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CONTENTS

Original Articles

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Effects of Oral Isotretinoin Therapy on Nasal Dryness and Nasal Obstruction in Patients with Acne Vulgaris: Objective and Subjective Assessments Based on the Dose and Duration of Therapy

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ABSTRACT

Introduction: This study aimed to evaluate the effect of oral isotretinoin therapy on nasal dryness and nasal obstruction in patients with acne vulgaris.

Methods: A total of 102 patients with acne vulgaris (mean ± standard deviation age, 21.1±3.4 years; female, 64.7%) initiating systemic isotretinoin treatment [in 0.25 mg/kg/day (n=35) or 0.5 mg/kg/day (n=67) doses] were enrolled in this prospective study. Data on nasal obstruction [via nasal obstruction symptom evaluation (NOSE)] and nasal dryness via a psychometric response scale [visual analog scale (VAS)] and nasal Schirmer test values (right and left Schirmer values) were recorded at baseline. Nasal dryness (VAS and nasal Schirmer test) and nasal obstruction (NOSE) assessments were repeated at months 2 and 4 of treatment in isotretinoin groups.

Results: The right Schirmer values at month 2 ($p<0.05$) in the 0.25 mg isotretinoin group and right ($p<0.01$ for each) and left ($p<0.001$ and $p<0.01$, respectively) Schirmer values at months 2 and 4 in the 0.5 mg isotretinoin group significantly decreased from baseline, while VAS scores at months 2 and 4 ($p<0.001$ and $p<0.01$, respectively) significantly increased in the 0.5 mg isotretinoin group.

Conclusion: Our findings revealed the association of isotretinoin treatment with the occurrence of nasal dryness but not with nasal obstruction in patients with acne vulgaris, particularly with the high-dose daily regimen, regardless of treatment duration. The nasal Schirmer test is an objective assessment of nasal dryness in patients receiving isotretinoin therapy and the potential benefit of low-dose isotretinoin in reducing the risk of nasal dryness.

Keywords: Nasal dryness, nasal obstruction, isotretinoin dose, acne vulgaris, nasal Schirmer test

Introduction

Isotretinoin, used orally, is successfully used for acne treatment for more than two decades. It is a first-generation retinoid with pleiotropic effects on etiological factors involved in acne pathogenesis such as keratinocyte differentiation, proliferation, and sebaceous gland activity (1-3). However, the mechanism of action is considered to adversely affect mucociliary regrowth, refunctioning, and clearance properties of the nasal epithelium (4,5).

Nasal secretion plays a vital role in humidification, heating, and cleaning of inspired air and participates in the first-line defense of the respiratory tract (6-9). Notably, the viscosity, elasticity, and adhesion properties of the mucus are important in mucociliary clearance and thus in the prevention of mucous stasis, secondary infection, and chronic dryness (4,5,8).

Several studies have reported that isotretinoin was associated with negative effects on the nasal mucosa and mucociliary functions, including the induced epithelial and mucociliary differentiation, inhibition of squamous cell differentiation, and impaired mucociliary clearance time (MCT) (4,5,10-13). However, despite the consideration of reduction in mucosal secretion and dryness of the nasal surface mucosa in the etiology of the two common side effects of isotretinoin treatment including the prolonged MCT and the epistaxis (2,4,5,12-15), nasal dryness has not been extensively studied using objective measures in patients receiving isotretinoin.

Problems related to nasal secretion (sensation of a dry or runny nose) are among the most frequent patient-reported complaints in otolaryngology practice (8,16). However, their diagnosis is mainly based on the subjective clinical description, as only a few objective tests are

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available for measuring nasal humidity with limited use in routine clinical practice because of the need for special equipment or associated patient discomfort (7,9,16-18).

As the nasal Schirmer test is an easily applicable, low-cost, and rapid tool in the objective assessment of nasal secretion and nasal mucosal moisture, it is considered promising in this regard (7,9,16). Thus, the nasal Schirmer test, a modified version of the Schirmer test used in evaluating lacrimation in ophthalmology practice, is now increasingly used in otolaryngology practice in evaluating the amount of nasal secretion (7,9,16).

This study aimed to investigate the effect of oral isotretinoin therapy on nasal dryness and nasal obstruction through objective (Schirmer values) and subjective [visual analog scale (VAS), nasal obstruction symptom evaluation (NOSE) scores] measures, with respect to the dose and duration of therapy in patients with acne vulgaris.

Methods

Study Population

A total of 102 dermatology outpatients [mean ± standard deviation (SD) age, 20.9±3.3 years; female, 65.1%] initiating systemic isotretinoin treatment [in 0.25 mg/kg/day (n=35) or 0.5 mg/kg/day (n=67) doses] for acne vulgaris were enrolled in this prospective 4-month isotretinoin follow-up study. The study was conducted at a tertiary care otolaryngology clinic. Patients with a history of nasal surgery, upper respiratory tract infection within the last 4 weeks, active or ex-smokers, and took topical or systemic medication (i.e., steroids), and had rhinitis, chronic sinusitis, nasal polyp, septum deviation, chronic otitis media, concha hypertrophy, or any systemic disease were excluded from the study.

Written informed consent was obtained from each patient. The study was conducted following the ethical principles stated in the Declaration of Helsinki and approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 2501, date: 21/08/2020).

Assessments

Data on patient demographics (age and gender), isotretinoin dose, nasal obstruction (via NOSE), and nasal dryness via a psychometric response scale (VAS; 0, none; 10, worst) and nasal Schirmer test values (right and left Schirmer values) were recorded at baseline. Nasal dryness (by VAS and nasal Schirmer test) and nasal obstruction (by NOSE) assessments were repeated at months 2 and 4 of treatment in isotretinoin groups (0.25 and 0.5 mg/kg/day).

NOSE Questionnaire

NOSE questionnaire, developed by Stewart et al. (19) in 2004, is a 5-item questionnaire with each item scored from 0 to 4. For total scores, each answer is multiplied by 5 to base the scale out of a possible score of 100 (most severe nasal obstruction) for analysis as previously described, whereby higher scores demonstrate more severe nasal obstruction (19,20). Adaptation and validation of the Turkish version of the NOSE questionnaire were performed by Onerci Celebi et al. (21) in 2018.

Nasal Schirmer Test

Before the procedure, patients were asked to irrigate their noses with tap water and to wait for 15 min in a room with 22.5 °C temperature and 33.8% humidity to adapt to the hospital environment. Whatman no. 41 strips of filter paper, known as the Schirmer test filter paper, with 35 mm length and 5 mm width (Dr. Gerhard Mann Chem. Pharm Fabrik GmBH Berlin, Germany) were used for all subjects. The moistened area on the strip removed from each nostril was recorded as left and right (bilateral) Schirmer values (in mm) as previously described (7,9).

Statistical Analysis

Statistical analysis was made by using MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013). The Mann-Whitney U test, Friedman test, and Wilcoxon test with Bonferroni correction were used for the analysis of non-normally distributed numerical variables. Data were expressed as mean ± SD, median (minimum-maximum), and percent (%) where appropriate; $p<0.05$ was considered significant.

Results

Baseline Characteristics

The mean ± SD of the patient age was 21.1±3.4 (range: 16-34) years, and 64.7% of the patients were female. The daily dose of isotretinoin was 0.25 mg/kg in 35 (34.3%) patients and 0.5 mg/kg in 67 (65.7%) patients. Overall, 60 and 46 patients adhered to month 2 and 4 visits, respectively. The daily isotretinoin dose was 0.5 mg/kg in 39 (65.0%) of 60 patients assessed at month 2 visit and 32 (69.6%) of 46 patients assessed at month 4 visit.

Study Parameters in All Patients Treated with Isotretinoin

When compared with pretreatment values, months 2 and 4 of isotretinoin treatment were associated with a significant increase in VAS scores [median (minimum-maximum), 0 (0-7) vs 3 (0.7) and 3 (0-9), $p<0.001$ each] and a significant decrease in both left [median (minimum-maximum), 19 (9-35) vs 17 (7-30) and 15 (5-35), $p<0.001$ each] and right [median (minimum-maximum), 17 (10-35) vs 15 (9-35) and 15 (4-35), $p<0.001$ each] Schirmer values. Month 4 left Schirmer values were also significantly lower than month 2 values ($p<0.05$) (Table 1, Figure 1).

Study Parameters in Isotretinoin Groups

No significant difference was noted between isotretinoin groups in terms of pretreatment and posttreatment month 2 and 4 VAS and NOSE scores and the right and left Schirmer values (Table 2).

In the 0.25 mg isotretinoin group, the only significant change from baseline was observed for month 2 right Schirmer values ($p<0.05$), with no significant change from baseline in month 2 VAS, NOSE, and left Schirmer values as well as in month 4 VAS, NOSE, and bilateral Schirmer values (Table 2, Figure 1).

In the 0.5 mg isotretinoin group, when compared with pretreatment values, month 2 and 4 therapy was associated with significantly increased VAS scores ($p<0.001$ and $p<0.01$, respectively) and

Table 1. Study parameters in all patients treated with isotretinoin

		Pretreatment (n=102)	Month 2 (n=60)	Month 4 (n=46)	p[1]
VAS score	Mean ± SD	1±2	3±2*	4±3*	<0.001
	Median (min.-max.)	0 (0-7)	3 (0-7)	3 (0-9)	
NOSE score	Median (min.-max.)	0 (0-40)	0 (0-40)	5 (0-35)	0.705
Nasal Schirmer test					
Right Schirmer value	Mean ± SD	20±6	17±6*	16±7*	<0.001
	Median (min.-max.)	17 (10-35)	15 (9-35)	15 (4-35)	-
Left Schirmer value	Mean ± SD	20±6	17±6*	16±7*,+	<0.001
	Median (min.-max.)	19 (9-35)	17 (7-30)	15 (5-35)	-

VAS: Visual analog scale, NOSE: nose obstruction symptom evaluation, SD: standard deviation, min.: minimum, max.: maximum, 1: Friedman test, *: p<0.001 compared with pretreatment values (Wilcoxon test with Bonferroni correction, p<0.016), +: p<0.05 compared with month 2 values (Wilcoxon test with Bonferroni correction, p<0.016)

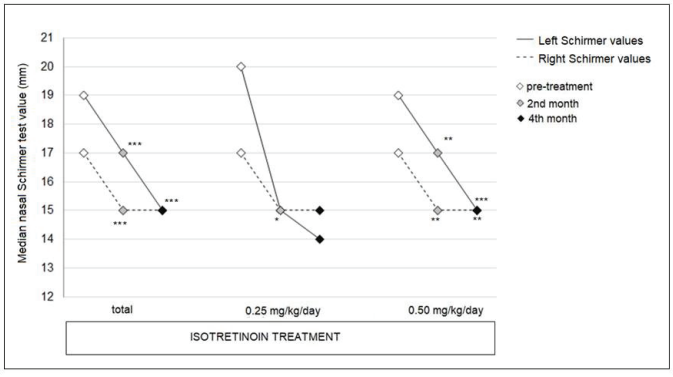

Figure 1. Nasal Schirmer test findings: right and left Schirmer values in all groups and isotretinoin groups, at baseline and months 2 and 4 of treatment

*: p<0.05, **: p<0.01, and ***: p<0.001; compared with pretreatment values

significantly decreased right (p<0.01 for each) and left (p<0.001 and p<0.01, respectively) Schirmer values (Table 2, Figure 1).

