOAE SNR amplitudes at 2 kHz. Additionally, the TEOAE amplitudes of individuals with blood type B were higher at 1.4 kHz in the left ear than those with blood types A and AB. However, no consistent relationship was observed for the other blood groups.

The normal ear canal resonance ranges between 2 and 3 kHz, and the middle ear resonance frequency spans 800-1200 Hz in adults (23). Because the outer and middle ear systems have higher permeability to sounds at these frequencies, it is possible to record higher OAE amplitudes. Prabhu et al. (24) noted that individuals with blood type O had higher middle ear resonance frequency and ipsi/contralateral acoustic reflex thresholds compared with other blood groups. Additionally, studies have found OAE amplitudes between 1 and 3 kHz to be higher than at other frequencies (25,26). Similarly, in our study, mean OAE amplitudes tended to be higher at 1.4-2.8 kHz (Table 2).

Recent studies have suggested differences in OAE responses among adults based on ABO and Rh blood types. Chow et al. (15) classified 60 female participants with normal hearing according to ABO blood type and found no statistically significant difference between right and left ear TEOAE results at different frequencies.

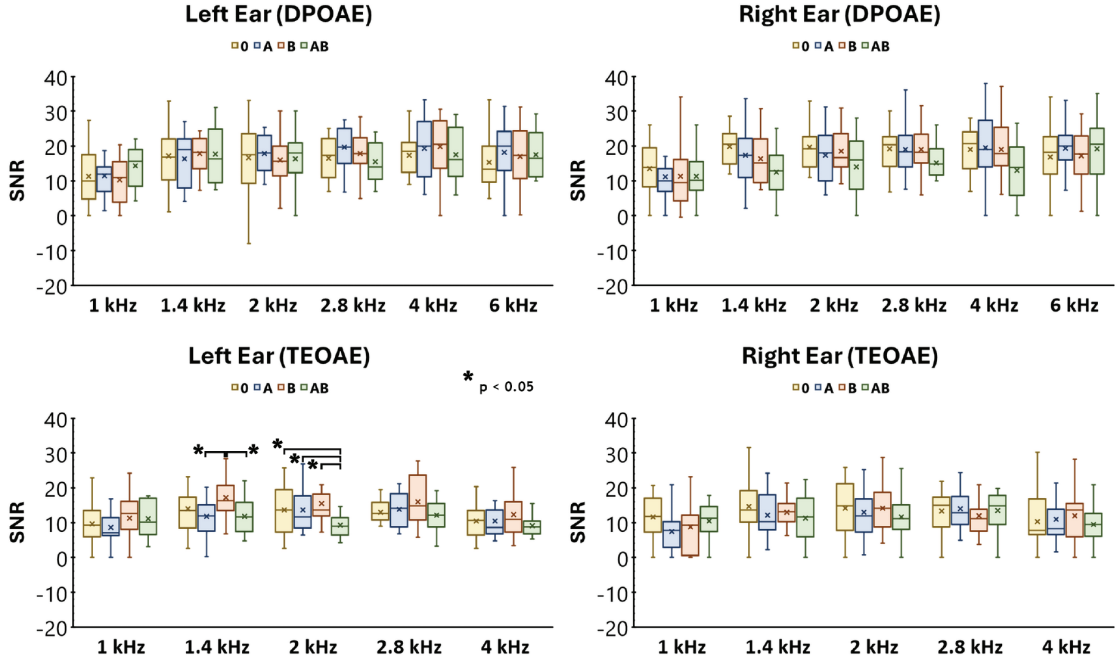

Figure 1. TEOAE and DPOAE test results for each blood type
DPOAE: distortion product otoacoustic emission, TEOAE: transient evoked otoacoustic emission

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Table 2. Descriptive statistics and statistical comparisons of the DPOAE and TEOAE test results according to blood type

	0 type			A type			B type			AB type			p-value (inter-group)
	N	M	IQR	N	M	IQR	N	M	IQR	N	M	IQR	
Left ear DPOAE													
1 kHz	20	10.00	11.00	19	10.00	6.00	19	11.00	9.00	12	18.00	10.00	0.553
1.4 kHz	20	16.85	10.75	19	19.00	14.50	19	19.30	6.05	12	16.70	14.60	0.932
2 kHz	20	17.45	12.83	19	18.00	8.60	19	19.00	13.30	12	17.00	8.20	0.728
2.8 kHz	20	17.40	8.00	19	21.00	8.85	19	19.60	9.20	12	14.00	9.65	0.299
4 kHz	20	17.50	9.75	19	20.00	14.00	19	22.30	10.70	12	15.00	17.40	0.604
6 kHz	20	12.65	12.08	19	20.00	11.55	19	17.40	11.05	12	17.00	13.15	0.412
Right ear DPOAE													
1 kHz	20	14.50	9.95	19	8.00	7.30	19	10.40	14.25	12	10.60	8.25	0.435
1.4 kHz	20	20.50	6.68	19	16.00	11.50	19	19.80	10.10	12	14.00	6.80	0.070
2 kHz	20	19.10	8.75	19	18.20	13.50	19	22.10	13.80	12	16.00	11.70	0.411
2.8 kHz	20	20.45	9.02	19	19.00	7.50	19	20.60	9.10	12	14.40	9.10	0.557
4 kHz	20	20.60	10.60	19	19.00	9.50	19	19.20	8.90	12	14.00	11.40	0.268
6 kHz	20	17.60	10.75	19	21.00	7.00	19	17.60	11.45	12	22.00	12.25	0.682
Left ear TEOAE													
1 kHz	20	9.55	8.00	19	7.10	4.00	19	13.20	8.00	12	10.00	10.00	0.195
1.4 kHz	20	12.85	12.53	19	11.30	7.90	19	18.90	10.35	12	11.20	6.50	0.030*
2 kHz	20	13.70	12.83	19	11.10	9.10	19	17.40	7.65	12	7.60	5.10	0.026*
2.8 kHz	20	12.55	4.50	19	14.40	7.95	19	16.90	13.15	12	13.50	6.95	0.439
4 kHz	20	7.40	6.30	19	8.30	6.40	19	11.00	13.20	12	9.20	3.35	0.859
Right ear TEOAE													
1 kHz	20	11.85	8.00	19	7.80	6.00	19	10.20	10.00	12	12.20	6.00	0.074
1.4 kHz	20	12.55	8.95	19	10.30	7.35	19	13.20	7.15	12	12.10	7.70	0.344
2 kHz	20	14.10	10.85	19	11.40	7.60	19	12.00	9.05	12	11.00	7.15	0.587
2.8 kHz	20	14.95	6.80	19	13.60	9.40	19	11.10	9.35	12	15.10	4.85	0.319
4 kHz	20	7.70	4.80	19	7.50	6.50	19	13.70	11.65	12	9.70	8.80	0.721

N: sample size, M: median, IQR: interquartile range, *p<0.05, DPOAE: distortion product otoacoustic emission, TEOAE: transient evoked otoacoustic emission

However, individuals with blood type O exhibited lower TEOAE amplitudes at 1.0, 1.4, and 4.0 kHz in the left ear and 1.4, 2.8, and 4.0 kHz in the right ear compared with the other blood types (15). In a similar study, Chen et al. (22) showed that the TEOAE and DPOAE amplitudes of 60 male participants varied significantly across the four blood types, with individuals having blood type O showing lower OAE amplitudes.

In another study by Prabhu et al. (27), the association between blood type differences and high-frequency hearing sensitivity were examined using high-frequency hearing and DPOAE tests. The findings indicated that although there was no significant difference in high-frequency hearing thresholds, individuals with blood type O exhibited lower DPOAE amplitudes. It has been suggested that these results might be due to the presence of fewer active OHC in individuals with blood type O (27). Although previous studies have shown that individuals with blood type O exhibited lower OAE amplitudes than those with other blood types, our study did not confirm a consistent pattern.

Another important factor in blood transfusion is the Rh system. Blood-type antigens are transiently expressed during the development of hair cells in the cochlea, influencing processes like hair cell development, synaptogenesis, and ciliogenesis, which are associated with the Rh system (20). Few studies have investigated the effects of the Rh factor on auditory function. Bener et al. (28) found a positive relationship between Rh+ blood type and hearing loss in infants. Conversely, Ayçiçek et al. (29) indicated that workers with Rh+ blood type were more likely to develop NIHL than those with Rh blood type. However, another study concluded that although blood type may be an individual risk factor for hearing loss, Rh antigens were not considered risk factors (30). Li et al. (31) did not examine the effect of Rh on OAE results because Rh- blood type is present in only 0.9% of cases. In our study, no significant difference was found between the DPOAE and TEOAE amplitudes of individuals with Rh+ and Rh blood types (p>0.05). Our research aims to contribute to the literature by examining the association between Rh antigens and hearing status.

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Other studies investigating the effects of ABO blood types on the auditory system have yielded contradictory results. Although some studies, such as those by Doğru et al. (16) and Nair and Kashyap (17), suggested a correlation between ABO blood types and NIHL, Ayçiçek et al. (29) found no significant difference. Factors like race and gender may also influence OAE responses, but there are no clear data on their relationship to OAEs in the literature. Structural differences, such as the length of the external ear canal, tympanic membrane, middle ear ossicles, and cochlea, might also affect OAE responses. In our study, gender and race were not proven to influence OAEs; thus, we did not consider these factors during evaluation.

In conclusion, our study investigated the association between ABO and Rh blood systems and OAE amplitudes and found different results compared with those reported for both TEOAE and DPOAE amplitudes across blood types. Unlike other studies that generally compared blood type O with others, our study included all ABO types and analyzed subgroups (Rh, right/left ear, DPOAE/TEOAE), providing more detailed information on the association between blood types and OAEs.

Study Limitations

The limitations of our study include the limited number of patients included in the analysis, failure to evaluate the effectiveness of the efferent system, anatomical differences, and the exclusion of gender factors due to the small number of participants. Although the ages of the individuals included in our study were similar, it is possible that age differences or exposure to unknown noise and ototoxicity may produce results that differ from those in the literature.

CONCLUSION

In our study, unlike many reports in the literature, the TEOAE and DPOAE SNR amplitudes tended to be lower for the AB blood type than for the other blood types. This difference may be due to all subjects in our sample were of the same race. In a larger group of subjects of different races, it will be possible to determine whether this is a racial variation. Measuring the potential produced by the OHC with DPOAE and TEOAE in subjects with different blood types, Rh factors, and right/left ears at different frequencies was thought to induce a better understanding of the differences in OAE among subjects. Various factors, such as the relatively large volume of the ear canal, mass of the ossicular chain, resonant frequency of the middle ear, and contralateral suppression, may affect OAEs. Conducting studies with larger groups may provide more consistent and generalizable information and shed light on individual differences.

Ethics Committee Approval: This study was approved by the Local Ethics Committee of İstanbul University-Cerrahpaşa Non-invasive Clinical Research Ethics Committee under protocol 10.04.2018-134269 (decision no: 2024/42, date: 25.01.2024) and was carried out in accordance with the Declaration of Helsinki.

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

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Investigation of The Effects of Fatty Acids on Growth Hormone, Insulin-like Growth Factor 1, and Insulin- and Hormone-sensitive Lipase Levels in Rats

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ABSTRACT

Objective: Several studies have investigated hormones such as growth hormone (GH), insulin (INS), insulin-like growth factor-1 (IGF-1), and hormone-sensitive lipase (HSL). However, there is insufficient data on the effects of the combination of short-, medium-, and long-chain fatty acids on hormone concentrations in serum/tissue, including GH, INS, IGF-1, and HSL. The purpose of this study was to investigate the effects of butyric acid (BA), caprylic acid (CA), and oleic acid (OA) alone or in combination on GH, INS, IGF-1, and HSL secretion.

Methods: Fifty-six male Wistar rats were used in the study. The animals were separated into 8 subgroups: control, BA, CA, OA, BA + CA, BA + OA, CA + OA, and BA + CA + OA groups. Fatty acids were administered orally to rats for 21 days. At the end of the study, GH, IGF, INS, and HSL levels were measured in serum using the enzyme-linked immunosorbent assay method.

Results: BA administration reduced GH, IGF-1, and INS levels but had no significant effect on HSL levels. CA administration increased HSL levels but had no significant effect on GH, INS, and IGF-1 levels. OA administration increased GH and HSL levels but had no significant effect on IGF-1 and INS levels.

Conclusion: The combined use of fatty acids increased GH levels while decreasing INS, IGF-1, and HSL levels.

Keywords: Butyric acid, caprylic acid, oleic acid

INTRODUCTION

Fatty acids are the building blocks of fats and contain carbon atoms ranging from 2 to 34 (1). They are classified based on the number of carbons in their structures. If the number of carbons is <6, they are classified as short-chain, approximately 6-12 as medium-chain, and >12 as long-chain fatty acids (LCFAs) (2).

Short-chain fatty acids (SCFAs) are predominantly produced by gut bacterial flora via the fermentation of unprocessed carbohydrates and dietary fiber. Acetic acid (C2), propionic acid (C3), butyric acid (BA) (C4), valeric acid (C5), and caproic acid (C6) are SCFAs with various carbon chain lengths that are produced in varying amounts depending on the diet and gut bacteria composition (3). BA is a 4-carbon, colorless, oily carboxylic acid with a characteristic odor. It is soluble in water and slightly volatile at room temperature. BA, also known as butter acid, is naturally found in milk. BA has been reported to play an important role in the modulation of many diseases (3).

Medium-chain fatty acids (MCFAs) consist of fatty acids with carbon chain lengths ranging from 6 to 12 m (2). They can be digested without the need for pancreatic enzymes and bile salts. Upon reaching the small intestine, they are already in the form of fatty acids. Therefore, they are quickly transported to the liver and metabolized there. MCFAs have recently been considered as alternative treatments for certain chronic diseases, such as type 2 diabetes mellitus, epilepsy, anorexia nervosa, disorders of lipid metabolism, obesity disorders, and inflammatory bowel diseases (1). Caprylic acid (CA) (C8), caproic acid (C6), and capric acid (C10) are medium-chain saturated fatty acids. MCFAs are unique nutrients present in certain fats, such as dairy products, date kernels, and coconut oils (4). The metabolic specificity of MCFAs is associated with beneficial physiological effects, such as increased catabolism in adipose tissue and reduced fat storage in tissues (5). Studies on overweight individuals have demonstrated that diets abundant in MCFAs lead to decreased fat storage and elevated energy expenditure compared with diets abundant in LCFAs, even when the caloric intake is matched (6).