Discussion

Our findings revealed a significant increase in nasal dryness measured via VAS scores and bilateral nasal Schirmer values in patients with isotretinoin-treated acne vulgaris, particularly when the daily dose was set at 0.5 mg/kg, even within 2 months of therapy. NOSE scores reported by patients at baseline and during treatment were associated with the lack of nasal obstruction; thus, isotretinoin treatment had no significant effect on NOSE scores, regardless of the treatment dose or duration.

In the present study, the significant increase in nasal dryness scores based on both subjective (increase in VAS scores) and objective (decrease in right and left Schirmer values) measures in patients who received isotretinoin supports the consideration of mucosal dryness as the most common side effect of isotretinoin, i.e., patients on isotretinoin twice likely complained of nasal dryness compared with healthy individuals (2,22).

The bilateral Schirmer values recorded at baseline in the present study were in line with the mean reference values (right, 19.8±6.9; left, 19.5±7.0) in the Turkish population in a previous study (7). Hence, our findings indicate the utility of the nasal Schirmer test in the objective evaluation of nasal humidity in patients with isotretinoin-treated acne vulgaris and the sensitivity of this test in discriminating the dose and treatment duration-dependent alteration in nasal dryness.

The association of 0.5 mg/kg daily dose of isotretinoin with an increase in mean VAS scores (1-3) after month 4 of treatment in our patients supports the data from previous studies indicated a significant increase in the mean VAS score of the patients from baseline (range: 0.1-2.7) to the end of isotretinoin treatment (range: 1.7-3.3) (4,14).

In a study by Tasli et al. (14) conducted with 54 patients with isotretinoin-treated acne vulgaris, authors reported a significant increase from baseline to months 1 and 3 of treatment in mean NOSE scores (14.04, 20.11, and 19.04, respectively), VAS scores (1.59, 2.14, and 2.21, respectively), and nasal dryness/crusting severity scores (0.47, 3.57, and 4.28, respectively) along with a significant increase in the percentage of patients with nasal dryness from 9.5% at baseline to 43% at month 3 of isotretinoin treatment.

In a study of 40 patients with acne vulgaris, Gorpelioglu et al. (12) revealed that the mean nasal MCT significantly increased after isotretinoin treatment along with a significant correlation between drug dose and prolonged nasal clearance. The authors also noted that nasal complications caused by isotretinoin, such as signs and symptoms of dry nose and disturbed mucociliary clearance, were mild in patients on the low-dose isotretinoin regimen (12).

In a study of 101 patients with isotretinoin-treated acne vulgaris, İşlek and Yıldız (4) reported significant increase from baseline values in MCT, NOSE, and nasal dryness VAS scores and indicated the role of routine ear-nose-throat control in patients with isotretinoin-treated acne vulgaris to timely recognize the potential adverse effects of the drug on the nasal mucosa (4).

While mucocutaneous dryness is suggested to cause crusting, increasing the likelihood of nasal passage obstruction and complaint of nasal obstruction (14), isotretinoin had no significant effect on pretreatment NOSE scores in the current study, and nasal obstruction was not reported as a significant problem by our patients, regardless of the dose and duration of isotretinoin treatment.

In the present study, a significant increase in VAS scores and a decrease in bilateral Schirmer values from baseline to months 2 and 4 of therapy were evident only in patients receiving 0.5 mg/kg daily dose of isotretinoin. Accordingly, given the dose dependency of side effects such as dry mouth, nasal dryness, and frequent nosebleeds, which are reported more frequently in the high-dose than in low-dose groups of patients who received isotretinoin, our findings appear to support the consideration of low-dose daily isotretinoin (0.25 mg/kg) regimen for 6 months as a logical treatment approach in patients with acne vulgaris (23). Indeed, several studies have reported that when considering tolerability, efficacy, and patient satisfaction, low-dose daily treatment (0.25-0.4 mg/kg) for a total period of 6 months is most suitable for patients with moderate acne (24-27).

Table 2. Study parameters in isotretinoin groups

	Pretreatment (n=102)		Month 2 (n=60)		Month 4 (n=46)		p[1]	
	0.25 mg/kg/day (n=35)	0.50 mg/kg/day (n=67)	0.25 mg/kg/day (n=21)	0.50 mg/kg/day (n=39)	0.25 mg/kg/day (n=14)	0.50 mg/kg/day (n=32)	0.25 mg/kg/day	0.50 mg/kg/day
VAS score								
mean ± SD	2±2	1±2	3±2	3±2***	4±2	3±3**	0.248	<0.001
median (min.-max.)	1 (0-7)	0 (0-5)	3 (0-7)	3 (0-7)	4 (0-7)	3 (0-9)		
p value[2]	0.092		0.893		0.353		-	
NOSE score								
median (min.-max.)	0 (0-40)	0 (0-30)	0 (0-35)	0 (0-40)	5 (0-35)	0 (0-30)	0.098	0.882
p value[2]	0.228		0.547		0.053		-	
Nasal Schirmer test								
Right Schirmer value								
mean ± SD	20±6	20±6	17±6*	17±6**	17±7	16±7**	0.008	0.001
median (min.-max.)	17 (13-35)	17 (10-35)	15 (9-34)	15 (10-35)	15 (7-30)	15 (4-35)		
p value[2]	0.502		0.810		0.950		-	
Left Schirmer value								
mean ± SD	21±6	20±6	17±6	17±6**	15±6	17±8***	0.059	<0.001
median (min.-max.)	20 (12-35)	19 (9-35)	15 (10-30)	17 (7-30)	14 (10-30)	15 (5-35)		
p value[2]	0.767		0.572		0.509		-	

VAS: Visual analog scale, NOSE: nose obstruction symptom evaluation, SD: standard deviation, min.: minimum, max.: maximum, [1]: Friedman test, [2]: Mann-Whitney U test, *: $p < 0.05$, **: $p<0.01$ and ***: $p<0.001$; compared with pretreatment values (Wilcoxon test with Bonferroni correction, $p<0.016$)

Study Limitations

First, the potential lack of generalizability appears to be an important limitation because of the relatively small sample size. Second, the short follow-up period and considerable loss to follow-up ratio also limited this study. Third, there was no data on epistaxis and mucociliary clearance, which otherwise could have extended the knowledge achieved in the present study.

Conclusion

Our findings revealed the association of isotretinoin treatment with nasal dryness but not with nasal obstruction in patients with acne vulgaris, particularly with the use of the high-dose (0.5 mg/kg) daily regimen, regardless of treatment duration. Our findings emphasize the utility of the nasal Schirmer test in the objective assessment of nasal dryness in patients who received isotretinoin treatment and the potential benefit of low-dose (0.25 mg/kg) isotretinoin regimen in reducing the risk of nasal dryness as a common etiological factor for eventual problems such as prolonged nasal clearance and epistaxis. Further larger-scale studies addressing the long-term nasal side effects of oral isotretinoin therapy are needed to develop optimal screening tools for the timely recognition, appropriate management, and follow-up of potential adverse effects of the drug on the nasal mucosa.

Ethics Committee Approval: The study was conducted following the ethical principles stated in the Declaration of Helsinki and approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 2501, date: 21/08/2020).

Informed Consent: Written informed consent was obtained from each patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - E.Y.; Concept - E.Y., D.E., Z.Ç., E.C.; Design - E.Y., D.E., Z.Ç., E.C., Ö.Y.; Data Collection or Processing - E.Y., Z.Ç., E.C.; Analysis or Interpretation - E.Y., D.E., Z.Ç., Ö.Y.; Literature Search - E.Y., D.E., Z.Ç., E.C.; Writing - E.Y.

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Comparison of Quadriceps Exercise Modalities on Pain, Muscle Strength, Function, and Balance in Bilateral Knee Osteoarthritis

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ABSTRACT

Introduction: This study aimed to investigate the effects of various exercises on quadriceps femoris muscle and on pain, strength, function, and balance in female patients with bilateral knee osteoarthritis (OA).

Methods: Forty-five female patients aged 40-65 years were diagnosed with bilateral knee OA according to the American College of Rheumatology criteria and randomized into three groups. The pain and function of the patients in each group were evaluated by the visual analog scale and Western Ontario and McMaster Universities Osteoarthritis Index questionnaires. Muscle strength and endurance were measured with the Isokinetic System Cybex 350, and balance was evaluated with Biodex Balance System SD. Group 1 performed a home-based isometric exercise program, while groups 2 and 3 performed strength and endurance exercises, for 4 days per week for 6 weeks.

Results: At week 6, only the activity pain scores decreased in group 1, whereas rest, night, and activity pain scores decreased significantly in groups 2 and 3 ($p<0.001$, $p<0.01$ and $p<0.001$, respectively). Significant improvements in physical functions were found in each group ($p<0.001$). The isokinetic muscle strength for knee extensors increased significantly in groups 2 and 3 ($p<0.001$, $p<0.01$, respectively). The balance scores of groups 2 and 3 were improved at certain positions ($p<0.001$, $p<0.05$, respectively).