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LCFAs are the primary source of energy for many organs, particularly the muscles and liver. Oleic acid (OA) is a monounsaturated fatty acid with 18 carbons. OA alone accounts for one-third or more of the lipids in breast milk. It serves as a significant energy source and can be synthesized within the body. In adults, OA reduces the total blood cholesterol concentration. Additionally, it regulates nutrition absorption in the gastrointestinal (GI) system, keeping blood glucose and INS levels within normal limits (7).

Growth hormone (GH) is produced by somatotropic cells located in the anterior pituitary gland. Its primary role is to promote linear growth (8). It exerts its hormonal effects via insulin-like growth factor-1 (IGF-1). GH stimulates amino acid uptake. It directly accelerates mRNA transcription and translation, leading to increased protein synthesis. It also facilitates the use of fats as an energy source, thereby reducing protein breakdown (9).

IGFs are small peptides that exert their effects primarily locally and stimulate growth in specific cells. Their primary amino acid sequences are similar to each other and to human proinsulin. Structurally and functionally, they belong to the growth factor family (10). They are peptides that are dependent on GH. IGFs lead to the anabolic effects of GH and the effects that enable cell division through mitosis (9).

Insulin hormone is produced by pancreatic beta cells and is stored in granules. It is then released into the bloodstream. Elevated blood glucose levels prompt beta cells to release insulin. Glucose is the most important factor that stimulates the synthesis and release of INS (11). Insulin stimulates lipoprotein lipase activity and facilitates the clearance of chylomicrons containing excess triglycerides from circulation (12).

Hormone-sensitive lipase (HSL) is an intracellular enzyme with neutral properties that can degrade various lipid substrates, including triacylglycerols, diacylglycerol, monoacylglycerol, cholesterol esters, and other lipid and water-soluble compounds (13).

Limited literature exists concerning the impact of combined SCFAs, MCFAs, and LCFAs on hormone concentrations in serum or tissues, including GH, IGF-1, INS, and HSL. Moreover, no published research has explored the synergistic effects of different fatty acid types on the secretion of GH, IGF, INS, and HSL. This study aimed to examine the effects of SCFAs, MCFAs, and LCFAs on GH, IGF, INS, and HSL levels.

METHODS

Animals

The rats were obtained from the Düzce University Animal Research and Application Center. Fifty-six male Wistar rats aged 4-5 months and weighing approximately 390±30 grams, were accommodated under ideal environmental conditions. These conditions included a room temperature of 23 °C, humidity maintained at 60±5% and a 12-hour light-dark cycle. The rats were provided *ad libitum* access to both food and water. All study methods were reported in accordance with the Animal Research: Reporting of *in Vivo* Experiments guidelines and approved by Düzce University Local Ethics Committee on Animal Testings (decision no: 2022/07/03, meeting date: 27.07.2022).

Substances and Dosages

BA, CA, and OA were procured from Sigma (Sigma-Aldrich, Inc., St. Louis, MO, US). Each of these fatty acids was orally administered at a dose of 100 mg/kg. As an anesthetic, 90 mg/kg ketamine hydrochloride and 10 mg/kg xylazine hydrochloride were intramuscularly administered (i.m.).

Experimental Design

The rats were divided into 8 groups, each consisting of 7 rats: control (CONT), BA, CA, OA, BA + CA, BA + OA, CA + OA, and BA + CA + OA. All substances were given orally by gavage. The CONT group received only 1 mL/kg saline for 21 days. Only the BA, CA, and OA groups received either 100 mg/kg of BA, CA, or OA fatty acids for 21 days. The dual-fatty acid combination (BA + CA, BA + OA, and CA + OA) groups received a combination of 100 mg/kg of BA, CA, or OA fatty acids for 21 days. Similarly, the triple combination (BA + CA + OA) group received a combination of 100 mg/kg of BA, CA, and OA fatty acids for 21 days. Throughout the study, to examine the effects of fatty acid administration on weight changes in the animals, their weights were measured at the beginning and end of the study.

Termination of the Study

The animals in each group were subjected to cardiac puncture under ketamine/xylazine anesthesia 24 hours after the last treatment to collect blood from the heart. Subsequently, the animals were euthanized under anesthesia by cervical dislocation. The blood samples were centrifuged at 4000 revolutions per minute (rpm) for 15 minutes to separate the serum, which was subsequently stored at a temperature of -80 °C until further analysis.

Determination of Biochemical Biomarkers

The levels of GH, IGF-1, INS, and HSL in the collected serum samples were measured using enzyme-linked immunosorbent assay (ELISA). For this purpose, ELISA kits for rat GH (Cat. 201-11-0552), rat INS (Cat: 201-11-0708), rat IGF-1 (Cat: 201-11-710), and rat HSL (Cat: SRB-T-84624) were procured from SunRed (Shanghai SunRed Biological Technology, China). All parameters were measured using an ELISA reader according to the kit procedure. Additionally, blood glucose levels were determined using blood glucose measurement devices and strips.

Statistical Analysis

In comparing the groups based on serum GH, IGF-1, INS, HSL, GH, and glucose levels, One-Way Analysis of Variance (ANOVA) and the Tukey-Kramer Multiple Comparison test were utilized to determine the different groups. To compare body weights, Two-Way ANOVA was employed, and groups showing significant differences were identified using the Šídák Multiple Comparison test. A statistical significance level of $p \leq 0.05$ was considered. Prism 9 software was used for the analyses.

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RESULTS

Effects of Fatty Acids on Biochemical Parameters

A significant difference in GH levels among the groups was evident upon comparison (p<0.001) (Figure 1). The study found that the OA, BA + CA, BA + OA, and BA + CA + OA groups had significantly greater mean GH levels than the CONT group (p<0.001, p=0.02, p<0.001, and p=0.005, respectively). The BA group had significantly lower mean GH levels than the CA, OA, BA + CA, BA + OA, CA + OA, and BA + CA + OA groups (p=0.02, p<0.001, p<0.001, p=0.002, and p<0.001, respectively). Similarly, the mean GH level of the CA group was found to be statistically lower than that of the BA + OA group (p=0.03).

A significant disparity in INS levels among the groups was evident upon comparison (p=0.001) (Figure 2). Upon closer examination of the results, we determined that the INS levels of the BA, CA + OA, and BA + CA + OA groups were statistically lower than those of the CONT group (p=0.02, p=0.02, and p=0.03, respectively). Additionally, the mean INS levels of the BA + OA and CA + OA groups were lower than those of the CA group (p=0.04 and p=0.04, respectively).

The groups exhibited a statistically significant difference in IGF-1 levels (p<0.001) (Figure 3). Upon closer examination of the results, we found that the IGF-1 levels of the BA + CA + OA group were statistically lower than those of the CONT, CA, OA, and BA + CA groups (p=0.02, p=0.001, p<0.001, and p=0.02, respectively). Similarly, the IGF-1 levels of the BA group were statistically lower than those of the CA and OA groups (p=0.01 and p=0.005). Additionally, it was determined that the IGF-1 levels of the BA + CA group were statistically lower than those of the OA group (p=0.04).

There was a substantial difference in HSL levels between the groups (p<0.001) (Figure 4). Upon detailed examination of the results, The BA + CA + OA group had significantly lower mean HSL levels than the CONT, BA, CA, OA, BA + CA, and BA + OA groups (p=0.04, p<0.001, p<0.001, and p=0.03, respectively). In contrast, the mean HSL level of the CA group was significantly higher than that of the CONT, BA, BA + OA, and CA + OA groups (p<0.001). The OA group showed significantly higher mean HSL levels than the CONT, BA, and BA + OA groups (p<0.001, p=0.002,

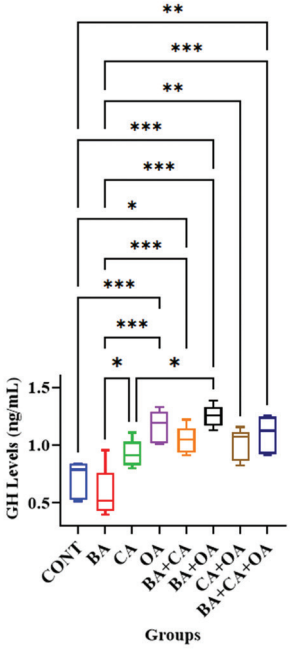

Figure 1. The effect of fatty acids on GH levels (*p<0.05, **p<0.01 and ***p<0.001)

CONT: control, BA: butyric acid, CA: caprylic acid, OA: oleic acid, GH: growth hormone

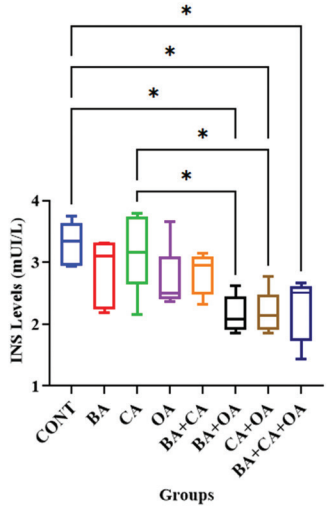

Figure 2. The effect of fatty acids on INS levels (*p<0.05)

CONT: control, BA: butyric acid, CA: caprylic acid, OA: oleic acid, INS: insulin

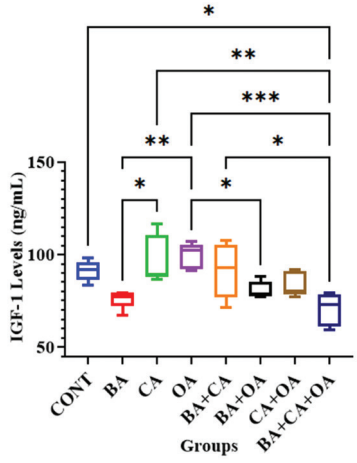

Figure 3. The effect of fatty acids on IGF-1 levels (*p<0.05, **p<0.01 and ***p<0.001)

CONT: control, BA: butyric acid, CA: caprylic acid, OA: oleic acid, IGF-1: insulin-like growth factor-1

and p<0.001, respectively). The BA + CA group had significantly higher mean HSL levels than the CONT, BA + OA, and CA + OA groups (p<0.001).

There was a substantial difference in blood glucose levels among the groups (p<0.001) (Figure 5). The BA + CA group had significantly lower mean glucose levels than the CONT, BA, CA, OA, BA + OA, CA + OA, and BA + CA + OA groups (p<0.001, p<0.001, p=0.01, p<0.001, p<0.001, and p<0.001, respectively). The mean glucose level in the CA group was significantly higher than that in the BA, BA + OA, and BA + CA + OA groups (p=0.02, p=0.01, and p=0.02, respectively).

Evaluation of the Effects of Fatty Acids on Body Weight Changes

When comparing the mean weights of the groups before and after the experiment, no significant difference was observed among them (p=0.07) (Figure 6). Overall, although the weights obtained from post-experiment measurements were higher than those obtained from pre-experiment measurements, they were not statistically significant (p>0.05). Conversely, although the weights of the CA and BA + OA groups were lower after the experiment compared with before the experiment, they were not statistically significant (p>0.05).

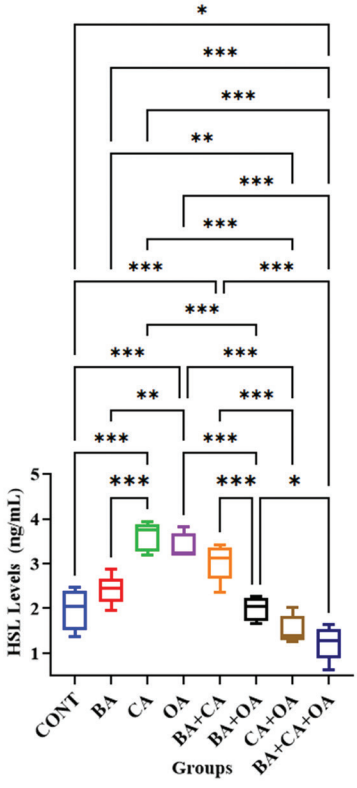

Figure 4. The effect of fatty acids on HSL levels (*p<0.05, **p<0.01 and ***p<0.001)
CONT: control, BA: butyric acid, CA: caprylic acid, OA: oleic acid, HSL: hormone-sensitive lipase

DISCUSSION

Various fatty acids are present in human nutrition, circulating in the bloodstream, and within human cells and tissues. SCFAs, MCFAs, and LCFAs serve as energy sources and membrane components. They possess biological activities that influence cellular and tissue metabolism, function, and sensitivity to hormonal and other signals. Although there has traditionally been an interest in the impact of fatty acids on health related to cardiovascular disease, it is now known that fatty acids also affect a range of other diseases, including metabolic diseases, such as type 2 diabetes, inflammatory diseases, and cancer (14). This study examined the relationships of SCFAs, MCFAs, and LCFAs with GH, IGF-1, INS, and HSL.

Substantial interactions occur between fatty acids and the endocrine system, with hormones exerting influence on fatty acid metabolism and tissue lipid composition. Insulin and GH

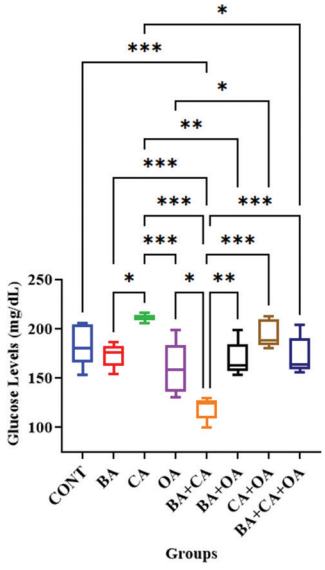

Figure 5. The effect of fatty acids on glucose levels (*p<0.05, **p<0.01 and ***p<0.001)
CONT: control, BA: butyric acid, CA: caprylic acid, OA: oleic acid

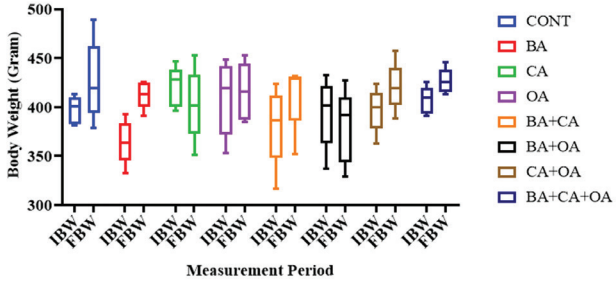

Figure 6. The effect of fatty acids on body weight
IBW: initial body weight, FBW: final body weight, CONT: control, BA: butyric acid, CA: caprylic acid, OA: oleic acid

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are prominent hormones involved in lipid metabolism. Their concentrations fluctuate in chronic degenerative conditions like diabetes and cardiovascular disease, thereby affecting tissue lipid profiles (15).

SCFAs have critical functions in intestinal epithelial cells. SCFAs also regulate diverse processes within the GI tract, including the absorption of electrolytes and water (16). A previous study found that BA, an SCFA, increased GH secretion in pituitary cells via GPR41/43 activation and intracellular Ca^{+2} accumulation (17). This suggests that BA may serve as a secondary mediator in the metabolic adaptations of GH during fasting, primarily involving increased lipolysis and protein retention (18). GH stimulates the release and oxidation of free fatty acids (FFAs). The most prominent metabolic effect of GH is a significant increase in lipolysis and FFA levels (19). The composition of the plasma membrane affects cell sensitivity to metabolically significant hormones like INS and vasoactive intestinal peptides. In a study investigating the impact of lipid and modified plasma membrane composition on the activation of the growth hormone secretagogue receptor (GHSR), it was noted that polyunsaturated fatty acids (PUFAs) enhance membrane fluidity by disrupting their structure. Long-term exposure (96 hours) to 18-carbon PUFAs, specifically oleic and linoleic acid, significantly heightened the sensitivity of GHSR cells to ghrelin, whereas acute treatment did not yield the same effect (20). Ghrelin, a hormone regulated by metabolism, activates the G protein-coupled receptor GHSR-1a, not only in the pituitary gland but also in peripheral tissues such as the pancreas, stomach, and T-cells in circulation (20). It has been shown that CA octanoylated ghrelin, the only known orexigenic peptide hormone (21). In the present study, we observed that OA, BA + CA, BA + OA, and BA + CA + OA applications increased GH levels. These data are consistent with the literature. However, only the BA group showed a decrease in GH levels. This difference is likely due to the fact that most studies in the literature are conducted on cell lines, as numerous uncontrolled mechanisms come into play in the *in vivo* environment, leading to different results from those obtained *in vitro*.

IGFs interact with GH during embryonic development and postnatal growth. IGF-1 directly enhances muscle mass, bone density, and bone structure. The intestinal microbiota triggers the secretion of IGF-1, which supports the development and remodeling of bones. SCFAs produced in microbial fermentable fibers induce the secretion of IGF-1, explaining how microbial activity affects bone health through IGF-1. Additionally, IGF-1 has both direct and indirect glucose-lowering effects. It increases FFA oxidation in muscles, reduces the flow of FFAs to the liver, enhances INS signaling, decreases hepatic glucose output, and improves INS sensitivity (22). The results of the present study indicate that the combined application of all three fatty acids reduces IGF-1 levels. This result is likely due to the increase in GH levels induced by fatty acids. Elevated blood GH levels may inhibit IGF-1 expression. However, because there are no studies in the literature regarding the effects of MCFAs and LCFAs on IGF-1, comparisons cannot be made.

Studies have shown that a high-fat diet supplemented with propionic acid and BA improves INS sensitivity and protects against the development of obesity and INS resistance (23,24). Additionally, a reduction in fat content was observed in obese mice treated with BA (23,24). This is consistent with weight loss and improved INS tolerance, suggesting a role for BA in the treatment of diet-induced obesity. SCFAs also inhibit lipolysis, a complex metabolic process performed by adipocytes during nutrient deprivation and stress, by releasing FAs and glycerol from triacylglycerol storage droplets, increasing glucose uptake stimulated by INS (25,26). Recent studies have shown that fatty acids induce INS resistance in skeletal muscle by blocking the activation of phosphatidylinositol 3-kinase (PI3-kinase) associated with insulin receptor substrate-1 (27). According to the results of a study, GPR40, a G-protein-coupled receptor abundantly expressed in the pancreas, functions as a receptor for LCFAs. Furthermore, LCFAs enhance glucose-stimulated INS secretion from pancreatic β cells by activating GPR40 (28). Acute increases in FFAs stimulate INS secretion, but long-term lipid exposure impairs β-cell function both *in vitro* and *in vivo* animal studies (29). Obesity and high FFA levels reduce INS clearance. A study examined the effects of some common FFAs and their acyl-coenzyme A thioester on partially purified INS-degrading enzymes in the livers of male Sprague-Dawley rats (30). The results of the study suggest that increased intracellular LCFA concentrations directly affect INS metabolism and alter INS action in intact cells, potentially contributing to hyperinsulinemia and INS resistance observed in high fatty acid and obesity (30). However, there are no studies on the effects of MCFAs on INS. In the present study, when groups were examined in terms of INS levels, we found that the groups treated with BA, CA + OA, and BA + CA + OA had lower INS levels. These findings are consistent with the literature.

HSL is a key enzyme in mobilizing fatty acids from intracellular stores (31). SCFAs regulate lipid metabolism when substrates are provided for lipid synthesis. SCFAs activate AMP-activated protein kinase (AMPK) (31). AMPK has been shown to positively regulate lipolysis by affecting HSL and adipose triglyceride lipase (32,33). A previous study reported that triglycerides containing MCFAs increased HSL activity and expression in the white adipose tissue of c57bl/6j mice (34). HSL knockout studies have shown that the removal of HSL disrupts lipolysis and leads to a significant decrease in lipogenesis (35). There are no studies in the literature regarding the effects of LCFAs on HSL. In the present study, when the groups were examined in terms of HSL levels, it was observed that the application of BA, CA, and OA alone increased HSL levels, whereas their combined application had the opposite effect. This may be due to the administration of high-dose fatty acid formulations (200 or 300 mg/kg) over a long period.

In a study investigating the effects of FFAs on glucose uptake and utilization in healthy women, acute increases in plasma FFA within the high physiological range for 4 h led to approximately 40% inhibition of INS-stimulated glucose uptake and glycogen synthesis in healthy normal-weight individuals (36). Another study

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involving seven pregnant women found that FFAs inhibited INS-stimulated glucose uptake by 42% (37). Another study also found that high fatty acid concentrations inhibit glucose utilization (36). An *in vitro* study conducted on isolated hepatocytes and perfused rat liver showed that SCFAs and MCFAs modulate the hepatic metabolism of carbohydrates and lipids. BA and CA inhibited glycolysis (38). In another study, it was demonstrated that MCFAs in rodents have protective effects against glucose homeostasis following high-fat overfeeding. In addition, small numbers of MCFAs in the diet were found to provide protection against INS resistance in humans during caloric excess (39). In the present study, we found that rats treated with BA + CA had lower blood glucose levels. In contrast, treatment with only CA increased blood glucose levels.

MCFAs (except for lauric acid) predominantly belong to the fast-metabolizing group (40). A recent systematic review showed that diets rich in MCFAs resulted in significantly higher high density lipoprotein-cholesterol levels compared with those rich in LFAs, but had no effect on triglycerides, low density lipoprotein-cholesterol, or total cholesterol concentrations (41). MCFAs in the diet have gained nutritional interest because of their easier absorption from dietary medium-chain triacylglycerols compared with LCFAs derived from vegetable oils (42). MCFAs can be directly absorbed and provide rapid energy, promoting intestinal epithelial cell renewal and repair, maintaining intestinal mucosal barrier function integrity, and reducing inflammation and stress (43). Animal and human studies have shown that the rapid oxidation rate of MCFAs leads to increased energy expenditure. Most animal studies have shown that MCFAs result in higher energy expenditure than LCFAs, leading to less weight gain and reduced adipose tissue size after several months of consumption (6). Additionally, both animal and human experiments indicate that medium-chain triglycerides have a greater satiating effect than long-chain triglycerides (6). All three major SCFAs (propionate, acetate, and butyrate) provide protection against diet-induced obesity (44). However, in the present study, although the weights obtained from post-experimental measurements were generally higher than those obtained from pre-experimental measurements, no significant difference was observed. Only groups treated with CA or BA + OA showed a non-significant decrease in weight compared with pre-experimental measurements.

Study Limitations

Due to financial restrictions, molecular parameters at the tissue level were not evaluated.

CONCLUSION

BA application resulted in a decrease in GH, IGF-1, and INS levels, but no significant effect was observed on HSL levels. CA application increased HSL levels but did not show a significant effect on GH, insulin, and IGF-1 levels. OA application increased GH and HSL levels but did not significantly affect IGF-1 and INS. CA application increased glucose levels, whereas BA and OA applications did not significantly affect glucose levels. The combined application of fatty acids increased GH levels while decreasing INS, IGF-1, and HSL levels. In conclusion, longer-term and comprehensive studies are needed to elucidate the effects of SCFAs, MCFAs, and LCFAs on GH, IGF-1, HSL, and INS.

Ethics Committee Approval: All study methods were reported in accordance with the Animal Research: Reporting of *in Vivo* Experiments guidelines and approved by Düzce University Local Ethics Committee on Animal Testings (decision no: 2022/07/03, meeting date: 27.07.2022).

Informed Consent: Experimental animal study.

Author Contributions: Surgical and Medical Practices - A.E., Ö.B., E.B., A.G.; Concept - Ö.B., E.B.; Design - A.E., Ö.B., E.B., A.G.; Data Collection and/or Processing - A.E., Ö.B., E.B., A.G.; Analysis and/or Interpretation - Ö.B., E.B.; Literature Search - A.E., Ö.B., E.B., A.G.; Writing - A.E., Ö.B., E.B., A.G.

Conflict of Interest: The authors have no conflict of interest to declare.

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Evaluation of f(QRS-T) Angle as a Marker of Coronary Artery Disease Risk in Term Pregnant Women

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ABSTRACT

Objective: An indication of instability in myocardium electrical characteristics is the frontal (QRS-T) [f(QRS-T)] angle. There is a known relationship between this angle and coronary artery disease, such as arrhythmias and sudden death. The purpose of the present study was to investigate the f(QRS-T) angle in term pregnant women and its relationship with advanced maternal age, parity, hemoglobin (Hb), and total blood viscosity.

Methods: A total of 247 term pregnant individuals who had no prior history of cardiac or chronic disease and similar body mess indexes (BMI) were included in the study. Patients were divided into two groups according to their ages: ≥35 and <35 years. f(QRS-T) angles were calculated manually. f(QRS-T) angles, Hb levels, and total blood viscosities were compared between the two groups.

Results: Our study revealed no statistically significant differences in f(QRS-T) angle, Hb levels, or high and low total blood viscosities between the two groups ($p>0.05$). Additionally, no correlation was found among age, total blood viscosity, and f(QRS-T) angle in term pregnancies with similar gestational weeks and BMI.

Conclusion: The angle of f(QRS-T) is narrower in term pregnancies of women aged ≥35, compared to those under 35, albeit both values fall within normal limits and are unrelated to Hb levels and total blood viscosity. Therefore, regarding this angle, there was no observed increase in extracardiac risk in term pregnancies among women aged ≥35 compared to younger pregnancies.

Keywords: Pregnancy, electrocardiography, blood viscosity

INTRODUCTION

It is possible to forecast future cardiovascular mortality by observing abnormalities in ventricular depolarization and, more specifically, anomalies during the susceptible repolarization period. The spatial QRS-T angle, which is the angle between the directions of ventricular depolarization and repolarization, has been shown in many studies to be predictive of cardiac mortality (1-4). However, most medical professionals are unfamiliar with measuring the spatial QRS-T angle, and currently used computerized electrocardiographic analysis tools do not typically provide this information. On the other hand, the frontal plane QRS-axis and T-wave axis are easily obtained from a typical 12-lead electrocardiogram (ECG) and are typically reported by automated ECG equipment. They make it simple to calculate the f(QRS-T) angle, which has been shown to correlate well with the spatial QRS-T angle for risk prediction (5).

The f(QRS-T) angle is a sign of instability in the myocardium's electrical characteristics. It can be determined by analyzing the absolute difference between the QRS and T axis. The frontal (QRS) angle can be easily calculated from ECG and is an easily accessible and evaluable data that has gained importance in recent years. According to prior research, a relationship between this angle and coronary artery disease has been observed; it is particularly associated with cardiac arrhythmias and sudden cardiac arrest (6-8).

Wide-ranging hemodynamic and hormonal changes occur throughout a typical pregnancy in response to the developing fetus's needs. Although the concept of high-risk pregnancy defined so far has obvious boundaries, in this physiological period, from a cardiac perspective, the f(QRS-T) angle has never been evaluated in term pregnancies. This study aimed to investigate the f(QRS-T) angle in pregnant women aged ≥35 and <35 years, and evaluate its relationship with other parameters that may change cardiac

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load (parity, hemoglobin (Hb) and blood viscosity differences). Therefore, we aimed to identify which pregnancies are associated with a higher risk of arrhythmia and cardiac events by examining this angle and potential related situations. This study is unique and will contribute to the literature.

METHODS

This retrospective cohort study was conducted at the Ankara Bilkent City Hospital, Obstetrics and Gynecology Clinic between June and December 2023. A total of 247 healthy pregnant women were included in the study, and the protocol was approved by the Clinical Research Ethics Committee of Ankara Bilkent City Hospital (decision no: E2-24-6150, date: 24.01.2024). Patients with multiple gestation, abnormal laboratory test results, diabetes mellitus, gestational or pre-gestational hypertension, coronary heart disease, or congenital heart disease were excluded from the study. Patients who had to take any medication, were addicted to drugs, or consumed alcohol or tobacco were also excluded. Patients were divided into two groups: ≥35 and <35 years. The commonly accepted threshold for advanced maternal age (AMA) in the literature is 35 years and older (9,10).

After the patients had rested for 10 minutes in the supine posture, the electrodes were positioned in standard anatomical positions to capture the ECG at a speed of 25 mm/s and a width of 10 mm/mV (Cardiofax M Model ECG -1250; Nichon Kohden Corporation, Tokyo, Japan). The absolute difference between the QRS and T axis, which can be easily acquired from digital ECG data, was used to determine the f(QRS-T) angle. The predicted f(QRS-T) angle from an autonomously produced surface ECG record is shown in Figure 1. The f(QRS-T) angle was determined as 360° minus the absolute difference between the f(QRS-T) and T axes if the difference was greater than 180°. One of the authors, a cardiologist, assessed the f(QRS-T) angles (Figure 1).