Conclusion: Isometric exercises are widely used in the treatment of patients with knee OA. However, high-intensity isotonic exercises is recommended because of the shorter time of intervention for improving muscle strength, slowing the progression of the disease, and reducing the future risk of falling by improving balance.

Keywords: Osteoarthritis, exercise, pain, function, balance

Introduction

Osteoarthritis (OA) is a progressive state of weight-bearing joints such as the knee and is common in geriatric patients (1). Knee OA is commonly associated with quadriceps femoris muscle weakness, functional impairment, reduced quality of life, and increased morbidity and mortality (2). Age-related sarcopenia and reduction in muscular strength result in the reduction of activities of daily living and mobility of the patients and increases falling risk. It also reduces proprioception of the knee joint, which further contributes to this process. OA has been shown to affect muscle strength and mechanoreceptors at the knee joint, thus increasing the risk of balance problems in patients (3,4).

The initial treatment for OA includes medications, lifestyle modification, and rehabilitation. This treatment aims to manage pain, preserve and improve joint functioning, provide functional independence, and improve quality of life (2,5-7). Exercise treatment is one of the critical components of the rehabilitation program, as emphasized by numerous studies (5,6,8). However, the target muscle group for an exercise program, type and intensity, and outcomes of such programs on patients' symptomatology have been debated. Most commonly, the quadriceps muscle group was the target for a specific exercise program, but a broader lower extremity program, as well as aerobic programs, has been studied. A specific exercise program targeting the quadriceps muscle group was most effective in reducing patients' symptoms (9). There is no definite consensus on the type, dose, and effect of exercise for the quadriceps femoris muscle on parameters such as pain, physical function, strength, and balance in OA (5,9).

This study aimed to investigate the effects of different types of quadriceps femoris muscle exercises with varying intensities on pain,

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muscle strength, physical function, and balance of female patients with bilateral knee OA.

Methods

The study recruited patients with newly diagnosed OA of the knee. Selection criteria were based on the clinical and radiological criteria defined by the American College of Rheumatology for knee OA. In addition, patients at grade 2 and 3, according to the Kellgren-Lawrence Classification, were included, and these patients in each group had homogeneous characteristics. Female patients aged 40-65 years with a diagnosis of bilateral knee OA who were admitted to the outpatient physical medicine and rehabilitation clinics of İstanbul University Faculty of Medicine and Şişli Florence Nightingale Hospital between March 2016 and December 2016 were included in the study.

The Clinical Research Ethics Committee of İstanbul University, İstanbul Faculty of Medicine (approval number: 2016-249, date: 29.02.2016) approved the study. This study was supported by İstanbul University Scientific Research Projects Unit (project no: 22047).

Patients who had a history of knee or hip surgery, who received an intra-articular injection in the previous 3 months, whose knee flexion range was <100° or with an extension loss >10°, patients with a neurological disorder that affects lower limb musculature, or patients with an inflammatory rheumatologic condition were excluded.

In total, 46 patients volunteered for the study and signed the informed consent forms. One patient withdrew from the study because of family commitments. The remaining 45 patients were divided into three groups according to the order of admittance to the clinic. Patients were assessed with the same measures before and after the 6-week treatment. The assessments included knee range of motion measurement, visual analog scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), knee strength and endurance assessment using an isokinetic dynamometer, and balance assessment using a Biodex Balance System.

Patient report forms: Each patient report form included demographic information including age, weight, height, history and family background, patient occupation, knee range of motion values, and progress charts for each session.

Assessment of pain levels: VAS was used to assess the patients' level of pain. Three measures were noted to assess pain at rest, with physical activity, and at night. Patients were provided with a 10 cm long horizontal scale, and they were asked to put a mark on this scale to represent their pain level. The scale was described to patients as "0" representing a state of no pain at all and "10" representing an unbearable pain. The distance was then measured and noted.

WOMAC index: This index is widely used by clinicians to assess pain, stiffness levels, and functional status of patients with OA. The index consists of 24 questions and three main sections. Pain is assessed with 5, stiffness with 2, and physical functioning with 17 questions in these sections. Higher scores in the WOMAC index represent increased pain and stiffness and worsened physical functioning (10,11).

Measurement of muscular strength and endurance: Muscular strength and endurance of the knee flexor and extensor muscle group were assessed with a Cybex 350® isokinetic dynamometer system. The patients warmed up with a stationary bike for 7 min at 65 rpm with an intensity of 2/10. The muscular strength of the knee was measured for five repetitions after a trial of three maximal knee flexion and extension movements at a low angular velocity (60°/s). The average peak torque, peak torque/body weight, total work done, and total work/body weight values of the five repetitions were noted. The same exercise specialist performed the measurements throughout the study and provided patients verbal motivation during the tests. Endurance was then measured using a high angular velocity (180°/s) for 15 repetitions after a trial of five repetitions. The average peak torque, peak torque/body weight, total work done, and total work/body weight values of the 15 repetitions noted. Both extremities were measured (12).

Measurement of balance: The static balance of the patients was measured using the Biodex Balance System®, which was regularly calibrated each year. The test platform was set to the static mode. The patients were asked to maintain a balanced stance position at these settings: i) eyes open, knees are at full extension; ii) eyes closed, knees at full extension; iii) eyes open, knees bent by approximately 30°; and iv) eyes closed, knees bent by approximately 30°. The anteroposterior index, mediolateral index, and overall index were assessed using the internal post-processing algorithm of the device. Each position was tested three times, and an average value representing each index was noted (13).

Treatment Groups

1. Isometric exercise group (group 1)

Isometric knee exercises were prescribed as a home-based exercise program. The patients were asked to perform maximal isometric knee extension exercise for 5 s and repeat this 10 times while sitting with their knees extended. A towel was placed under the exercising knee to facilitate the knee extension at this position. Exercise intensity was assessed via the OMNI 0-10 scale (0 as "extremely easy" to 10 as "extremely hard") (14). When perceived exertion was reduced to ≤5 on a 10-point scale, they were asked to perform 20 repetitions instead of 10. Patients performed these exercises four times per week within 6 weeks. Each patient was followed up via phone calls, which reviewed the technique of exercise, total exercise duration and frequency, and rate of perceived exertion.

2. Strength exercise group (group 2)

Patients were allocated into a high-intensity low-repetition isotonic strength exercise program supervised by a physiotherapist for 6 weeks (Table 1). Patients performed these exercises four times per week. The intensity was determined by the 1-RM method, and patients performed the exercise for five repetitions at an intensity of 80% of 1-RM during the first 3 weeks and five repetitions at 90% during the second 3 weeks (15). Sandbags were used to achieve the desired intensity. There were no pain flare-ups during or after the high-intensity sessions.

3. Endurance exercise group (group 3)

Patients were allocated into a low-intensity high-repetition isotonic endurance exercise program (Table 1). Patients performed these exercises four times per week. group 3 performed the same exercise as group 2, with a different intensity and repetition. The patients performed the exercise for 20 repetitions at an intensity of 40% of 1-RM during the first 3 weeks and for 20 repetitions at 50% during the second 3 weeks (15). Sandbags were used to achieve the desired intensity.

Statistical Analysis

Statistical analysis of the data was performed with SPSS version 21.0® (Statistical Package for Social Sciences). Data normality was assessed using the Shapiro-Wilk test, which showed a normal distribution. Therefore, parametric tests were used for further analysis. $P<0.05$ was set as a significance threshold for all values. A One-Way analysis of variance test was used to assess between-group differences, and Bonferroni correction was applied. Paired sample t-test was used to assess within-group differences before and after treatment. A mean difference was also calculated before and after treatments.

Results

The average age, height, and weight of the groups were comparable (Table 2). Activity pain reduced significantly after the exercise therapy in group 1 ($p<0.001$). Activity pain ($p<0.001$), resting pain ($p<0.01$), and night pain ($p<0.001$) reduced significantly in groups 2 and 3 (Table 3). Average pain, stiffness, and physical functioning values of the WOMAC index reduced significantly in group 1 ($p<0.05$, $p<0.01$, and $p<0.001$, respectively) and in group 2 ($p<0.001$, $p<0.01$, and $p<0.001$ respectively). The average pain ($p<0.001$) and physical function ($p<0.001$) values of the WOMAC index reduced significantly in group 3, whereas the stiffness value did not change (Table 3).

In group 1, isokinetic muscle strength and endurance measures (peak torque, peak torque/body weight, total work done, and total work/body weight) were not different from baseline in the knee extensor muscle group of both extremities, whereas the peak torque of the flexor muscle group of both knees ($p<0.05$) and the peak torque/body weight of the left knee ($p<0.05$) showed significant changes (Table 4). In group 2, all measures from the isokinetic assessment showed remarkable increases in both extensor and flexor muscle group in both knees (Table 4, 5). In group 3, extensor muscles had increased maximal strength, such as peak torque [right knee ($p<0.05$), left knee ($p<0.01$)] and peak torque/body weight ($p<0.01$), in both knees (Table 4). Moreover, the peak torque, peak torque/body weight, total work done, and total work/body weight showed remarkable changes for the flexor muscle group of the left knee ($p<0.05$) (Table 5).

Balance assessment of group 1 did not result in significant changes in either of the scores. Group 2 showed significant improvements in "eyes open, knees in extension" ($p<0.001$), "eyes open, knees in flexion" ($p<0.05$), and "eyes closed, knees in flexion" conditions ($p<0.001$). However, no significant changes were observed in the "eyes closed, knees extended" condition. In group 3, only "eyes closed, knees in flexion" and "eyes open, knees in flexion" balance conditions showed improvements ($p<0.05$) (Table 6).