The complete blood viscosity was calculated using pre-approved formulas using hematocrit and total plasma protein concentrations at both high cutting rate [high shear rate (HSR) =208/s] and low cutting speed [low shear rate (LSR) =0.5/s]. The formula for whole blood viscosity for HSR (208/s) is as follows: (0.12 × hematocrits) + 0.17 (total protein – 2.07) and whole blood viscosity for LSR (0.5/s): (1.89 × hematocrit) + 3.76 (total protein- 78.42). Here, hematocrit was calculated as %s, total protein concentration as g/L, and whole blood viscosity from the centipoise (cP).

Statistical Analysis

For statistical analysis, SPSS for Windows 18.0 was used (IBM, Chicago, IL, USA). The significance levels of the tests were reported as follows: for normally distributed data, mean ± standard deviation was provided, whereas for non-normally distributed data, the median (minimum-maximum) was reported. The numerical values were examined for normality using the Kolmogorov-Smirnov test. Values with a normal distribution were compared using the Student's t-test, whereas values with a non-normal distribution were compared using the Mann-Whitney U test. For correlation analysis, bivariate Pearson's test was performed. P<0.05 was considered statistically significant.

RESULTS

Table 1 shows the demographic, laboratory, and ECG data of 247 term pregnant women divided into groups 1 and 2. As shown in Table 1, no significant differences were observed between maternal age and f(QRS-T) angle.

Subsequently, an analysis was conducted to determine the correlation between blood viscosity and age. As illustrated in Table 2, no correlation was found among blood viscosity, age, and f(QRS-T) angle in term pregnancies with similar gestational weeks and BMI.

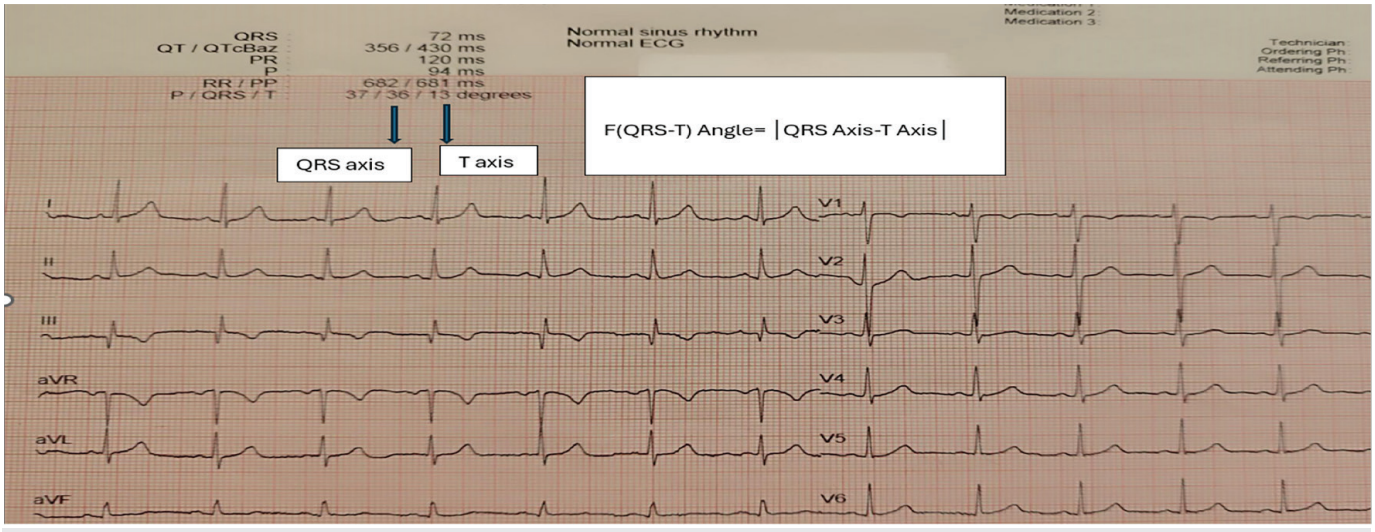

Figure 1. Calculation of the frontal QRS-T angle from the automatic report of surface ECG
ECG: electrocardiogram, f(QRS-T): frontal QRS-T

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DISCUSSION

According to our study, the f(QRS-T) angle was narrower in term pregnancies of women aged 35 years and older than in those under 35 years, although both measurements fell within normal ranges and showed no correlation with Hb levels or total blood viscosity. Consequently, there is no discernible elevation in extracardiac risk in term pregnancies in women aged 35 years and older compared with younger pregnancies.

Table 1. Demographics, laboratory test results, and f(QRS-T) angle findings of group 1 and 2

Parameters	Group 1 n=187	Group 2 n=60	p-value
Parity	1 (0-3)	2 (0-4)	<0.001*
Gestational week	38 (37-41)	38 (37-41)	0.068
Body mass index	28 (25-31)	29 (27-30)	0.008
f(QRS-T) angle	18 (0-73)	15.5 (0-76)	0.756
Hemoglobin (g/dL)	11.55±1.26	11.6±1.28	0.714
Hematocrit, %	35.59±3.76	35.58±3.72	0.988
Total protein level, g/dL	62.3±3.92	61.3±4.08	0.091
Albumin, g/dL	37 (33-44)	36 (31-44)	0.017
Total blood viscosity, HSR, cP	14.5±0.82	14.34±0.78	0.192
Total blood viscosity, LSR, cP	51.16 (3.69-69.34)	51.36 (35.52-66.85)	0.474

*P<0.05 was considered statistically significant. HSR: high shear rate, LSR: low shear rate, cP: centipoise, f(QRS-T): frontal QRS-T
The significance levels of the tests were reported as follows: for normally distributed data, mean ± standard deviation was provided, whereas for non-normally distributed data, the median (minimum-maximum) was reported.

The orientation difference between ventricular depolarization and repolarization is known as the f(QRS-T) axis angle. This represents shifts in the length of the regional action potential and the orientation of the normalization process. Deviations from this metric suggest modified ventricular repolarization associated with underlying anatomical and functional modifications to the heart. As a result, an abnormal f(QRS-T) angle indicates an increased risk of cardiovascular disease (CVD) and all-cause mortality (1,3,4,6,8).

The f(QRS-T) angle varies by gender and age, with women generally having a smaller angle at baseline and widening with age. However, in a study conducted with healthy participants, the upper limits of normal were determined to be between 45° and 60° (6). In a 2012 cohort study of elderly patients considered not to have CVD, the top limits of normality, unique to sex, were 39° for women and 81° for men (11). According to Jogu et al. (12), an abnormal f(QRS-T) angle (for women >104° on the ECG) offers significant predictive data about the likelihood of atrial fibrillation in the elderly (12). An increased risk of arrhythmic death was observed by Aro et al. (8) when the f(QRS-T) angle was more than 100°. As a result, a wide range of factors have been related to cardiac mortality in the general population and are thought to be signs of heterogeneity in ventricular repolarization.

Throughout a typical pregnancy, a wide range of hemodynamic and hormonal changes occur in response to the requirements of the developing fetus. The compensatory physiological adjustments that begin in the initial trimester substantially affect the maternal cardiovascular system. These adjustments encompass a reduction in peripheral vascular resistance alongside an increase in plasma volume, heart rate, and cardiac output (13). Specifically, pregnancy-induced hemodynamic and hormonal alterations influence the maternal heart, potentially leading to eccentric hypertrophy characterized by the enlargement of cardiac cavities and increased left ventricular wall thickness and mass (14). Cardiac remodeling, heightened sympathetic nervous system

Table 2. Correlation analysis between demographic and laboratory test results and f(QRS-T) angle findings of 247 pregnant women

	Age	Parity	Gestational week	BMI	f(QRS-T) angle	Hb	Total protein	HSR, cP	LSR, cP
f(QRS-T) angle	r=0.039 p=0.543	r=0.052 p=0.417	r=0.048 p=0.452	r=0.025 p=0.696	r=1	r=-0.024 p=0.711	r=0.011 p=0.864	r=-0.027 p=0.673	r=-0.018 p=0.776
Hemoglobin (g/dL)	r=0.104 p=0.101	r=0.026 p=0.689	r=0.034 p=0.591	r=0.073 p=0.255	r=-0.024 p=0.711	r=1	r=-0.080 p=0.208	r=0.423* p=0.000	r=-0.308* p=0.000
Hematocrit, %	r=0.098 p=0.123	r=0.012 p=0.851	r=-0.040 p=0.535	r=0.067 p=0.294	r=-0.061 p=0.344	r=0.821 p=0.000	r=-0.045 p=0.486	r=0.559* p=0.000	r=0.424* p=0.000
Total protein level, g/dL	r=-0.164 p=0.010	r=-0.019 p=0.764	r=-0.009 p=0.891	r=0.014 p=0.831	r=0.111 p=0.864	r=-0.080 p=0.208	r=1	r=0.803* p=0.000	r=0.886* p=0.000
Albumin, g/dL	r=-0.137 p=0.303	r=-0.004 p=0.946	r=0.001 p=0.990	r=0.035 p=0.588	r=-0.171 p=0.007	r=0.093 p=0.145	r=0.548* p=0.000	r=0.461* p=0.000	r=0.502* p=0.000
Total blood viscosity, HSR, cP	r=-0.077 p=0.225	r=-0.009 p=0.891	r=-0.031 p=0.629	r=0.051 p=0.422	r=-0.027 p=0.673	r=0.423* p=0.000	r=0.803* p=0.000	r=1	r=0.988* p=0.000
Total blood viscosity, LSR, cP	r=-0.103 p=0.106	r=-0.012 p=0.853	r=-0.026 p=0.681	r=0.043 p=0.496	r=-0.018 p=0.776	r=-0.308* p=0.000	r=0.886* p=0.000	r=0.988* p=0.000	r=1

r: correlation coefficient, BMI: body mass index, HSR: high shear rate, LSR: low shear rate, cP: centipoise, Hb: hemoglobin, f(QRS-T): frontal QRS-T

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activity, and pregnancy-related hormonal shifts may predispose patients to proarrhythmic effects (15). Notably, arrhythmic events were the third most common etiology of cardiovascular-related mortality, accounting for 22.2% of maternal mortality during and after pregnancy (16). Maternal Hb levels physiologically decrease throughout pregnancy due to hemodilution. The third trimester is when this impact reaches its peak (17,18). Studies conducted during this period revealed no change in plasma viscosity when physiological hemodilution and hypercoagulability were detected in low-risk pregnancies. However, plasma viscosity was observed to increase in pregnancy-induced hypertension or complicated pregnancy outcomes at the time of their delivery (19-21). Under the 2019 American College of Cardiology/American Heart Association guidelines on the primary prevention of CVD, conditions like early menopause, polycystic ovary syndrome, rheumatologic disorders, and unfavorable pregnancy outcomes are considered risk enhancers due to their significance regarding sex-specific or sex-predominant risk markers (22).

Despite extensive research on the negative effects of AMA and delay in childbirth on unfavorable maternal and perinatal outcomes, the definition of AMA remains unclear. This phrase, which is frequently applied to women over 35, describes the latter years of a woman's reproductive life span (9,10). Over-35-year-old pregnant women are at an increased risk of two- to three-fold higher rates of hospitalization, cesarean delivery, and other pregnancy-related complications due to the significant rise in the prevalence of coexisting conditions with aging, such as diabetes, obesity, cancer, and cardiovascular, renal, and autoimmune diseases (23-26). In this study, we conducted a comparative analysis between term pregnancies in women aged ≥35 and those aged <35 years. Our study revealed no statistically significant differences in f(QRS-T) angle, Hb level, or high and low total blood viscosities between the two age groups. Furthermore, we observed no statistically significant differences after evaluating these parameters, regardless of maternal age. This suggests that the physiological hemodynamic and hormonal changes occurring during pregnancy, regardless of AMA or not, do not lead to significant alterations in the f(QRS-T) angle in low-risk term pregnancies. In addition, our analysis revealed the absence of a significant correlation between Hb, hematocrit, blood viscosity, and f(QRS) angle value in pregnant women in all term, irrespective of age.

Study Limitations

The retrospective nature of this study necessitated a limited sample size, which is considered a limitation of the study.

CONCLUSION

In conclusion, assessing the f(QRS-T) angle showed that AMA did not result in supplementary cardiac risk compared with younger pregnancies.

Ethics Committee Approval: The Clinical Research Ethics Committee of Ankara Bilkent City Hospital approved the study protocol (decision no: E2-24-6150, date: 24.01.2024).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Author Contributions: Surgical and Medical Practices - G.Y.; Concept - G.Y., K.G.B.; Design - G.Y., K.G.B.; Data Collection and/or Processing - G.Y.; Analysis and/or Interpretation - G.Y., K.G.B.; Literature Search - G.Y., K.G.B.; Writing - G.Y., K.G.B.

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The Relationship Between Normal-range Ejection Fraction and Diastolic Function

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ABSTRACT

Objective: Understanding ejection fraction (EF) limits are crucial for the evaluation of diastolic function (DF). Therefore, in our study, we aimed to compare the DFs between patients with low-normal and high-normal EFs.

Methods: A total of 70 patients who were followed in our clinic were prospectively included in our study. Those with an EF of 55-62% were included in the low-normal EF group, and those with an EF >62% were included in the high-normal EF group. Subsequently, the relationship between DF and EF was analyzed.

Results: Both groups exhibited similarities in demographic characteristics, such as age, sex, and additional medical conditions, demonstrating homogeneous distribution among the groups. No statistically significant difference was observed between the groups in terms of diastolic and systolic parameters.

Conclusion: No relationship was found between normal EF and DF. Nonetheless, our work can serve as a model for more extensive research on this topic.

Keywords: Diastolic function, ejection fraction, diastolic parameters, echocardiography

INTRODUCTION

In patients with known or suspected heart disease, despite certain limitations, the most commonly used parameter for evaluating left ventricular systolic function is still the ejection fraction (EF). According to expert recommendations in clinical guidelines, the normal thresholds for EF are 54% or higher in women and 52% or higher in men (1). However, in some studies involving a large number of patients, individuals with EF levels of approximately 65% had the lowest mortality (2,3). Therefore, some argue that normal EF values should be redetermined. In the assessment of diastolic function (DF), as in many other fields, a defined threshold value for EF exists, thereby altering the DF evaluation algorithm. According to the 2016 DF guidelines, a threshold of 50% is considered normal for EF (4). Our study aimed to investigate the relationship between EF values above this threshold and DF.