Table 1. Applied exercises

Exercises for group 1	Exercises for groups 2 and 3
- Hamstring stretching	- Hamstring stretching
- Quadriceps femoris stretching	- Quadriceps femoris stretching
- Supine straight leg raise	- Supine straight leg raise
- Supine knee press	- Supine short-arc knee extension
- Supine ball squeeze in between legs	- Knee extension while sitting
- Straight leg raise in side-lying	- Short-arc knee extension while sitting

Table 2. Demographic data

Parameters	Group 1 (mean ± SD)	Group 2 (mean ± SD)	Group 3 (mean ± SD)	p
Age (year)	48.20±7.5	53.6±9.1	52.4±6.7	0.121
Height (m)	1.63±0.5	1.59±0.7	1.60±0.5	0.148
Body weight (kg)	82.6±13.9	78.0±10.3	82.7±5.9	0.383
Body weight (after 6 weeks) (kg)	82.2±14.2	78.3±10.7	82.5±7.06	0.515

SD: Standard deviation

Discussion

The management of knee OA involves medical treatment, lifestyle modification, and rehabilitation. Exercise is one of the critical components of the rehabilitation program (5,6,8). The effectiveness of specific exercises for the quadriceps femoris muscle is widely accepted. However, the type, intensity, duration, and frequency of the planned exercise are still not established. Thus, this study investigated the effects of different types and intensities on strength, pain, function, and balance.

Our results revealed that the VAS score only improved for "pain during activity" in group 1, whereas all types of pain improved in groups 2 and 3. These results are consistent with the literature. Additionally, all three groups have significantly improved pain, stiffness, and daily physical functioning scores in the WOMAC index compared with the pretreatment values. These results also support the literature data (6,9,16-21).

Fransen et al. (18) compared the effect of knee flexor and extensor muscle strength exercises in reducing pain and increasing physical function in patients with knee OA. They found that the increase in knee extensor muscle strength is more related to improvement in both parameters than to flexor muscle strength. Moreover, they reported that exercise treatment is more effective in decreasing pain than analgesic medication. They also noted that exercise therapy was more effective than analgesic drugs for reducing pain. Our study revealed that pain decreased and physical function improved in all types of muscle strengthening that were applied to the extensor muscle group. Juhl et al. (9) examined the effect of exercise type and dose on pain and disabilities in knee OS in a systematic review and meta-regression analysis of randomized controlled trials. They suggested that an optimal exercise program for knee OA is performed at least three times a week. Pelletier et al. (19) also reported that an 8-week exercise program consisting of

Table 3. Comparison of VAS and WOMAC scores before and after exercise

Parameters		Group 1		Group 2		Group 3	
		BE	AE	BE	AE	BE	AE
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
VAS	Rest	3.2±3.4	2.2±2.1	3.4±3.06	0.9±1.5***	4.06±3.1	1.1±2.03***
	Night	2.6±3.3	1.9±2.3	3.3±3.5	0.8±1.8**	4.1±3.1	0.8±1.4**
	Activity	6.3±3.4	4.5±2.6***	7.6±2.1	3.4±2.09***	6.7±2.3	3.2±2.3***
WOMAC	Pain	6.7±4.5	5.4±3.6*	9.4±4.3	4.5±2.5***	9.2±4.2	4.3±2.8***
	Stiffness	3.3±2.7	2.1±1.8**	3.5±2.5	1.2±1.3**	2.7±1.6	1.8±1.8
	Physical function	21.9±16.5	17.4±14.3***	23.4±12.9	12.0±5.9***	27.5±10.8	14.8±13.7***

BE: Before exercise, AE: after exercise, SD: standard deviation, *: p<0.05, **: p<0.01, ***: p<0.001, VAS: visual analog scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Table 4. Isokinetic assessment of knee extensor muscle group before and after exercise

Parameters		Group 1		Group 2		Group 3	
		BE	AE	BE	AE	BE	AE
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Right knee extensors	Peak torque (N.m)	108.8±22.5	106.8±23.1	82.1±17.7	97.7±20.9***	88.8±24.6	94.8±23.2*
	Peak torque/body weight (N.m/kg)	130.0±25.8	132.8±35.9	107.1±26.05	127.06±32.2***	106.5±30	115.06±27.9**
	Total work (N.m)	658.2±154.8	635.4±169.6	502.3±153.3	587.8±131.4*	543.8±218.4	521.6±173.2
	Total work/body weight (N.m/kg)	811.2±195.6	790±229.4	661.4±220.9	765.9±202.4*	649.6±240.6	631.2±203.8
Left knee extensors	Peak torque (N.m)	104.2±18.7	106.6±22.04	87.8±21.6	101.8±20.5***	84.06±23.7	92.8±22.6**
	Peak torque/body weight (N.m/kg)	128.4±26.1	131.8±30.8	114.1±31.09	131.4±29.9***	100.7±26.6	112.8±28.3**
	Total work (N.m)	593.7±123.1	599.7±161.4	493.9±143.3	586.8±135.8**	481.8±183.7	526.06±186.8
	Total work/body weight (N.m/kg)	729.6±149.3	739.3±198.1	646.7±214.9	759.2±193.4*	575.8±197.7	635.2±210.6

BE: Before exercise, AE: after exercise, SD: standard deviation, *: p<0.05, **: p<0.01, ***: p<0.001)

Table 5. Isokinetic assessment of knee flexor muscle group before and after exercise

Parameters		Group 1		Group 2		Group 3	
		BE	AE	BE	AE	BE	AE
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Right knee flexors	Peak torque (N.m)	62.6±11.8	66.8±12.6*	50.9±10.08	64.3±15.2***	60.6±17.3	63.9±16.4
	Peak torque/body weight (N.m/kg)	76.4±13.4	83.2±18.1	67.06±16.8	83.6±22.7***	73.2±19.5	77.6±20.6
	Total work (N.m)	446.1±93.6	474.2±130.2	373.6±116.3	478.8±192.3**	407.9±121.9	441.06±137.5
	Total work/body weight (N.m/kg)	552.5±131.4	591.2±178.4	492.1±172.0	628.4±266.6**	487.9±130.7	534.9±165.4
Left knee flexors	Peak torque (N.m)	64.1±11.5	69.0±15.2*	52.5±8.8	64.4±13.6***	58.5±17.3	662±20.3*
	Peak torque/body weight (N.m/kg)	77.8±11.5	84.7±18.5*	68.4±12.7	83.7±19.1***	70.3±19.2	80.4±25.2*
	Total work (N.m)	473.6±103.8	511±128.01	383.1±119.7	464.4±138.8**	406.1±134.5	477.8±175.5*
	Total work/body weight (N.m/kg)	585.0±152.7	631.2±166.6	501.7±183.3	606.6±206.6*	485.7±143.1	582.6±219.01*

BE: Before exercise, AE: after exercise, SD: standard deviation, *: p<0.05, **: p<0.01, ***: p<0.001

three times weekly sessions of quadriceps femoris strength exercises (knee flexion-extension) reduced pain and improved daily functions in patients with knee OA. In the present study, we determined the duration and frequency of exercise as a 6-week exercise program consisting of four sessions per week, which is consistent with the literature. At the end of this period, we found significant improvements in pain and physical function in all groups.

Table 6. Comparison of balance scores before and after exercise

Parameters	Group 1		Group 2		Group 3	
	BE	AE	BE	AE	BE	AE
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
EOKE	0.50±0.13	0.48±0.20	0.62±0.14	0.43±0.13***	0.74±0.43	0.54±0.30
ECKE	1.12±0.45	0.91±0.32	1.40±0.82	1.12±0.46	1.79±1.13	1.22±0.66*
EOKF	0.74±0.38	0.71±0.22	0.92±0.42	0.70±0.25*	1.17±0.65	0.94±0.54*
ECKF	2.18±0.88	1.92±0.82	2.80±1.15	1.76±0.56***	2.22±1.18	1.92±0.97

EOKE: Eyes open knee in extension, ECKE: eyes closed knee in extension, EOKF: eyes open knee in flexion, ECKF: eyes closed knee in flexion, BE: before exercise, AE: after exercise, SD: standard deviation, *: p<0.05, **: p<0.01, ***: p<0.001

The isokinetic strength of the knee extensor muscle group in group 1 did not show significant changes in our study. This suggests that a 6-week home-based isometric knee exercise program does not significantly increase muscular strength in patients with knee OA. However, this could be an expected outcome, as the exercises were isometric, and isometric exercises should be performed for an extensive period to gain significant strength. In group 2, all isokinetic strength parameters improved significantly. We believe that these improvements are mainly due to neuronal adaptation, as 6 weeks is a relatively short duration to observe hypertrophy to its full extent. These results regarding both isometric and strength exercises also overlap with the physiological mechanisms expressed in a previous study (22).

Messier et al. (21) suggested that higher-intensity exercises worsen the knee pain, degenerate structures around the joint, increase the risk of injury, and may increase blood pressure of patients with knee OA. Raymond et al. (23) emphasized the positive effects of high-intensity progressive muscle strengthening exercises on muscle strength, physical function, depression, and quality of life in patients aged >65 years in a systematic review of 21 randomized controlled studies. Their results suggest that higher-intensity isotonic exercises are superior in gaining muscular strength; however, other types and intensities of exercises could be preferred for improving other parameters such as physical function, depression, and life quality index. We did not encounter risk events of high-intensity exercise in our study. Our results are consistent with the literature finding that supports the benefits of high-intensity isotonic exercise to strengthen knee muscles. We also showed that other types and intensity of exercises could improve other parameters such as pain reduction and physical function.

We investigated balance with both eyes open and closed and knees in extension and flexion separately. In group 1, none of these parameters had significant changes, and the other two groups had significant improvements. The strength exercise group showed an increase in several parameters (i.e., more tested positions) and higher significance values than the endurance exercise group. Strengthening the quadriceps femoris muscle becomes highly important in exercise therapy in OA because it is the most significant antigravity muscle of the lower extremity and has a significant role in maintaining balance. Bellew et al. (24) investigated a 12-week low-intensity quadriceps strength exercise program in the elderly and did not find an improvement in balance measures. These conflicting results in the literature are possibly due to methodological differences among studies, OA stage of the patients, exercise type, and intensity of the exercise sessions. Kim et al. (25) compared strength and balance exercises in different platforms in a 30-knee OA patient cohort. After 6 weeks, no between-group difference was found in balance, but balance measures improved significantly within the groups before and after experiments. Our study supports the findings of Kim et al. (25) by showing improvements in balance measures in the strength exercise group.

Study Limitations

This study is not a double-blind placebo-controlled randomized study. However, for most patients presenting with knee OA, nonintervention may lead to dropouts and an unacceptable option for patients. As all groups showed improvement, there is a need for studies with larger study samples. Long-term exercises with different load intensities and duration should be addressed in future studies by increasing the sample size.