METHODS

Study Population

Patients admitted to the outpatient clinic of our center between April and June 2022 were included in this cross-sectional, single center study. Comprehensive clinical histories were obtained from the hospital system and during assessment. Detailed physical examinations and electrocardiograms were conducted for the patients, followed by two-dimensional transthoracic echocardiography (TTE) using the Vivid S60 (GE Healthcare, USA) device at our center. TTE procedures were performed by an operator holding the European Association of Cardiovascular Imaging TTE certification.

Our study adhered to the standards of the Declaration of Helsinki and was conducted with the approval of the University of Health Sciences Türkiye, Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee (no: 387) on December 22, 2021.

Inclusion Criteria

Patients aged 18-80 years were eligible for the study. Individuals with an EF ranging from 55% to 62% were categorized as the low-normal EF group, whereas those with an EF value exceeding 62% were classified as the high-normal EF group.

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Exclusion Criteria

The exclusion criteria included conditions hindering the assessment of DF, such as moderate to severe mitral insufficiency, advanced aortic insufficiency, and atrial fibrillation. Patients with wall motion abnormalities in regions where Doppler parameters were assessed were also excluded. Patients with a history of cardiac surgery, constrictive pericarditis, hypertrophic cardiomyopathy, or extreme tachy-bradyarrhythmia during TTE evaluation were excluded.

Two-dimensional Transthoracic Echocardiography

All patients underwent detailed TTE using the parasternal long-axis, parasternal short-axis, apical 2-, 3-, and 4-chamber views, and subcostal windows. EF was measured using the biplane Simpson method. DF was evaluated using the parameters outlined in Nagueh et al.'s (4) 2016 guidelines. Assessment included left atrial volume index, E/e', mitral E/A, tricuspid regurgitation peak velocity, mitral septal and lateral e' velocities, tricuspid E/A, tricuspid lateral e', as well as tricuspid annular plane systolic excursion (TAPSE), tricuspid lateral S wave velocity, inferior vena cava diameter, and right atrial pressure evaluations. Additionally, indexed echocardiographic data were obtained from the patient's height, weight, and body surface area. Cardiac output and stroke volumes were calculated for all patients.

Assessment and Grading of the Diastolic Function

Patients were initially evaluated for the presence of diastolic dysfunction (DD). The criteria outlined by Nagueh et al. (4) were taken into consideration. Those with low EF or left ventricular hypertrophy were considered to have DD, and staging was performed. In the other patient groups, the presence of DD was initially assessed, followed by staging. DD was staged as grade 0 (no dysfunction), grade I (impaired relaxation), grade II (pseudonormalization), or grade III (restrictive pattern).

Consent to Publish the Report

Informed consent was obtained from the patients.

Artificial Intelligence

Artificial intelligence was not used in this study.

Statistical Analysis

Continuous data was expressed as the mean ± standard deviation or median (interquartile range) values, whereas categorical data was described as proportions and was evaluated using the chi-square test or Fisher's Exact test. Kolmogorov-Smirnov test was used to evaluate the distribution of the data. Student's t-test or Mann-Whitney U test was used to compare continuous variables. The correlation between left ventricular ejection fraction (LVEF) and the degree of DD was assessed using Spearman's correlation test. Data were analyzed using SPSS version 29.0 (SPSS Inc., Chicago, IL, USA). A two-sided p-value <0.05 was considered statistically significant.

RESULTS

Demographic Characteristics

The study included a total of 70 patients, further divided into two groups based on LVEF: 55-62% (n=40) and LVEF >62% (n=30). The mean age of the entire cohort was 50±14 years, and there was no significant difference between the two LVEF groups (p=0.146). Female proportion was 40%, with a non-significant distribution between LVEF categories (p=0.338). Other baseline characteristics, including body surface area, hypertension, diabetes mellitus, coronary artery disease, heart rate, and blood pressure, showed no statistically significant differences between the groups (Table 1).

Left ventricular end-systolic diameter was significantly lower in the high-normal EF group (p=0.005). The left ventricular wall thickness, left atrium size, stroke volume, and TAPSE [were similar between the groups (Table 2)].

Table 1. Demographic characteristics of the patients

	All patients (n=70)	LVEF 55-62% (n=40)	LVEF >62% (n=30)	p-value
Age, years	50±14	47±14	52±14	0.146
Female, n (%)	28 (40)	14 (35)	14 (47)	0.338
BSA, m^2	1.9±0.2	1.9±0.2	2.0±0.3	0.305
HT, n (%)	30 (43)	17 (43)	13 (43)	0.944
DM, n (%)	5 (7)	4 (10)	1 (3)	0.284
CAD, n (%)	11 (16)	5 (13)	6 (20)	0.394
Heart rate, bpm	75±13	74±15	75±11	0.713
SAP, mmHg	128±22	128±27	127±15	0.911
DAP, mmHg	76±12	78±13	75±10	0.421

LVEF: left ventricular ejection fraction, BSA: body surface area, HT: hypertension, DM: diabetes mellitus, CAD: coronary artery disease, SAP: systolic arterial pressure, DAP: diastolic arterial pressure

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Two-dimensional Transthoracic Echocardiography Parameters

Diastolic Function Parameters

Parameters such as the mitral E-wave, mitral A-wave, E/A ratio, deceleration time, and E' velocities did not differ significantly between the LVEF groups. Similarly, the tricuspid regurgitation velocity and the parameters related to the tricuspid inflow and E' velocities did not differ significantly (Table 3).

Diastolic Dysfunction

The study assessed DD, and the distributions across grades (none, grade I, grade II, grade III, indetermined) was comparable between the LVEF groups (p=0.837) (Table 4). There was no significant correlation between LVEF and the degree of DD (r=0.004, p=0.837) (Table 4).

Correlation Analysis

A scatterplot demonstrated no significant relationship between LVEF and DD in the study population (r=0.004, p=0.978), emphasizing the independence of these parameters (Figure 1).

DISCUSSION

DF assessment is a critical component of echocardiography (4). This is because distinguishing between normal and abnormal DF is crucial for diagnosing diastolic heart failure (HF), which accounts for half of all heart failure (HF) cases and has a mortality rate of least as high as that of HF with reduced EF (5). Therefore, addressing uncertainties in this area through research could contribute to a more accurate evaluation of DF and to advancements in the diagnosis and treatment of diastolic HF.

In our study, we tested the hypothesis that 'if the lower limit of normal EF is in the range of 60-65%, patients with EF below this range should have worse DF and diastolic parameters'. DF and diastolic parameters were compared between patients with low-normal (55-62%) and high-normal (>62%) EF, aiming to investigate the relationship between normal-range EF and DF and diastolic parameters. Although numerical differences were observed for various diastolic parameters, our study did not identify statistically significant distinctions between the two groups.

EF is a crucial metric for assessing cardiac systolic function and is often considered a cornerstone in clinical decision-making.

Table 2. TTE parameters of patients

	All patients (n=70)	LVEF 55-62% (n=40)	LVEF >62% (n=30)	p-value
LVEDD, mm	46±4	47±4	45±4	0.083
LVESD, mm	30±4	32±5	29±3	0.005
IVSD, mm	11±2	10±2	11±2	0.488
PWD, mm	9±2	9±1	9±2	0.358
RWT	0.39±0.08	0.37±0.07	0.40±0.08	0.137
LV mass index	81±20	83±23	80±17	0.491
LA, mm	37±6	37±7	37±7	0.735
LAVI, mL/m^2	26±8	25±9	27±8	0.337
SV, mL	83±20	80±20	87±20	0.182
TAPSE, mm	22±4	22±4	23±5	0.281

TTE: two-dimensional transthoracic echocardiography, LVEF: left ventricular ejection fraction, LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, IVSD: interventricular septal diameter, PWD: pulse wave Doppler, RWT: relative wall thickness, LV: left ventricular, LA: left atrial, LAVI: left atrial volume index, SV: stroke volume, TAPSE: tricuspid annular plane systolic excursion

Table 3. Diastolic parameters of patients

	All patients (n=70)	LVEF 55-62% (n=40)	LVEF >62% (n=30)	p-value
Mitral E-wave (cm/s)	72±19	71±21	76±17	0.296
Mitral A-wave (cm/s)	65±11	69±15	69±15	0.998
Mitral E/A	1.1±0.3	1.1±0.4	1.1±0.3	0.643
DT, ms	170±45	188±57	170±42	0.134
Mitral septal E' wave (cm/s)	8±3	8±3	9±3	0.938
Mitral septal E/E' joints	9±4	9±4	10±3	0.503
Mitral lateral E/E' joints	7±3	6±2	7±3	0.398
Peak TRV m/sc	2.2±0.4	2.2±0.4	2.3±0.5	0.610

LVEF: left ventricular ejection fraction, DT: deseleration time, TRV: tricuspid regurgitation velocity

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Table 4. Diastolic function of patients

DD	All patients	EF 55-62% n (40)	EF >62% n (30)	p-value: 0.837
None	31 (44)	17 (45)	14 (47)	
Grade I	31 (44)	17 (45)	14 (47)	
Grade II	5 (7)	3 (8)	2 (7)	
Grade III	1 (2)	1 (3)	0 (0)	
Indetermined	2 (3)	2 (5)	0 (0)	

EF: ejection fraction, DD: diastolic dysfunction

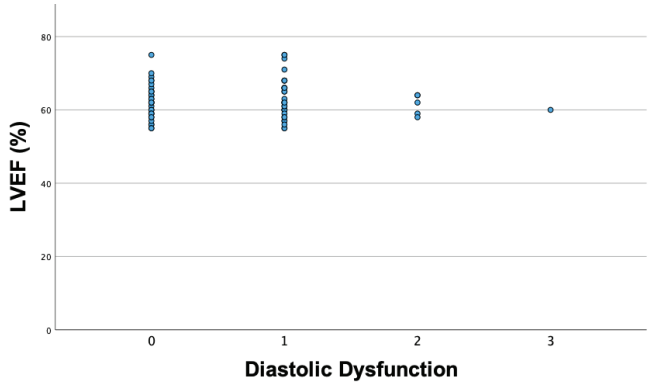

Figure 1. The scatterplot demonstrates no relationship between left ventricular ejection fraction and DD in the study population
DD: diastolic dysfunction, LVEF: left ventricular ejection fraction

The conventional normal range for EF is generally regarded as 50-55%. However, recent research has introduced nuances to this understanding, revealing potential variations in mortality and morbidity outcomes associated with different EF ranges (6). A landmark study by Wehner et al. (3) (2020), which included a substantial cohort of 400,000 patients, challenged the traditional norm by identifying an EF range of 60-65% as associated with the lowest mortality rate. These findings hinted at a potential shift in the definition of normal EF. Similarly, Tsao et al. (7) demonstrated increased morbidity and mortality in patients with EF values 50%, emphasizing the clinical significance of variations within the normal range. The PARAGON-HF trial further nuanced this understanding by highlighting therapeutic benefits for women with an EF of up to 57% (8).

In guidelines related to DF, it is generally accepted that patients with impaired systolic function will have also impaired DF. For example, in the guidelines published in 2016, an EF value of 50% was considered a threshold value (4). The notion that the work performed during the systolic and diastolic phases of the heart may not be independent is not new. This occurs because the energy of external work performed during systole is restored by internal work performed during diastole (9). Therefore, if there is a disturbance in either of these phases, there should be a disturbance in the other as well. In a study conducted by de Simone (10), it was emphasized that systolic functions calculated from the midwall level and DFs show parallelism, and changes in both phases could occur concomitantly.

Study Limitations

In this study, we did not find the expected result, and there were limitations that could have contributed to this outcome. The most important limitation was the restriction in the number of patients and the inability to use strain echocardiography to evaluate left ventricular systolic function (11,12). Additionally, the single-center nature of the study and the inclusion of relatively healthy patients were other study limitations. However, we believe that elucidating the relationship between EF and DF is crucial, and conducting studies in this regard is essential. Therefore, we believe that the current study could pave the way for research in this area, as we could not identify any study directly evaluating the relationship in the literature.

CONCLUSION

In our study, no relationship was found between EF within the normal range and DF and parameters. To provide a clearer understanding of the relationship between EF within the normal range and DF, more extensive studies are required. Our study provides a nucleus for future studies in the field of normal-range LVEF and DD.

Ethics Committee Approval: Our study adhered to the tenets of the Declaration of Helsinki and was conducted with the approval of the University of Health Sciences Türkiye, Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee with 387 number on December 22, 2021.

Informed Consent: Informed consent was obtained from the patients.

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Conflict of Interest: The authors have no conflict of interest to declare.

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Factors Affecting Physician Fear of Malpractice and Defensive Medicine Practices: A Cross-sectional Study

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ABSTRACT

Objective: The aim of this study was to determine the attitudes of a group of physicians toward defensive medicine, their fears of malpractice and the affecting factors.

Methods: Data was collected between April and July 2022 in this cross-sectional study. The sample size was 248 physicians. Data was collected using the Defensive Medicine Attitude Scale and Malpractice Fear Scale. Data was analyzed using frequency tables, descriptive statistics, Mann-Whitney U test (Z-table value) and the Kruskal-Wallis H test (χ^2-table value).

Results: Most participants 99.2% (n=246) thought that a doctor's professional liability insurance should be taken out and 72.6% (n=180) avoided giving treatment to difficult patient groups. In our study, the mean score on the Defensive Medicine Attitude Scale was moderate (32.12±6.12), and the mean score on the Malpractice Fear Scale was high (24.31±2.86). A weak positive correlation was found between the Malpractice Fear Scale score and the scores for positive defensive medicine, negative defensive medicine, avoidance, and the Defensive Medicine Attitude Scale total score ($p<0.05$).

Conclusion: Our study determined that the fear of malpractice increased the tendency toward defensive medicine practice. Most physicians adopted the defensive behavior in medicine and were afraid of facing malpractice lawsuits in near future.

Keywords: Malpractice, defensive medicine, attitude

INTRODUCTION

Defensive medicine practice is becoming more common. The emergence of patient rights, health policies, and the increase in expectations from health professionals in health institutions negatively affect the physician-patient relationship, causing physicians to experience fear of malpractice. Physicians more frequently prefer defensive medicine practices to avoid legal problems. Thus, physicians prioritize their professional knowledge and values less in the diagnosis, treatment, and care and adopt an attitude of self-protection.