Conclusion

Exercise therapy should be performed in addition to controlling pain and inflammation in the treatment and rehabilitation of patients with OA. Even though isometric exercises are widely used in this setting, to shorten the time of intervention for improving muscle strength, slowing disease progression, and reducing the risk of falling by improving balance in this population, we believe that including isotonic strength or endurance exercises to support the treatment should be considered.

Ethics Committee Approval: The Clinical Research Ethics Committee of İstanbul University, İstanbul Faculty of Medicine (approval number: 2016-249, date: 29.02.2016).

Informed Consent: In total, 46 patients volunteered for the study and signed the informed consent forms.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - D.Ç., T.Ş., L.Ö.; Concept - D.Ç., S.Y., L.Ö.; Design - D.Ç., S.Y., L.Ö.; Data Collection or Processing - D.Ç., S.Y., T.Ş., Ş.D., Ö.B.G., L.Ö.; Analysis or Interpretation - D.Ç., S.Y., T.Ş., Ş.D., Ö.B.G., L.Ö.; Literature Search - D.Ç., S.Y., T.Ş., Ş.D., Ö.B.G.; Writing - D.Ç., S.Y., T.Ş., Ş.D., Ö.B.G., L.Ö.

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Musculoskeletal Disability Examination by the Health Committee in Patients with Disabilities

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ABSTRACT

Introduction: This study aimed to retrospectively analyze the extent of disability, age, gender, and diagnoses to determine the areas of social support for patients who applied to the disability health board of our hospital and were found to have a musculoskeletal disability.

Methods: This study retrospectively analyzed the data of 410 patients who were evaluated in the orthopedics and traumatology outpatient clinic of our hospital's adult disability health board between 01.02.2019 and 08.06.2021. The age, gender, diagnosis, affected anatomic region, and disability rate information of patients was recorded. The musculoskeletal disability rate of all patients was determined using the "Regulation on Disability Assessment for Adults."

Results: No significant difference was found between both genders in terms of total musculoskeletal system disability rate ($p=0.17$). The musculoskeletal system disability of the senior group was significantly higher than that of the adult group ($p<0.001$). The most frequently affected anatomical region is the lower extremity (232 patients, 56.59%). The most common diagnosis that leads to musculoskeletal disability includes neurological disease sequelae (23.62% of 103 patients).

Conclusion: Our study revealed that musculoskeletal disabilities especially affect the lower extremities and the elderly patient group. Additionally, lower extremity disabilities affect the mobility of patients and create the need for social support thus should be taken into account in social planning.

Keywords: Musculoskeletal system, disability, health, sequele

Introduction

Disability is a human trait that includes medical, functional, and social aspects (1). The World Health Organization developed the International Classification of Functioning, Disability, and Health in 2001 to provide a reference framework for defining disability from a holistic biopsychosocial perspective. The purpose of classification is to form the basis to determine the policies on issues, such as health-related insurance, education, social security, economy, and fair health services delivery (2,3). One of the most important issues concerning these policies is social support. Social support is defined as an asymmetric exchange of resources that is perceived as beneficial by the recipient between at least two people, the recipient and the support provider(s). Individuals with visible physical disabilities were observed to exhibit more adaptive behaviors in receiving social support than individuals without physical disabilities (4). However, disability can significantly affect an individual's access to social support, including health care. People in groups of multiple disabilities accompanied by physical disability were observed to have more problems in getting protective services and accessing health services than people with other types of disability (1). Musculoskeletal diseases are very common; however, the physical disability incidence is reported to be limited (5).

This study aimed to retrospectively analyze the amount of disability, age, gender, and diagnoses to determine the needed areas of social support in patients who applied to the disability health board of our hospital for social support and were found to have a musculoskeletal disability.

Methods

Patient Selection and Data Collection

The study retrospectively analyzed the data of 410 patients with a musculoskeletal disability who agreed to participate in the study who were evaluated in the orthopedics and traumatology outpatient clinic of our hospital's adult disability health board between 01.02.2019 and 08.06.2021. All patients were 18 years or older. The age, gender, diagnosis, affected anatomic region, and disability rate information of patients was recorded. All data were collected using the hospital registry system

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Ethical Approval and Informed Consent

Our study approval was obtained from the "University of Health Sciences Turkey, İstanbul Training and Research Hospital Clinical Research Local Ethics Committee" (approval number: 2854, date: 04.06.2021). An informed consent form was obtained from all patients or their legal representatives.

Statistical Analysis

From descriptive statistical data, number, percentage, average, median, and standard deviation values were used. The normal distribution was evaluated using the Kolmogorov-Smirnov test. The data did not fit the normal distribution, thus the Mann-Whitney U test was used for pairwise comparisons, and the Kruskal-Wallis analysis for multiple comparisons. P-values of <0.05 were considered statistically significant. Statistical analysis was performed using International Business Machines Statistical Package for the Social Sciences Statistics for Windows Version 23.0 (IBM Corp. Released 2015. Armonk, NY: IBM Corp.).

Results

This study retrospectively analyzed the data of 410 patients, of whom 238 were males and 172 were females. The mean musculoskeletal system disability rate of all patients was 25.98% (minimum-maximum: 1-98%, median: 18%). The mean musculoskeletal system disability rate of male patients was 25.03% (minimum-maximum : 1-98%, median: 18%) and that of females was 27.29% (minimum-maximum: 2-98%, median: 19.5). No significant difference was found between both genders in terms of total musculoskeletal system disability rate ($p=0.17$).

The mean age of patients was 53.12 years (minimum-maximum: 18-95, median: 50). Patients were divided into 3 groups according to their age: 18-24 age group was defined as "young," 25-64 age group as "adult," and 65 and over age group as "senior." The young group consisted of 19 patients, the adult group with 286 patients, and the senior group with 105 patients. The mean musculoskeletal system disability rate was 31.79% (minimum-maximum: 4-98%, median: 22%), 21.09% (minimum-maximum: 1-98%, median: 8%), and 38.23% (minimum-maximum: 4-98%, median: 24%) in the young, adult, and senior groups, respectively. The statistical analysis using the Kruskal-Wallis analysis revealed a significant difference between the 3 groups ($p<0.001$). The musculoskeletal system disability of the senior group was significantly higher than the adult group ($p<0.001$) (Table 1, 2).

The anatomical regions of patients that cause musculoskeletal disability were divided into 3 regions as upper extremity, lower extremity, and spine. The most frequently affected anatomical region is the lower extremity (232 patients, 56.59%) followed by the upper extremity (152 patients, 37.07%) and spine (117 patients, 28.54%).

The evaluation of patients in terms of disease diagnosis that caused musculoskeletal disability revealed that 410 patients were diagnosed with 436 diseases. The most common diagnosis that leads to musculoskeletal disability was neurological disease sequelae (23.62% of 103 patients) followed by traumatic injuries (21.33% of 93 patients). The detailed distribution according to the diagnoses is shown in Table 3. The evaluation of diagnoses according to age groups revealed that the most common diagnoses in the young group are traumatic injuries (33.3%) and neurological disease sequelae (33.3%), whereas traumatic injuries (24.10%) in the adult group and degenerative disease sequelae (44.14%) in the senior group.

Discussion

With an increased care condition, the demand for health services increases in parallel with the increased number of the disabled population and increased life expectancy. Disabilities affect people, especially in medical, psychological, and physical aspects (6). Physiological effects are especially the result of pathologies that concern the musculoskeletal system. A few original research has been conducted to describe the musculoskeletal disability in the Turkish population. However, knowing the content of disabilities will pave the way for the development of physical and social support projects that will be necessary for many steps, from prevention to rehabilitation.

Musculoskeletal disability is one of the most common causes of disability (7). Koçak et al. (8) revealed that the most common causes of disability were cardiovascular, musculoskeletal, and visual system pathologies. Our study revealed that the most common causes of musculoskeletal disability are neurological disease sequelae, traumatic injuries, and degenerative diseases. A Kocaeli-based study from our country revealed that the most common pathologies include degenerative diseases and neurological disease sequelae (9).

Aging also increases degenerative diseases. Arslan and Kutsal (10) revealed osteoarthritis as the second most common cause of disability in geriatric patients. Our study revealed a significantly higher disability rate of the senior group than the adult group. The most common diagnoses include degenerative disease sequelae in the senior group, which supports our current opinion.

Musculoskeletal disabilities are thought to physically affect people; however, they can affect many systems of the body. Psychologically, Razuvaeva et al. (11) revealed that people with musculoskeletal

Table 1. Evaluation of disability rates by age groups (*according to the Kruskal-Wallis analysis)

Musculoskeletal system disability	Young group	Adult group	Senior group
Rate (%)	31.79	21.09	38.23
Standard deviation (±)	28.36	17.34	14.02
Median (%)	22	8	24
Minimum-maximum (%-%)	4-98	1-98	4-98
p-value*	-	p<0.001	-

Table 2. Comparison of disability rates by age groups (*according to the Mann-Whitney U analysis)

	Young group-adult group	Young group-senior group	Adult group-senior group
p-value*	0.095	0.162	p<0.001

Table 3. Distribution of musculoskeletal disabilities by age groups and diagnoses

	Young group		Adult group		Senior group		Total	
Diagnosis	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Cervical discopathy	0	0.00	28	9.12	3	2.70	31	7.11
Traumatic injury	6	33.33	74	24.10	13	11.71	93	21.33
Lumbar discopathy	0	0.00	56	18.24	7	6.31	63	14.45
Degenerative disease	0	0.00	39	12.70	49	44.14	88	20.18
Congenital disease	4	22.22	18	5.86	1	0.90	23	5.28
Acquired deformity	1	5.56	8	2.61	1	0.90	10	2.29
Neurologic disease	6	33.33	65	21.17	32	28.83	103	23.62
Rheumatologic disease	0	0.00	6	1.95	0	0.00	6	1.38
Vascular disease	0	0.00	7	2.28	5	4.50	12	2.75
Chronic infection	0	0.00	1	0.33	0	0.00	1	0.23
Tumor	1	5.56	5	1.63	0	0.00	6	1.38
Total	**18**	**100**	**307**	**100**	**111**	**100**	**436**	**100**

disabilities have the low adaptive capacity, high neuropsychic stress, low self-regulation, and no ability to plan conscious activities. Additionally, it can cause secondary comorbidities, such as obesity, hypertension, and pressure sores (12). Therefore, the need for medical support and rehabilitation of people with disabilities is high. According to the study of Yöndemli (13), the need for rehabilitation in people with disabilities is 29.8%.