Malpractice is defined as "harm" caused by the doctor's failure to perform standard practice during treatment, lack of skill, or not giving treatment to the patient in the World Medical Association's Medical Malpractice Announcement (1). Malpractice includes the damage caused by lack of care, education, experience, good interpretation or competence, and inadequate patient care (2). Diagnostic errors, application of incorrect and/or invalid tests and techniques, or incorrect application or interpretation of appropriate tests, incomplete or delayed diagnosis, medication dose errors, inappropriate treatment technique, inadequate follow-up, incorrect and/or inadequate follow-up of treatment and disease, delayed or incomplete prophylaxis, and equipment-related or system-related errors are considered within the scope of medical malpractice (3). Fear of malpractice can be defined as fear arising from the possibility of a medical malpractice lawsuit being filed against physicians while performing their profession. Increased malpractice cases in recent years have significantly affected both the medical profession and society, causing physicians to turn into safe practices (4).

Catino (5) (2011) defined defensive medicine as hospital personnel, particularly physicians, requesting unnecessary examinations and procedures or avoiding high-risk treatment methods and patients. Defensive medicine is a method for physicians to

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protect themselves from possible negative outcomes that may arise from interventions and practices. Çalıkoğlu and Aras (6) (2020) defined defensive medicine as the behavior of health professionals that aims to protect themselves from administrative, criminal, legal, and ethical sanctions. Defensive medicine practices can take two forms: positive and negative. Positive defensive medicine includes performing unnecessary medical procedures for diagnosis, treatment, or follow-up of the disease, to protect oneself from legal liability, and to create the impression that everything necessary is done with great care. Negative defensive medicine refers to the behavior of physicians to avoid high-risk patients and treatments to eliminate claims of medical malpractice (7,8). Concerns and perceptions of medical responsibility drive practitioners to practice defensive medicine (4,9). By using their autonomy in line with the information they have acquired, patients can exhibit attitudes that may harm the patient-physician relationship. This causes physicians to turn into defensive medicine and carry diagnostic treatment to protect themselves (8-11). At the same time, health policies, the complex structures of the developed reference protocols that do not clearly state the roles and responsibilities of physicians, and the constant concern of being sued by patients lead physicians to defensive medicine (11,12). Defensive medicine practices come to forefront in the context of patient-physician relationship and appear to be a problem of both professionalism and medical ethics (8).

The aim of this study was to determine the defensive medicine attitudes of a group of physicians, their fear of malpractice and the factors affecting them.

METHODS

This research is a cross-sectional descriptive study. The study population consisted of 260 physicians. Physicians working in the public sector and in local centers in the Central Anatolia region of Türkiye were part of the study population. All physicians who agreed to participate after being informed and who completed the data collection form were included in the study. Data were collected from 248 participants in the study. Data were collected between April and July 2022.

Data Collection Form

The questions were prepared by the researchers after scanning the relevant literature (6,13,14).

Defensive Medicine Attitude Scale (DMAS): This scale was developed by Kolcu and Özceylan (15) (2021). In confirmatory factor analysis, a model was created with 3 sub-dimensions. These factors are divided into three groups: cost-increasing behavior, defensive behavior involving negative defensive medicine, and avoidance behavior. Total scores were grouped as low (11-23), medium (24-41), and high (44-55). The Cronbach-α coefficient for internal consistency was 0.84 (15). In our study Cronbach-α coefficient was 0.82.

Malpractice Fear Scale: A validity and reliability study of the scale developed by Katz et al. (16) (2005) to measure the malpractice fear levels of physicians was conducted by Uğrak and Işık (14) (2020). Total score below 15 is considered low, approximately 15-20 medium, and above 20, high-level fear of malpractice. The Cronbach-α coefficient was 0.86 (14). In our study Cronbach-α coefficient was 0.874.

Statistical Analysis

Statistical analysis was performed using SPSS (IBM SPSS Statistics 24). To identify the methods employed in the analyses, the normality distribution of each parameter was evaluated on an individual basis. In accordance with the number of samples, either the "Kolmogorov-Smirnov" or the "Shapiro-Wilk" tests were utilized (17).

Frequency tables and descriptive statistics were used to interpret the findings. Non-parametric methods were used for the values that did not conform to normal distribution. Spearman's correlation coefficient was used to analyze the relationships between two quantitative variables that did not have a normal distribution. "Spearman" correlation coefficient was used to examine the relationship between two quantitative variables that did not have a normal distribution.

Ethical Aspects of Research

Approval was obtained from the Ethics Committee of the Karamanoğlu Mehmetbey University Faculty of Medicine where the research was conducted (decision no: 21, date: 08.03.2022). Institutional approval was obtained from the chief physician of the university hospital where the research was conducted. Before data collection, written informed consent was obtained from the participants after the purpose of the research was explained in accordance with the Helsinki Declaration.

RESULTS

The average age of the participants was 37.08±7.80 (years), the average time worked as a physician was 11.06±7.29 years, the average time worked as a specialist was 4.97±6.27 years, the average hours worked weekly was 49.90±11.52 hours, the number of patients cared per day was 66.70±29.88 people, and the mean number of night/weekend shifts worked in a month was 2.70±3.01. 55.6% (n=138) were male and 74.6% (n=185) were working in internal medicine units. Almost all of the participants, 99.2% (n=246) thought that the physician should have professional liability insurance, 92.3% (n=299) needed someone from the same gender as the patient during the examination, and 72.6% (n=180) avoided treating difficult patient groups. 63.3% (n=157) of the participants avoided treating patients with impaired psychological state, tendencies to attack, act, and blame, 13.7% (n=34) avoided patients who were generally dissatisfied with the service and complained, 39.9% (n=99) avoided treating patients who refused treatment, 10.5% (n=26) avoided patients who refused to communicate with healthcare professionals, 52.4% (n=130) avoided patients that engaged in sexual behavior in the dimension of harassment, 2.8% (n=7) avoided patients whose expectations and hopes were at the point of exhaustion and who

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had a sense of helplessness, and 64.5% (n=160) avoided following addicted patients who used substances or drugs.

A weak positive correlation was found between the Malpractice Fear Scale score and the positive defensive medicine, negative defensive medicine, avoidance, and DMAS total scores (p<0.05) (Table 1).

The three expressions with the highest mean in the DMAS were "I explain medical practice to my patients in more detail in order to avoid legal problems." (4.52±0.87), "I keep more detailed records in order to avoid legal problems." (4.50±0.88), and "I seek more consultation in order to avoid legal problems." (3.36±0.69) (Table 2).

The three items with the highest mean in the Malpractice Fear Scale were "I am worried that I will be involved in a malpractice lawsuit in the next 10 years." (4.35±0.67), "I sometimes ask for expert opinion to reduce the risk of being sued." (4.04±0.56), and "I had to make significant changes to my professional practice due to legal developments regarding provision of health services." (4.02±0.58) (Table 2).

Significant differences were detected between the positive defensive medicine score (p=0.012), negative defensive medicine score (p=0.006), avoidance score (p<0.001) and DMAS total score (p<0.001) and Malpractice Fear Scale score (p=0.002) according to age group. As a result of pairwise comparisons with Bonferroni correction, there was a significant difference between those <30 years and those between 30 and 39 and ≥40 years. A significant difference was found in the positive defensive medicine score (p=0.038), avoidance score (p=0.033), and DMAS total score (p=0.035) according to gender. A significant difference was found in the positive defensive medicine score (p<0.001), negative defensive medicine score (p=0.000), avoidance score (p<0.001), DMAS total score (p<0.001) and Malpractice Fear Scale score (p<0.001) according to the title of the participants. A significant difference was found between the defensive medicine score (p=0.041) and avoidance score (p=0.004) according to the patient's need to have someone from the same sex with them during the examination. A significant difference was found between positive defensive medicine score (p<0.001), negative defensive medicine score (p<0.001), avoidance score (p=0.002), DMAS total score (p<0.001) and Malpractice Fear Scale score (p<0.001) according to avoidance of difficult patients (Table 3).

A very weak negative significant relationship was found between the duration of practice (years) and positive defensive medicine, negative defensive medicine, avoidance, DMAS total score and Malpractice Fear Scale score (p<0.05). There was a weak negative significant relationship between the duration of residency (years) and positive defensive medicine, negative defensive medicine, avoidance, DMAS total score and Malpractice Fear Scale score (p<0.05). There was a weak negative significant relationship between working hours weekly and positive defensive medicine,

Table 1. Examining the relationship between scales

Correlation* (n=248)			Malpractise Fear Scale
Defensive Medicine Attitude Scale	Positive defensive medicine	r p	0.422 <0.001
	Negative defensive medicine	r p	0.454 <0.001
	Avoidance	r p	0.296 <0.001
	Total-DMAS	r p	**0.474** <0.001

Linear relationship intensity: r<0.2 very weak, 0.2-0.4 weak, 0.4-0.6 moderate, 0.6-0.8 high, and 0.8> very high. *The Spearman correlation coefficient was used to analyze the relationships between two quantitative variables that did not have a normal distribution. DMAS: Defensive Medicine Attitude Scale

Table 2. Distribution of lowest and highest-rated items

Defensive Medicine Attitude Scale-3: Highest and lowest rated items	M	SD	Min	Max
1. I explain medical practices to my patients in more detail to avoid legal problems.	4.52	0.87	1.0	5.0
2. I will keep more detailed records to avoid legal problems.	4.50	0.88	1.0	5.0
3. I seek more consultations to avoid legal problems.	3.36	0.69	1.0	5.0
1. I avoid patients with complex medical problems to avoid legal problems.	2.08	0.95	1.0	5.0
2. I avoid treatment protocols with high complication rates to avoid legal problems.	2.06	0.97	1.0	5.0
3. I prefer noninterventional treatments to interventional treatments to avoid legal problems.	2.01	0.98	1.0	5.0
Malpractise Fear Scale-3: Highest and lowest rated items	**M**	**SD**	**Min**	**Max**
1. I am worried that I will be involved in a malpractise lawsuit in the next 10 years.	4.35	0.67	1.0	5.0
2. Sometimes, I ask for expert opinion to reduce the risk of being sued.	4.04	0.56	1.0	5.0
3. I had to make significant changes to my professional practices due to legal developments related to the provision of health services.	4.02	0.58	1.0	5.0
1. In some instances, I request tests and consultation to avoid malpractise.	4.02	0.49	1.0	5.0
2. Relying on clinical judgment rather than technology when making a diagnosis has become increasingly risky in terms of medical practice.	3.94	0.64	1.0	5.0
3. I feel pressure in my daily medical practice because of the threat of malpractise lawsuit.	3.93	0.68	1.0	5.0

M: mean, SD: standard deviation, min: minimum, max: maximum

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negative defensive medicine, avoidance, DMAS total score and Malpractice Fear Scale score (p<0.05). There was a weak negative significant relationship between the number of patients who cared for daily and positive defensive medicine, negative defensive medicine, avoidance, DMAS total score and Malpractice Fear Scale score (p<0.05). A weak negative significant relationship was found between the number of night/weekend shifts worked a month and positive defensive medicine, negative defensive medicine, avoidance, DMAS total score and Malpractice Fear Scale score (p<0.05) (Table 4).

Table 3. Comparison of participants' demographic characteristics and scale scores

Variable (n=248)	n	Positive defensive medicine [median (IQR)]	Negative defensive medicine [median (IQR)]	Avoidance [median (IQR)]	Total DMAS [median (IQR)]	Malpractise Fear Scale [median (IQR)]
Age						
<30 (1)	55	10.0 (1.0)	13.0 (1.0)	12.0 (4.0)	34.0 (5.0)	25.0 (1.0)
30-39 (2)	100	9.0 (1.0)	12.0 (1.0)	9.0 (5.0)	29.0 (5.8)	24.0 (1.0)
≥40 (3)	93	9.0 (1.0)	12.0 (1.0)	9.0 (7.0)	30.0 (6.0)	24.0 (1.0)
Probability difference		**p=0.012** (1-23)	**p=0.006** (1-23)	p<0.001 (1-23)	p<0.001 (1-23)	**p=0.002** (1-23)
Gender						
Female	110	10.0 (1.0)	12.0 (1.0)	11.0 (7.0)	32.5 (8.0)	24.0 (1.0)
Male	138	9.0 (1.0)	12.0 (1.3)	10.0 (7.0)	31.0 (6.0)	24.0 (1.0)
Probability		**p=0.038**	p=0.436	**p=0.033**	**p=0.035**	p=0.163
Title						
Practitioner (1)	122	10.0 (1.0)	13.0 (1.0)	11.0 (5.0)	34.0 (7.0)	25.0 (1.0)
Specialist (2)	93	9.0 (0.0)	12.0 (2.0)	8.0 (4.5)	29.0 (5.0)	24.0 (0.0)
Professor (3)	33	9.0 (0.0)	12.0 (1.0)	8.0 (2.0)	29.0 (1.5)	24.0 (0.0)
Probability difference		p<0.001 (1-23)	p<0.001 (1-23)	p<0.001 (1-23)	p<0.001 (1-23)	p<0.001 (1-23)
Need for the same-sex companion						
Yes	229	9.0 (1.0)	12.0 (1.0)	10.0 (7.0)	31.0 (6.5)	24.0 (1.0)
No	19	8.0 (5.0)	11.0 (4.0)	13.0 (6.0)	33.0 (15.0)	24.0 (5.0)
Probability		p=0.041	p=0.194	**p=0.004**	p=0.670	p=0.234
Avoiding difficult patients						
Yes	180	9.0 (1.0)	12.0 (1.0)	10.5 (7.0)	33.0 (8.0)	24.0 (1.0)
No	68	8.0 (2.8)	11.5 (4.0)	9.0 (6.0)	28.0 (8.0)	23.0 (2.0)
Probability		p<0.001	p<0.001	**p=0.002**	p<0.001	p<0.001

IQR: interquartile range, DMAS: Defensive Medicine Attitude Scale

Table 4. Examining the relationships between some parameters and scales

Correlation* (n=248)			Duration in the profession (years)	Duration of working as a specialist (years)	Weekly work hours	Patients seen daily	Night/weekend shifts worked
Defensive Medicine Attitude Scale	**Positive defensive medicine**	r p	-0.133 **0.036**	-0.302 **0.000**	-0.259 **0.000**	0.253 **0.000**	-0.251 **0.000**
	Negative defensive medicine	r p	-0.154 **0.015**	-0.357 **0.000**	-0.294 **0.000**	0.283 **0.000**	-0.300 **0.000**
	Avoidance	r p	-0.203 **0.001**	-0.258 **0.000**	-0.299 **0.000**	0.251 **0.000**	-0.279 **0.000**
	Total-DMAS	r p	-0.204 **0.001**	-0.344 **0.000**	-0.327 **0.000**	0.295 **0.000**	-0.297 **0.000**
Malpractise Fear Scale		r p	-0.137 **0.031**	-0.373 **0.000**	-0.289 **0.000**	0.310 **0.000**	-0.342 **0.000**

*Linear relationship intensity: r<0.2 very weak, 0.2-0.4 weak, 0.4-0.6 moderate, 0.6-0.8 high, and 0.8> very high. DMAS: Defensive Medicine Attitude Scale

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DISCUSSION

Due to the fear of malpractice, physicians tend to recommend defensive medicine practices instead of practices that benefit the patient within the framework of their professional values. In our study, physicians' fear of malpractice was high, and their defensive medicine attitudes were moderate. In the context of defensive medicine attitudes, the most common practices of physicians in our study to protect themselves were within the scope of negative defensive medicine practices; providing detailed information to the patient, detailed record keeping, and cost-increasing positive defensive medicine application of seeking consultation to avoid legal problems. In addition, participants were the most worried about being involved in a malpractice lawsuit in the next 10 years, and they stated that asking for advanced expert opinion is sometimes necessary to reduce the risk of lawsuits and that changes in health policies cause changes in their professional practice. In a similar study, anesthesiologists attached more importance to informed consent forms to protect themselves legally (12).