As in our study, such descriptive studies will guide the necessary projects for the problems of patients with musculoskeletal disabilities. One of the important problems of people with musculoskeletal disabilities is the obstacles they encounter in doing active sports. In 2010, Gegenwarth and Reinelt (14) developed suitable equipment for people with a musculoskeletal disability as defined in their society to do winter sports.

Disability diagnosis is made with the health reports prepared by the disability health boards in our country. However, the increased number of disabled patients over the years increased the amount of work in health boards. Therefore, people with disabilities experience problems. Additionally, recent studies focused on computer-aided diagnosis methods. Öztuna and Elhan (15) used a computer-assisted method to determine the disability in low back pain and osteoarthritis pathologies and detected a high degree of compatibility. Thus, a transition to these methods may occur in the future.

Study Limitations

Our study limitations include its retrospective design, single-center, and registry data basis. The inclusion of many health institutions from many regions in such descriptive studies will provide a more objective distribution.

Conclusion

Our study revealed that musculoskeletal disabilities especially affect the lower extremities. Elderly patients have a higher disability rate than adult patients. No difference was found between genders in terms of disability rate. The most common causes in etiology include neurologic disease sequelae, traumatic injuries, and degenerative diseases. Lower extremity disabilities also affect patients' mobility and lead to necessary social support. Therefore, these data should be considered in planning for future projects for the disabled.

Ethics Committee Approval: Our study approval was obtained from the "University of Health Sciences Turkey, İstanbul Training and Research Hospital Clinical Research Local Ethics Committee" (approval number: 2854, date: 04.06.2021).

Informed Consent: An informed consent form was obtained from all patients or their legal representatives.

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The Relationship Between Vertebral Artery Hypoplasia and Posterior Circulation Stroke

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ABSTRACT

Introduction: Vertebral artery hypoplasia (VAH) is a common variation; however, its role in posterior circulation stroke (PCS) has not been fully elucidated. Thus, this study aimed to evaluate the relationship between VAH and PCS with clinical and laboratory parameters.

Methods: Between January 2016 and June 2020, 178 patients with PCS who were hospitalized in the neurology department were included. The demographic characteristics, vascular risk factors, stroke patterns, and the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) scores of patients were recorded. Patients with VA diameter of ≤2.0 mm or 1:1.7 ratio difference in computed tomography angiography were included in the VAH group.

Results: This study included 115 females and 63 males. The mean age of patients was 65.8±12 years. VAH was determined in 74 (41.6%) patients, whereas none in 104 patients (58.4%). No significant difference was determined in terms of gender and age in patients with and without VAH (p=0.310 and p=0.676, respectively). No statistically significant difference was found between the two groups in terms of vascular risk factors (p>0.05). Lacunar stroke pattern was less frequently found in patients with VAH (p=0.045). Other stroke patterns were similar in both groups (p>0.05). The NIHSS (p=0.01) and mRS (p=0.018) scores were significantly higher in patients with VAH than those without.

Conclusion: The presence of VAH in PCS may adversely affect the clinical severity.

Keywords: Vertebral artery hypoplasia, posterior circulation stroke, clinical severity, stroke pattern

Introduction

Posterior circulation stroke (PCS) occurs within the vascular region of the vertebrobasilar arterial system. Anatomical variations are very common in the posterior circulation vessels, and the vertebral arteries, particularly, are highly variable in diameter, length, and course (1,2). Vertebral artery hypoplasia (VAH) is a common embryonic variation of the posterior circulation (mostly seen in the right) with reported frequencies between 1.9% and 26.5%. Despite its high prevalence, relatively little information is known about the clinical significance of VAH (3).

VAH has become the focus of interest in many studies that showed it as a predisposing factor for stroke, especially when accompanied by atherosclerotic risk factors (4,5). However, some uncertainties are still presented. First of all, VAH has no standard definition; currently, VA diameters ranging from 2 to 3 mm or asymmetry ratios of ≥1:1.7 have been identified in different studies. Moreover, the role of VAH as a stroke risk factor remains controversial, while its etiology and pathogenesis are unclear (6).

PCS may present with a wide range of clinical signs due to the alterations in the vertebrobasilar system and the clinical severity of the stroke itself. This situation makes the diagnosis difficult for vascular neurologists (1,6). Studies that suggested an association between VAH and PCS are mainly prevalence-based and provide data in the context of relationships between risk factors and PCS (7-11). A limited number of studies demonstrated the clinical severity of VAH and PCS (12-14). Therefore, our study aimed to evaluate the relationship between VAH and PCS and determine the extent of their clinical association.

Methods

Patients

We retrospectively screened all patients with an acute ischemic stroke who are admitted to our clinic between January 2016 and June 2019. Among the patients with a definite acute ischemic stroke diagnosis with diffusion-weighted imaging, patients with PCS and computed

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tomography angiography (CTA) taken within 1 week of admission were included in the study. Patients with bilateral VAH, vertebral artery dissection, total occlusion, and hemorrhagic infarction and patients with lacking information about the initial National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) score were excluded from the study, thus a final total of 178 patients were included. The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee (approval number: 1855, 24.05.2019).

The demographic characteristics and vascular risk factors [diabetes mellitus (DM), cardiac disease, hyperlipidemia, smoking, and arterial hypertension] of patients were recorded. The ischemic lesion patterns were radiologically grouped as territorial, embolic (>1.5 cm in diameter or a single lesion that affects a vascular site with multiple acute lesions), and lacuna (isolated lesion with a diameter of ≤1.5 cm). Additionally, posterior circulation ischemic lesions were divided into the following five groups based on anatomy: bulbus, pons, mesencephalon, cerebellum, and occipital (Table 1).

Clinical Assessment

Stroke severity was measured by the NIHSS score (range: 0-42) and mRS-a neurological functional disability scale-ranging from 0 to 6 at 90 days after stroke.

Vessel Analysis

A Toshiba Aquilium 64 CT Scanner (Toshiba Medical Systems Corporation, Shimoishigami, Japan) was used for all head and neck CTA scans (120 kV, 494 mA, 0.5 mm thickness, 40 cm FOV, 25.9 cm reconstruction diameter, 512×512 matrix, and 500 ms exposure time). Bolus triggering was used for optimum enhancement with the administration of 350 mgI/mL contrast media at a rate of 4-5 mL/s. Multiplanar reformations, three-dimensional volume renderings, maximum-intensity projections, and curved planar reformations were post-processed from the source images obtained from the aortic arch to the vertex.

The CTA images of all patients were evaluated based on the VAs. VAH was defined as follows: diameter of ≤2.0 mm or a difference in diameter with the contralateral side that is >1:1.7 (3,10,11).

Statistical Analysis

For descriptive statistics, mean, standard deviation, median, minimum, and maximum values were used for quantitative variables, and frequency and percentage values were used for qualitative variables. The distribution of variables was measured using the Kolmogorov-Smirnov test. Independent samples t-test and the Mann-Whitney U test were used depending on distribution normality for the analysis of quantitative independent data. The chi-square test was used for the analysis of qualitative independent data and the Fisher's test when data did not meet the chi-square assumptions. All statistical analyses were performed using the Statistical Package for the Social Sciences version 22.0 software (SPSS Inc., Chicago, IL, USA). A p-value of ≤0.05 was considered significant.

Results

Of the 178 patients with acute PCS, 115 (64.6%) were female and 74 (41.6%) were diagnosed with VAH. No significant difference was found in gender (female/male: 51/23 vs 64/40, p=0.310) and age (65.4±10.6 vs 66.1±12.9, p=0.676) distribution of the groups with and without VAH. Among the patients with VAH, 44 (59.5%) had right-sided.

No statistically significant difference was found between the two groups in terms of vascular risk factors (hypertension, DM, hyperlipidemia, coronary artery disease, and smoking) (p>0.05).

The NIHSS score was 3.8±2.9 and mRS was 1.6±1.1 in patients with VAH, whereas 2.4±1.7 and 1.2±0.9 in the patients without VAH, respectively. The NIHSS (p=0.01) and mRS (p=0.018) scores were significantly higher in patients with VAH compared to patients without VAH.

In terms of the stroke patterns, the lacunar stroke pattern was significantly more common in patients without VAH (p=0.045), while other stroke patterns were similar in both groups (p>0.05). Posterior circulation infarct localization did not significantly differ in the patients with and without VAH (p>0.05) (Table 2).

Table 1. Characteristics of the study group

		Minimum-maximum	Mean ± SD/(n, %)
Age		28.0-89.0	65.8±12.0
Gender	Female	-	115 (64.6%)
	Male	-	63 (35.4%)
VAH	(+)	-	74 (41.6%)
	(-)	-	104 (58.4%)
Right VAH		-	44 (59.5%)
Left VAH		-	30 (40.5%)
Clinical assessment			
NIHSS		0.0-15.0	3.0±2.5
mRS		0.0-5.0	1.4±1.0
Risk factors			
Hyperlipidemia		-	116 (65.2%)
Diabetes		-	73 (41.0%)
Arterial hypertension		-	121 (68.0%)
Cigarette smoke		-	52 (29.2%)
Coronary heart disease		-	38 (21.3%)
Stroke pattern			
Territorial		-	82 (46.0%)
Lacunar		-	53 (29.8%)
Embolic		-	43 (24.2%)
Location of infarction			
Medulla oblongata		-	23 (12.9%)
Pons		-	74 (41.6%)
Mesencephalon		-	8 (4.5%)
Cerebellum		-	56 (31.5%)
Occipital lobe and thalamus		-	28 (15.7%)

SD: Standard deviation, VAH: vertebral artery hypoplasia, NIHSS: National Institutes of Health Stroke Scale, mRS: modified Rankin Scale

Table 2. Demographics, clinical characteristics, and clinical outcome of patients concerning VAH presence/absence

		VA hypoplasia (+) (n=74)	VA hypoplasia (-) (n=104)	p	
Age		65.4±10.6	66.1±12.9	0.676	m
Gender	Female	51 (68.9 %)	64 (61.5%)	0.310	X^2
	Male	23 (31.1%)	40 (38.5%)		
Risk factors					
Hyperlipidemia		48 (64.9%)	68 (65.4%)	0.943	X^2
Diabetes		26 (35.1%)	47 (45.2%)	0.179	X^2
Arterial hypertension		48 (64.9%)	73 (70.2%)	0.453	X^2
Cigarette smoke		23 (31.1%)	29 (27.9%)	0.644	X^2
Coronary heart disease		16 (21.6%)	22 (21.2%)	0.940	X^2
Clinical assessment					
NIHSS score		3.8±2.9	2.4±1.7	**0.010**	m
mRS score		1.6±1.1	1.2±0.9	**0.018**	m
Stroke pattern					
Territorial		37 (48.6%)	45 (44.1%)	0.310	X^2
Lacunar		16 (21.1%)	37 (36.3%)	0.045	X^2
Embolic		23 (30.3%)	20 (19.6%)	0.069	X^2
Location of infarction					
Medulla oblongata		11 (14.9%)	12 (11.5%)	0.514	X^2
Pons		32 (43.2%)	42 (40.4%)	0.703	X^2
Mesencephalon		2 (2.7%)	6 (5.8%)	0.330	X^2
Cerebellum		27 (36.5%)	29 (27.9%)	0.240	X^2
Occipital lobe and thalamus		8 (10.8%)	20 (19.2%)	0.128	X^2

^{m}: Mann-Whitney U test, $^{X^2}$: chi-square test (Fischer's test), VAH: vertebral artery hypoplasia, Boldface values indicate significant results (p<0.05).

Discussion

This study assessed the association between VAH and PCS by retrospective analysis of patient data and revealed some similarities and differences from studies on this subject in the last 20 years, which seems to be a trend in studies of this type. However, the most important output of our study was the worse clinical severity in patients who suffered from posterior ischemic stroke in the presence of VAH. Despite the limitations that are present in this study and many studies in this field (due to the inability to perform population-based analyses), this is an important finding that could help in clinical settings.

VAH is common in society; however, there are differences between the prevalence values. The incomplete consensus on VAH definition and the use of different measurement methods [magnetic resonance angiography (MRA), CTA, and ultrasonography] in studies may explain the reason for these differences. A review by Katsanos and Giannopoulos (6) revealed that VAH was two times more common in PCS than in anterior system stroke. A study with 129 patients with acute stroke by Mitsumura et al. (8) identified 44.4% of VAH cases in patients with PCS. Similarly, among the 750 patients with stroke evaluated by Kulyk et al. (13), 193 have PCS and 33.7% of this group had VAH. Another similar percentage comes from a study by Park et al. (11), who revealed that VAH was present in 45.6% of patients with PCS. Our study revealed that 41.6% of patients had VAH. We could not perform direct comparisons with these previous studies because anterior system strokes were excluded from our study. However, our findings, at least, seem to be consistent with previous studies in terms of the relationship between PCS and VAH.

Previous studies have predominantly demonstrated the relationship between prevalence and risk factors (7-11). VAH has been studied in a limited number of studies in terms of clinical outcome, and these have not proposed any association with VAH and stroke severity (12-14). Kulyk et al. (13) revealed that mRS was similar in patients with and without VAH. Yang et al. (14) compared the NIHSS scores in patients with PCS (with and without VAH) and revealed no relationship. A study with 815 patients that had had an acute ischemic stroke, by Sauer et al. (12), revealed no significant difference between the median NIHSS and mRS scores in patients with and without VAH. However, when we look at the details of this study, comparisons were performed in the whole patient group (anterior and posterior) rather than separately (12). Our study revealed that the NIHSS score was 3.8±2.9 and the mRS score was 1.6±1.1 in patients with VAH. Both scores were significantly higher compared to those without VAH. These findings may provide a new perspective for the clinical severity of PCS with different clinical findings.

Considering the imaging-based studies that examine the relationship between PCS and VAH, Doppler ultrasonography (7,13,14) and MRA (5,9,13,14) are revealed as the most popular methods used. Doppler ultrasonography is a rapid and noninvasive technique for the assessment of vertebral arteries, but it may fail to identify aplasia, hypoplasia, occlusion, or dissection (15). CTA has been shown to have higher sensitivity and positive predictive value in detecting intracranial vessel stenosis and occlusion compared to MRA (16). Our study was performed with the CTA measurement method and we think that it gave more objective results in this sense compared to the other studies.

Different results have been obtained regarding the embolic stroke patterns in patients with VAH. Perren et al. (7) revealed that the embolic stroke pattern was more frequent in patients with VAH. Quite conversely, Sauer et al. (12) revealed that the embolic stroke pattern was less frequent in patients with VAH. Data is limited on this topic, as previously mentioned, and even available data seems to be biased; however, most were probably based on the clinical characteristics of patients, imaging modalities, and genetic/phenotypic differences. Our study revealed that the lacunar stroke pattern was less frequent in patients with VAH, and no differences were found regarding other stroke patterns. This situation can be explained by the possibility that risk factors contributing to the etiopathogenesis of lacunar stroke were more common among patients without VAH.

Many imaging studies have demonstrated that VAH may independently predispose patients to regional hypoperfusion in the posterior circulation (17). Other evidence from relevant research revealed that VAH may lead to ischemic events in the posterior circulation, especially when accompanied by other atherosclerotic risk factors (4,16,18). In our study, the evaluation of risk factors regarding the relationships revealed that none of the vascular risk factors were associated with a significant difference among the groups.

Study Limitations

Our study has some limitations. The number of patients was low to draw a generalized conclusion. However, there is very little conclusive data on this topic and available studies have not focused on the relationships between VAH and only PCS. Anterior group strokes were not included in the study by design, thus no comparison could be made concerning VAH frequencies. In a study, a 42% decrease of flow was detected in the posterior inferior cerebellar artery (PICA) territorial area of the ipsilateral VAH (3). Case reports and some studies revealed a relationship between VAH and ipsilateral PCS, especially PICA strokes (11). However, we did not evaluate the side of hypoplasia and the side of stroke. Additionally, long-term outcomes should be observed to better assess the clinical outcome and severity.

Conclusion

Our study results suggest a significant relationship between VAH and clinical severity of stroke in patients with PCS. Detailed prospective and clinical studies with larger groups will be useful to determine the relationship between VAH and clinical outcomes.

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee (approval number: 1855, 24.05.2019).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - Y.E.; Concept - U.E.; Design - Y.E.; Data Collection or Processing - Y.E., B.B., Ç.Ş., A.B.D.; Analysis or Interpretation - U.E., A.S.M.; Literature Search - Y.E.; Writing - Y.E., A.S.M., U.E.

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Attitudes and Behaviors of Gastroenterology Specialists Toward Sedation Practices in Endoscopy Units in Turkey: Is Anesthesia Mandatory?

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ABSTRACT

Introduction: At present, sedation and analgesia have become an integral part of gastrointestinal endoscopy. This study aimed to provide data on the attitudes and behaviors of gastroenterology specialists toward sedation practices in endoscopy units in Turkey.

Methods: This cross-sectional and descriptive study included a total of 744 gastroenterology specialists, who are members of the Turkish Gastroenterology Association. They were invited by e-mail to participate in the study. The questionnaire consisted of 18 items on sedation practices implemented during procedures in the endoscopy unit. Questionnaire responses were statistically analyzed.

Results: All patients who underwent endoscopic procedures, such as endoscopic ultrasound, endoscopic retrograde cholangiopancreatography, and endoscopic submucosal dissection, received sedation. The sedation rates were 97.9% (n=138) in colonoscopy and 72.3% (n=102) in gastroscopy. With regard to the frequency of sedation, 33 (23.4%) used sedation for all patients, 55 (39%) used it frequently, and 15 (10.6%) used it rarely. The current anesthesia team in endoscopy units consisted of anesthesiologists (53.2%) and anesthesia technicians (60.3%).

Conclusion: It is necessary to prepare guidelines on sedation use in endoscopy units to assist care providers and health managers in providing quality service.

Keywords: Gastrointestinal endoscopy, Turkey, survey, sedation practice

Introduction

Initially, endoscopic procedures were solely performed for diagnosis; however, they have recently been used frequently for therapeutic purposes. Such procedures are usually performed under sedoanalgesia in the supine, lateral, and prone positions. The quality of the sedoanalgesia and comfort it provides may vary depending on the practitioner's experience level and the drug combinations used.

At present, sedation and analgesia have become an integral part of gastrointestinal endoscopy. Sedation and analgesia aim to enable endoscopists to perform procedures safely and effectively by increasing patient satisfaction and compliance (1,2). However, the use of sedation in gastrointestinal endoscopy includes disadvantages such as prolonged procedure time, increased health care costs, and increased risk for cardiopulmonary complications, which appear as limiting factors (2).

Although various sedation and analgesia techniques are used for gastrointestinal endoscopy procedures, the gold standard is still debated. It is recommended to adapt sedation for each patient according to the clinical risk assessment and type of the planned procedure (3). In some countries, the use of some sedative/analgesic agents is limited to anesthesiologists. There is still ongoing debate about who should be responsible for the use of propofol for sedation. While some studies have reported that propofol can be used safely by an endoscopist for healthy individuals, other studies have disclosed that it can only be used by anesthesiologists trained in the administration of general anesthesia (4,5). Previous studies on sedation models adopted by endoscopists have demonstrated that patient-monitoring practices, such as sedation rates, preferred sedation regimens, and routine use of pulse-oximetry, vary worldwide (6-12).

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Research on endoscopic sedation is important in understanding "where we stand" and planning future strategies. Many national survey studies have been conducted worldwide on endoscopic sedation (6-13). These studies are also highly useful in evaluating the implementation of sedation guidelines in clinical practice (14). However, to the best of our knowledge, no domestic study has been conducted on endoscopic sedation and monitoring practices during gastrointestinal endoscopy in Turkey. Thus, this study aimed to provide data on the attitudes and behaviors of gastroenterology specialists toward sedation practices in endoscopy units in Turkey.