In recent years, with an emphasis on patient autonomy, obtaining consent has become extremely important. Informing patients is one of the basic principles of medical ethics and the professional responsibility of physicians. However, this practice is also viewed as a defensive medicine practice, which is a controversial issue. Patient autonomy is damaged by defensive medicine practices because it is not possible to fully explain the diagnosis and treatment methods of defensive practice (8). In a study, the most frequently used defensive medicine practices by physicians working in surgical fields were asking for more tests and using non-invasive protocols to protect themselves (6). In a study conducted with psychiatrists, although not necessarily, the participants adopted hospitalization and frequent follow-up in the context of defensive medicine (18). Studies emphasize that defensive medicine is against medical ethics, professionalism (8,19), the principle of not harming the patient (8), and medical law. Defensive medicine is viewed as benefiting physicians by avoiding medical responsibility (19) rather than for the benefit of the patient.

In our study, the positive defensive medicine approaches and malpractice fears of physicians under the age of 30 were significantly higher than those among other age groups. Studies have found that individuals between 31 and 40 (13) and those over 30 years old (4) have higher mean scores for medical error attitude. In one study, physicians over the age of 60 preferred defensive medicine practices (20), whereas in other studies (12,18), young physicians from different specialties were more likely to engage in defensive medicine practices. Vento et al. (21) (2018) stated that young clinicians should avoid providing services only by considering legal regulations and that standard evidence-based practices based on protocols and guidelines are not holistic patient care. Studies have found that age is not an effective feature of defensive medicine attitudes (6,9,22).

In our study, although there was no significant difference between the malpractice fear scores of different genders, the malpractice fear and defensive medicine attitude of females were significantly higher. Similar results were found in the literature (6,9,23). Studies have found that males have significantly higher perceptions of medical errors (13) and defensive medicine attitude scores are higher (22).

In our study, general practitioners had higher fears of malpractice and adopt defensive medicine practices. Contrary to our study, no significant difference was found between physicians and residents regarding defensive medicine practice attitudes in one study. The reason for this is that physician candidates are taught to take responsibility for the decisions they make during medical education (20). In one study, the defensive medicine attitude scores of associate professors were found to be high (6). We can say that this difference is due to differences in the education and practice experiences during medical education at universities and practices aimed at developing responsibility-taking skills.

The defensive medicine attitudes of the physicians who did not want to treat difficult patients were moderate, and their fear of malpractice was high. In this study, defensive medicine attitudes of physicians who needed someone of the same gender during examinations were lower, but their fear of malpractice was higher. In this study, it was found that physicians who perceive patient pressure excessively apply defensive medicine practices more and prefer to avoid conflict with the patient, even if it is contrary to their professional values (20). In a study conducted with general practitioners, physicians stated that the pressure of patients for referral was effective in their defensive attitudes and negatively affected the trust between the physician and patient (24). Defensive medicine practices due to the physician's fear of medical responsibility or aggressive behavior of the patient's relatives prevent maintaining the patient-physician relationship (25).

In our study, as the duration of work and expertise as a physician increased, attitudes toward defensive medicine and fear of malpractice decreased. Similar results were found in the studies (13,22). Contrary to these studies, years working in the profession was not an effective feature of defensive medicine attitude (6,26). This difference between the studies suggests that this is due to the personalities of physicians.

In our study, as the number of hours worked weekly, the number of patients cared for daily, and the number of monthly night/weekend shifts decreased, the defensive medicine attitude and fear of malpractice increased. Similarly, in the study conducted with physicians and nurses, there was no significant difference between work hours and medical error attitude scores, and those with fewer hours worked had a higher awareness of medical errors (13). In another study, the defensive medicine attitude scores of those with fewer night/weekends shifts were found to be lower (22). In previous studies, defensive medicine practices were found to increase with the fatigue of physicians (12) and the number of patients cared for in a limited time, increased (27). This difference

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between studies can be explained by the fact that with the increase in the experience of physicians in our country, the fear of malpractice and their defensive attitudes decrease.

In our study, as physicians' fear of malpractice increased, the defensive medicine attitude score also increased. In the literature, physicians tend to avoid high-risk patients and avoid diagnosis and treatment by asking for additional examinations and allocating more time to the patient (7,28), and they resort to defensive medicine to share the burden of responsibility with others (11). Defensive medicine attitudes negatively affect the autonomy of physicians and undermine the trust between physicians and patients (21). In a study, 89% of physicians sometimes practice positive defensive medicine, whereas 42% practice negative defensive medicine behavior, and these practices are used to apply the standardized care imposed by the system (20). Concerns and perceptions about medical responsibility lead physicians to adopt defensive medicine practices that increase health care costs by requesting more frequent diagnostic tests, consultations, and radiological examinations (9,10). Treatment and good care based on professionalism and professional values are extremely important in medicine, and it is important to prevent excessive costs arising from defensive medicine practices and provide fair service. Medical procedures take place in doctor-patient relationship, and the relationship continues when both parties fulfill their rights and responsibilities (4,27,29). Defensive medicine behaviors damage the patient-physician relationship and undermine patients' confidence in the medicine. Fear of malpractice plays an important role in defensive medicine practices (4,27), on the other hand, it is extremely important for physicians to adopt good medical practices and decide for the benefit of the patient (8,27,30).

Study Limitations

This study was conducted with a group of physicians working in the center of a province; therefore, it cannot be generalized to all physicians.

CONCLUSION

The increased fear of malpractice increases the tendency of physicians to unnecessarily use technological medical tools. Physicians who try not to harm patients can still waste time by asking patients for costly tests and treatments. The negative reflection of this on the physician-patient relationship may lead to the deterioration of secure communication. While physicians care about the principle of avoiding harm to the patient, they may unknowingly cause harm. The fear of malpractice increases the tendency toward defensive medicine attitudes. Physicians mostly adopt the defensive behavior of negative medicine and are afraid of facing malpractice lawsuits in the near future. It is extremely important for physicians to continue their profession by adhering to their professional and ethical values without having malpractice fears and having to worry about protecting themselves while maintaining the doctor-patient relationship in a safe manner.

Ethics Committee Approval: Approval was obtained from the Ethics Committee of the Karamanoğlu Mehmetbey University Faculty of Medicine where the research was conducted (decision no: 21, date: 08.03.2022).

Informed Consent: Before data collection, written informed consent was obtained from the participants after the purpose of the research was explained in accordance with the Helsinki Declaration.

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Incidence of Hyponatremia in Geriatric Patients Presenting to the Emergency Department with Headache

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ABSTRACT

Objective: Headache is one of the most common neurological complaints in elderly population. Hyponatremia is a rare condition that can cause headache. The aim of our study was to evaluate the frequency and etiology of hyponatremia in geriatric patients presenting to the emergency department (ED) with atraumatic headache.

Methods: This is an observational, retrospective study. Patients aged 65 years and older with serum sodium levels who presented to the ED with headache were included in the study. Demographic data, comorbidities, other admission complaints, medications, and sodium levels were retrospectively reviewed.

Results: The study included 429 patients. Hyponatremia was detected in 17.7% (n=76) of the patients and was mostly mild (56.6%). In comparison with normonatremic patients, hyponatremic patients had increased frequency of hypothyroidism and diuretic use, longer hospital stays, higher blood urea nitrogen, and lower serum osmolarity, hemoglobin, and albumin levels ($p<0.05$ for all values).

Conclusion: Our results showed the presence of hyponatremia in a significant proportion of patients presenting to the ED with headache. Most cases of hyponatremia were hypovolemic and was caused by diuretic use, dehydration, and inappropriate antidiuretic hormone syndrome. In patients with comorbidities and polypharmacy, hyponatremia should be prioritized as a potential cause of secondary headache and should contribute to the management of patients in emergency settings.

Keywords: Geriatric, headache, hyponatremia

INTRODUCTION

Headache is one of the most common neurological complaints in elderly population (1-3). The assessment and management of headache in geriatric patients can be challenging both diagnostically and therapeutically. New-onset headache in older patients is more likely to be secondary. In one study, 15% of people over 65 years of age with new-onset headache had a serious underlying cause, compared to 1.6% of people under 65 years of age (2). Hyponatremia is one of the conditions that can cause secondary headache, although it is not common (4).

Hyponatremia is the most common electrolyte disturbance in older adults and can increase morbidity and mortality (5). Elderly patients presenting to the emergency department (ED) may present with medical conditions related to hyponatremia or traumatic conditions related to possible neurological effects (6). Hyponatremia is common in geriatric population, particularly due to physiologic decline, comorbidities, and/or polypharmacy (7-9). In addition, several elderly patients with heart failure or hypertension are on a salt diet, which is associated with decreased serum sodium levels. This may increase their hyponatremia susceptibility. Changes in sodium concentration can cause neurologic symptoms (imbalance, dizziness, headache, cognitive deterioration, confusion), seizures, coma, and even death. Clinical symptoms are generally related to the severity of hyponatremia (1,9,10). While common symptoms include nausea, fatigue, and headache, recent studies have shown that low serum sodium may be related to cognitive health in older adults in the general population and associated with poorer scores on cognitive assessments of attention, memory, and psychomotor function (11,12). Although mild chronic hyponatremia is classically defined as asymptomatic, recent studies have shown that mild

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hyponatremia may be clinically significant in geriatric patients and may be associated with gait disturbances and new-onset neurologic symptoms (5,6). In a study evaluating hyponatremia in geriatric patients, the majority of patients (81%) were symptomatic and most (62%) had more than one symptom (13). Fatigue (50%), headache (40%), and abnormal behavior (39%) were reported as common symptoms (11). Another study from Türkiye reported that nausea/vomiting and changes in consciousness (confusion, etc.) were the most common symptoms, while headache was less common (10). In our clinical practice, we observed a significant rate of hyponatremia in geriatric patients presenting to the ED with atraumatic headache. In this study, we aimed to evaluate the presence and etiologies of hyponatremia, a cause of secondary headache, in geriatric patients presenting to the ED with atraumatic headache.

METHODS

Study Design and Settings

Our study is a retrospective study. The study was conducted in a level three ED with an annual admission rate of 360,000 patients. The study got approval from the University of Health Sciences Türkiye, Ankara Atatürk Sanatorium Training and Research Hospital Scientific Studies Ethics Committee (no: 2024-BÇEK/35, date: 28.02.2024). Patient data was collected from patient charts and electronic medical records.

Study Population

Patients aged 65 years and older with documented serum sodium levels who presented to the University of Health Sciences Türkiye, Ankara Atatürk Sanatorium Training and Research Hospital with headache between 01.01.2023-31.12.2023 were included in the study. Patients were screened according to ICD-10 (International Statistical Classification of Diseases: R51, G44 and its subcodes). Patients without sodium levels, patients with neurological deficits, patients diagnosed with acute cerebrovascular disease after imaging, patients with a history of head trauma and headache, ICD codes defined as end-stage malignancy, decompensated heart failure, decompensated cirrhosis, and hemodynamically unstable (oxygen saturation <90, systolic blood pressure <90 mmHg, PCO_2>50 mmHg, body temperature >37.3 °C) were excluded. Patients with pseudohyponatremia due to multiple myeloma and other monoclonal gammopathies were excluded from the study. Meanwhile, pseudohyponatremia due to hyperlipidemia could not be evaluated because lipid profiles were not obtained from patients in the ED.

In hyperglycemic patients, the "corrected sodium" level was calculated using the following formula, and patients with a corrected sodium level below 135 mmol/L were considered hyponatremia.

For glucose levels between 100 and 399 mg/dL; Corrected Na = Measured Na+1.6x[(Glucose-100)/100] mmol/L

For glucose level ≥400 mg/dL; Corrected Na = Measured Na+2.4x[(Glucose-100)/100] mmol/L.

Methods

Demographic data, comorbidities (diabetes mellitus, cardiac disease, hypertension, pulmonary disease, hypothyroidism, dementia, malignancy), complaints other than headache on admission, vital signs, laboratory results, medications [proton pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs), diuretics (loop and/or thiazide diuretics)], and computed tomography (CT) scan were retrospectively reviewed. Discharge, hospitalization status, and length of stay were analyzed. Patients were classified as having either primary (migraine, tension, and cluster) or secondary headaches. The secondary headache etiologies were evaluated (1). Patients with no cause in their records were classified as unknown. In patients with normal glucose levels and hyperglycemia, hyponatremia was considered if the sodium level was less than 135 mmol/L. Patients were classified as severe hyponatremia (<125 mmol/L), moderate hyponatremia (125-129 mmol/L), and mild hyponatremia (130-134 mmol/L) according to plasma sodium concentrations.

Statistical Analysis

Data analysis was performed with the statistical program IBM SPSS 20.0 (Chicago, IL, USA). Continuous numerical variables are presented as median (interquartile range: 50), and categorical variables are presented as number of cases and (%). The Kolmogorov-Smirnov test was used to determine whether the distribution of discrete and continuous numerical variables was normal. Categorical variables were evaluated using the chi-square test, and continuous variables by Mann-Whitney U test. Although a multivariate regression analysis was planned at baseline to identify risk factors that could predict hyponatremia, a multivariate regression analysis was not performed to create a model with only unadjusted odds ratio (UOR) values because the frequencies of risk factors that were significant in the univariate analyses did not meet the required sample size and the number of patients with significant hyponatremia was low. Results were considered statistically significant at $p<0.05$.

RESULTS

During the study period, 946 patients were found to have presented to the ED with headache. Five hundred and four patients with missing data (without sodium level) and 13 patients who did not meet the inclusion criteria were excluded from the study, and 429 patients were included. 71.1% of the patients were female, and the median age was 72 (68-78) years. The most common comorbidities were hypertension and diabetes mellitus. Head CT imaging was performed in 19.6% of patients. In addition to headache, the most common complaint was fatigue (15.6%). Tension-type headache was the most common type of headache, and hypertension-induced headache was the most common secondary headache. Hyponatremia was found in 17.7% (n=76) of the patients, and the majority of these hyponatremia cases were mild (56.6%). Additionally, 5.4% of all patients were hospitalized, with 2.3% specifically due to hyponatremia. Patient demographics are presented in Table 1. Possible etiologies of hyponatremia are shown in Table 2. When the hyponatremic patients were

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Table 1. Demographic data of patients (n=429)	
Age > years, median (IQR)	72 (10)
Sex, n (%)	
Female	305 (71.1)
Co-morbidity, n (%)	
Hypertension	255 (59.4)
Diabetes mellitus	173 (40.3)
Cardiac disease	185 (43.1)
Chronic renal failure	44 (10.3)
Hypothyroidism	18 (4.2)
Dementia	33 (7.7)
Chronic obstructive pulmonary disease	110 (17)
Drugs, n (%)	
ACE-I	134 (31.2)
Antidepressant	25 (5.8)
PPI	195 (45.5)
Diuretic	143 (33.3)
Symptoms, n (%)	
Fatigue	67 (15.6)
Dizziness	55 (12.8)
Nasua/vomiting	46 (10.7)
Weakness	30 (7)
Convulsion	1 (0.2)
Vital signs, median (IQR)	
GCS	15 (0)
Pulse	86 (9)
Systolic	129 (14)
Diastolic	86 (8)
Temperature	36.2 (0.1)
Headache type, n (%)	
Primer	
Tension	173 (40.3)
Migraine	42 (9.8)
Seconder	
Hypertension	134 (31.2)
Hyponatremia	33 (7.7)
Cervical spine disorders	6 (1.4)
Drugs	6 (1.4)
Unknown	45 (10.5)
Cranial computed tomography, n (%)	182 (19.6)
Hyponatremia, n (%)	76 (17.7)
Severity of hyponatremia, n (%)	
Mild	43 (56.6)
Moderate	28 (36.8)
Severe	5 (6.6)

Table 1. Continued	
Laboratory, median (IQR)	
Hemoglobin	13.1 (1.1)
Glucose	108 (6)
Sodium	138 (6)
Corrected sodium	138.3 (5.1)
BUN mg/dL	46 (23)
Creatinine mg/dL	1.02 (0.19)
Albumin g/dL	4 (0.4)
Osmolarity	287 (11)
Hospitalization rate, n (%)	23 (5.4)
Hospitalization due to hyponatremia	10 (2.3)
Hospital stay duration, (days) median (IQR)	4 (4)
IQR: interquartile range, ACE-I: angiotensin-converting enzyme inhibitors, PPI: proton pump inhibitor, GCS: Glasgow coma scale, BUN: blood urea nitrogen	

Table 2. Possible causes of hyponatremia according to volume status	
Hypovolemic • Diuretic use • Decreased oral intake/vomiting	48 (63.2%) 38 (79.2) 10 (20.8%)
Normovolemic • SIADH • Hypothyroidism	22 (28.9%) 15 (68.2%) 7 (31.8%)
Hypervolemic • Chronic renal disease • Hypoalbuminemia	6 (7.9%) 4 (75%) 2 (25%)
SIADH: syndrome of inappropriate antidiuretic hormone secretion	

evaluated according to volume status, the most common type of hyponatremia was hypovolemic hyponatremia (63.2%), which was most often related to diuretic use. When normonatremic and hyponatremic patients were compared, hyponatremic patients had more frequent hypothyroidism and diuretic use, longer hospital stays, higher blood urea nitrogen, and lower serum osmolarity, hemoglobin, and albumin levels ($p<0.05$ for all values, Table 3). A univariate regression analysis was performed to determine the impact of the parameters listed in Table 3 on hyponatremia risk (Table 4). In this regression analysis, hypothyroidism (UOR: 3.154, 1.181-8.423), Diuretic use (UOR: 1.695, 1.022-2.813), and decreased oral intake/vomiting (UOR: 2.554, 1.301-5.014) were found to be predictors of hyponatremia.

DISCUSSION

In this study, in which we investigated the prevalence and factors influencing hyponatremia in geriatric patients who presented to the ED with headache, we found that the prevalence of hyponatremia was 17.7% and was mostly mild. Most hyponatremia cases were hypovolemic hyponatremia. We found that diuretic use, dehydration, and inappropriate antidiuretic hormone (ADH) syndrome caused hyponatremia and prolonged hospital stay.

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Table 3. Comparisons of patients according to sodium levels

Characteristic	Hyponatremia patients (n=76)	Normonatremic patients (n=353)	p-value
Sex, n (%)			
Female	58 (76.3)	247 (70)	0.268
Age > years, median (IQR)	73 (12)	71 (10)	0.131
Co-morbidity, n (%)			
Hypertension	48 (63.2)	207 (58.6)	0.467
Diabetes mellitus	35 (46.1)	138 (39.1)	0.262
Cardiac disease	35 (46.1)	150 (42.5)	0.570
Chronic renal failure	6 (7.9)	38 (10.8)	0.454
Hypothyroidism	7 (9.2)	11 (3.1)	0.025
Dementia	10 (13.2)	23 (6.5)	0.049
Drugs, n (%)			
ACE-I	26 (34.2)	108 (30.6)	0.537
Antidepressant	7 (9.2)	18 (5.1)	0.177
PPI	32 (42.1)	163 (46.2)	0.518
Diuretic	33 (43.4)	110 (31.2)	0.040
Symptoms, n (%)			
Fatigue	38 (50)	29 (8.2)	<0.001
Dizziness	6 (7.9)	49 (13.9)	0.157
Nasua/vomiting	15 (19.7)	31 (8.8)	0.005
Weakness	4 (5.3)	25 (7.1)	0.567
Convulsion	1 (1.3)	0 (0)	0.177
Laboratory, median (IQR)			
Hemoglobin	12.8 (2.1)	13.2 (1.3)	0.002
Glucose	108 (34)	108 (36)	0.293
BUN mg/dL	44 (22.5)	47 (22)	0.039
Creatinine mg/dL	1.25 (0.41)	1.25 (0.51)	0.306
Albumin g/dL	3.9 (0.2)	4.05 (0.4)	0.002
Osmolarity	278 (264-280)	289 (9)	<0.001
Hospital stay duration, days, median (IQR)	5 (2.5)	2.5 (3)	0.011

IQR: interquartile range, ACE-I: angiotensin-converting enzyme inhibitors, PPI: proton pump inhibitor, BUN: blood urea nitrogen

Table 4. Univariate regression analysis to predict the development of hyponatremia

	Wald	p-value	Unadjusted odds ratio (95% CIs)
Age	1.67	0.196	1.024 (0.998-1.062)
Sex	1.21	0.27	0.723 (0.407-1.286)
Hypertension	0.52	0.467	1.209 (0.725-2.017)
Diabetes mellitus	1.25	0.263	1.33 (0.807-2.191)
Cardiac disease	0.323	0.570	1.155 (0.702-1.901)
Chronic renal failure	0.459	0.456	0.711 (0.289-1.746)
Hypothyroidism	5.25	0.022	3.154 (1.181-8.423)
Dementia	3.73	0.053	2.174 (0.989-4.781)
Hypoalbuminemia	1.46	0.226	0.548 (0.207-1.451)
ACE-I	0.38	0.538	1.18 (0.698-1.994)
Antidepressant	1.84	0.171	1.888 (0.759-4.694)
PPI	0.41	0.518	0.848 (0.514-1.399)
Diuretic	4.17	0.041	1.695 (1.022-2.813)
Decreased oral intake/vomiting	7.426	0.006	2.554 (1.301-5.014)

ACE-I: angiotensin-converting enzyme inhibitor, PPI: proton pump inhibitor, CIs: confidence intervals

Headache prevalence in older adults, ranges from 12% to 50% (1,2). In 17% of people over 65 years of age, frequent headache occurs more than 2 times per month (2). Although headache in older adults is usually caused by a primary headache disorder; aging, comorbidities, medication use, polypharmacy, and altered pharmacokinetics increase the risk of secondary headache (1,2). As with younger individuals, the first step in diagnosing new-onset headache in the elderly is to exclude secondary causes. New-onset geriatric headache and possible secondary headache disorders should be systematically managed, and diagnostic evaluation, ranging from neuroimaging to blood tests, should be performed in appropriate patients.

Sodium disturbances are common in geriatric patients (5-7). Changes in sodium levels can cause seizures, coma, and even death due to mild neurologic symptoms (14). Nausea and weakness are the earliest symptoms; as the severity of hyponatremia increases, headache, drowsiness, confusion, and finally seizures, coma, and respiratory arrest may occur (15). In our study, the most common symptom besides headache was weakness. We observed that altered consciousness and vomiting were more common in hyponatremia patients. Vomiting may have developed secondary to hyponatremia, or vomiting and dehydration may have predisposed to hyponatremia. One patient presented with post-ictal headache who was found to have severe hyponatremia.

Hyponatremia in the elderly is often secondary to multifactorial medications and ADH syndrome (8,16). Inappropriate ADH syndrome is often asymptomatic and idiopathic in the elderly (8). In addition, many classes of medications, such as thiazide diuretics, renin-angiotensin-aldosterone system inhibitors, antidepressants, PPIs, and antipsychotics can increase both volume and sodium loss, leading to inappropriate ADH syndrome and hyponatremia in this age group (8,16,17). The most common type in our study was hypovolemic hyponatremia. Most hypovolemic hyponatremia cases were the result of side effects caused by diuretic use. Although no statistically significant difference was observed in the hyponatremia group, the rate of antidepressant use was higher (9.2%). Hyponatremia due to antidepressant use is mostly hypotonic (dilutional) hyponatremia, and the underlying cause is often elevated plasma ADH levels. Again, most of our patients were taking more than one drug that can cause hyponatremia. Hyponatremia may also develop because of drug interactions. Many non-analgesic drugs, especially nifedipine, nitrates, SSRIs, and PPIs, which are commonly prescribed to elderly patients, may also be associated with headache (1). New-onset headache should be considered an adverse effect of recently started medications (1,18). Patients may develop headache due to hyponatremia as well as due to adverse drug reactions.

One of the causes of hyponatremia is hypothyroidism. The main mechanism of hyponatremia in patients with hypothyroidism is the decrease in free water excretion due to high ADH levels, which has been shown to be mainly due to the decrease in cardiac output caused by hypothyroidism (19). In our study, hypothyroidism was present in 9.2% of patients in the hyponatremic group and was statistically more frequent in the normonatremic group. In Uyar et al.'s (10) study, hypothyroidism was found at a rate of 7.2% in normovolemic hyponatremia patients, and although the literature on this subject is insufficient, it has been suggested that the frequency of hyponatremia due to hypothyroidism is higher. The presence of hypothyroidism in our study may have predisposed patients to hyponatremia.

Although a multivariate regression analysis was planned at baseline to identify risk factors that could predict hyponatremia, a multivariate regression analysis was not performed to create a model with only unadjusted OR values because the frequencies of risk factors that were significant in univariate analyses did not meet the required sample size. A univariate regression analysis was performed to determine the impact of the parameters on the prediction of hyponatremia and hypothyroidism. Diuretic use and decreased oral intake/vomiting were found to be predictors of hyponatremia. In our study, most patients had mild hyponatremia, and after appropriate management in the ED, these patients were discharged. However, 2.3% of patients were hospitalized due to hyponatremia. We believe that medication adjustments, appropriate fluid and electrolyte replacement, and ordering thyroid function tests, when necessary, could contribute to better patient management in patients with secondary headaches due to hyponatremia in the ED.

Study Limitations

Due to the retrospective nature of the study, missing hospital records may have affected the study results. Because this was a single-center study, our results cannot be generalized to all centers. Sodium levels measured at the time of presentation to the ED were used, and follow-up was not performed. Pseudohyponatremia due to hyperlipidemia was not evaluated because a lipid profile was not obtained from the ED patients. Although the prevalence of hyponatremia due to hyperlipidemia was low, this condition may have influenced our results.

Regression analysis could not be performed because we did not have a sufficient sample size to perform regression analysis, and data losses that may occur due to the retrospective nature of our study (drugs that may cause hyponatremia, conditions that we did not obtain from patient records, etc.) may cause various biases. Again, due to missing data, it was not possible to differentiate acute hyponatremia from chronic hyponatremia.

CONCLUSION

Older adults are at higher risk for secondary headache. We demonstrated the presence of hyponatremia in a significant proportion of patients presenting to the ED with headache. We have shown that most hyponatremia is hypovolemic and is caused by diuretic use, dehydration, and inappropriate ADH syndrome. Although primary headaches are more common in the geriatric age group, hyponatremia should be prioritized as a potential cause of secondary headaches in patients with comorbidities and polypharmacy, as it may play a role in the emergency management of these patients.

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Ethics Committee Approval: This study protocol was approved by Scientific Studies Ethics Committee of University of Health Sciences Türkiye, Ankara Atatürk Sanatorium Training and Research Hospital (no: 2024-BÇEK/35, date: 28.02.2024). The study was conducted in accordance with the Good Clinical Practice and the Declaration of Helsinki ethical standards.

Informed Consent: This study was a retrospective study based on anonymous data; patient consent was not obtained.

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