Methods

Study Design

Ethical approval for the study was obtained from Bezmialem Vakıf University Faculty of Medicine Clinical Research Ethics Committee (approval number: 21/30, date: 18.11.2015) and registered on clinicaltrials.gov (identifier: NCT03540238).

Study Protocol

This was a cross-sectional and descriptive study. A total of 744 gastroenterology specialists, who are members of the Turkish Gastroenterology Association, were invited via e-mail to participate in the study. Feedback was received from 141 of the 744 gastroenterology specialists who were sent the questionnaire. The responses were statistically analyzed.

The questionnaire consisted of 18 items on sedation use during procedures in the endoscopy unit (Appendix A). Survey questions were related to demographics, types of endoscopic procedures, anesthesia methods, anesthetic agents, monitoring methods, anesthesia team members, pre-anesthetic examination and consent forms, recovery unit, complications, and interventions during sedation.

Statistical Analysis

All statistical analyses were performed using the SPSS 22.0 software package (IBM Corp., Armonk, NY, USA). The sample size was calculated with around 20 individuals falling into each category of questions under the survey. Descriptive statistics of the obtained data were calculated as numbers and % frequencies and presented in Tables. The Fisher-Freeman-Halton test was used to analyze the change in the quality and/or type of people in the anesthesia team according to various factors. A p-value of <0.05 was considered significant.

Results

Demographic Characteristics

Of the 744 gastroenterology specialists invited to complete the questionnaire, 141 (18.95%) participated in the study. Analysis of the demographic characteristics of the participants demonstrated a higher rate of university practice hospital employees and young gastroenterologists who responded to our survey call (Table 1).

Anesthesia Method, Anesthetic Agents, Endoscopic Procedure, and Patient Characteristics

All respondents (100%) used sedation practices in endoscopy units. All patients who underwent endoscopic procedures, such as endoscopic ultrasound, endoscopic retrograde cholangiopancreatography and endoscopic submucosal dissection, received sedation, and the sedation rate was 97.9% (n=138) in colonoscopies and 72.3% (n=102) in gastroscopies. With regard to the frequency of sedation use, 33 (23.4%) used sedation for all patients, 55 (39%) used it frequently, and 15 (10.6%) used it rarely.

Practitioners did not use sedation in 86 (61%) patients who refused sedation, 74 (52.5%) patients with other diseases (cardiac, pulmonary, renal, etc.), 28 (19.9%) elderly patients, and 6 (4.3%) patients with anxiety (Table 2).

Among anesthesia methods, conscious sedation was used by 75.9%, deep sedation by 73%, general anesthesia by 14.2%, and local pharyngeal anesthesia by 65.2% of the respondents (Table 2).

The most commonly used anesthetic agent was midazolam (92.2%), followed by propofol (75.2%), fentanyl (23.4%), ketamine (9.9%), and remifentanil (5.7%) (Table 2).

Endoscopy Unit, Monitoring Methods, Oxygen Administration, Sedation Recovery Unit, and Preoperative Evaluation

Oxygen supply (100%), aspirator (98%), emergency trolley (91.5%), and monitor (90.8%) were available in all endoscopy units at a high rate.

Nasal oxygen was routinely administered to each patient (53.9%), and peripheral oxygen saturation was monitored (97.2%). Sedation recovery was achieved in a separate recovery unit (57.4%).

Table 1. Respondents' demographic characteristics

Demographic characteristics (n=141)		n (%)
Age group (year)	30-49	111 (78.7)
	50-64	29 (20.6)
	≥65	1 (0.7)
Gender	Male	102 (72.3)
	Female	39 (27.7)
Length of experience (years)	0-9	78 (55.7)
	10-19	44 (31.4)
	20-29	16 (11.4)
	≥30	2 (1.4)
Type of hospital	University	75 (53.2)
	Training and research	30 (21.3)
	State	15 (10.6)
	Private	21 (14.9)
Region	Marmara	76 (53.9)
	Aegean	10 (7.1)
	Central Anatolia	23 (16.3)
	Black Sea	7 (5.0)
	Mediterranean	11 (7.8)
	Eastern Anatolian	9 (6.4)
	Southeast	5 (3.5)
Hospital size (number of beds)	<300 (small)	32 (22.7)
	301-500 (medium)	22 (15.6)
	>501 (big)	87 (61.7)

Moreover, 66% performed pre-anesthetic evaluation before the procedure (n=93), and 87.2% routinely received written consent for sedation (n=123).

Anesthesia Team

The current anesthesia team in endoscopy units consisted of anesthesiologists (53.2%) and anesthesia technicians (60.3%). However, there was an increasing trend in endoscopists' preferences toward the presence of an anesthesiologist (86.5%) and anesthesia technician (81.6%), whereas a decrease was observed in the preference rates for nurses and other health personnel.

Anesthesia-Related Complications, Frequency of Code Blue, and Causes of Mortality

Desaturation (88.7%) was the most common anesthesia-related complication, whereas respiratory arrest was the most common (32%) cause of mortality. "Code blue" in the endoscopy unit was observed once a year (56.7%) and once a month (12.8%). In addition, 17.7% (n=25) of gastroenterology specialists encountered complications that resulted in mortality.

Relationship Between Anesthesia Team and Sedation Practices

A significant positive correlation was found among centers where anesthesia technicians are present during sedation practices and general anesthesia and deep sedation, midazolam, ketamine, fentanyl and remifentanil use, electrocardiogram (ECG), non-invasive blood pressure, and bispectral index monitoring.

A significant positi ve correlation was found among centers where anesthesia technicians are present during sedation practices and general anesthesia, use of propofol and fentanyl, and use of ECG and non-invasive blood pressure monitoring.

A significant positive relationship was found among centers where nurses are present during sedation practices and conscious sedation.

Those with a code blue frequency of once yearly had a significantly lower frequency of having an anesthesiologist in their team. Those

Table 2. Anesthesia method and anesthetic agents, endoscopic procedure, and patient characteristics

Frequency of sedation use	**n (%)**
All patients	33 (23.4)
Usually	38 (27)
Often	55 (39)
Rarely	15 (10.6)
Patients deemed unfit for sedation	
Patients who refuse sedation	86 (61)
Patients with additional diseases (cardiac, pulmonary, renal etc.)	74 (52.5)
Elderly patients	28 (19.9)
Patients without anxiety	6 (4.3)
Other causes	6 (4.3)
Anesthesia methods	**n (%)**
Conscious sedation	107 (75.9)
Local pharyngeal anesthesia	92 (65.2)
Deep sedation	103 (73)
General anesthesia	20 (14.2)
Anesthetic agent	
Midazolam	130 (92.2)
Propofol	106 (75.2)
Fentanyl	33 (23.4)
Ketamine	14 (9.9)
Remifentanyl	8 (5.7)
Others	10 (7.1)

Table 3. Endoscopy unit, monitoring methods, oxygen administration, sedation recovery area, pre-anesthetic evaluation and consent forms

Equipment	**n (%)**
Oxygen supply	141 (100)
Aspirator	139 (98)
Emergency trolley	129 (91.5)
Monitor	128 (90.8)
Defibrillator	92 (65.2)
Appropriate area with sufficient width	72 (51.1)
Anesthesia device	61 (43.3)
Perfusor	22 (15.6)
Monitoring method	**n (%)**
Peripheral oxygen saturation	137 (97.2)
Non-invasive blood pressure	68 (48.2)
ECG	64 (45.4)
BIS monitoring	8 (5.7)
Capnography	0 (0)
Nasal oxygen administration	**n (%)**
All patients	76 (53.9)
Only desaturated patients	46 (32.6)
Only high-risk patients	32 (22.7)
None	3 (2.1)
Sedation recovery area	**n (%)**
In recovery unit	81 (57.4)
At the operation site	54 (38.3)
In the waiting room	11 (7.8)
In the department	7 (5)
Pre-anesthetic examination	**n (%)**
Yes	93 (66.0)
No	48 (34.0)
Anesthesia consent forms	**n (%)**
We have written consent forms, and I routinely ask patients to complete and sign them.	123 (87.2)
We have written consent forms, but I do not ask all patients to complete and sign them.	17 (12.1)
We do not have written consent forms, and I do not receive written consent from patients.	1 (0.7)

with a code blue frequency of once monthly and once yearly had a significantly higher frequency of having a nurse in their team.

Discussion

Based on our literature review, we think that our study is the first national survey to evaluate sedation practices in endoscopy units in Turkey. With a response rate of 18.95% (141/744), the results of our study were similar to those of Germany (17%), Korea (22.7%), USA (27%), and Portugal (26%) according to gastroenterologists' response rates to survey request. However, it was lower than those of Spain (65%), Switzerland (78%), Italy (41%), and Greece (40%) (6-8,11,12,14-17).

In our study, sedation practices were applied in the majority of the endoscopy units in Turkey; however, sedation was applied to 72% of the patients (33% for each patient, 39% frequently). This rate was lower than that in the USA (98%) and Germany (82% for gastroscopy and 91% for colonoscopy), similar to that in Greece (68.2%, 2015) (74.8%, 2018), and higher than those in China (48.3%) and India (36.8%) (14,18-21). Available studies have shown that the sedation rate mainly differs according to the hospital type and economic conditions (12,18). In addition to these factors, we think that restricted time because of the high number of patients can be included as one of the reasons that negatively affect our sedation rate.

Table 4. Anesthesia team members

Anesthesia team	**n (%)**
Anesthesiologist	75 (53.2)
Anesthesia technician	85 (60.3)
Nurse	81 (57.4)
Other	24 (17)
Who do you think the anesthesia team should consist of?	**n (%)**
Anesthesiologist	122 (86.5)
Anesthesia technician	115 (81.6)
Nurse	70 (49.6)
Other	3 (2.1)

Table 5. Anesthesia-related complications, frequency of code blue, and causes of mortality

Complications	**n (%)**
Desaturation	125 (88.7)
Bradyarrhythmias	29 (20.6)
Hypotension	25 (17.7)
Nausea/vomiting	13 (9.2)
Other	2 (1.4)
Frequency of code blue	**n (%)**
Once a year	80 (56.7)
Once a month	18 (12.8)
Once a week	2 (1.4)
Other	41 (29.1)
Cause of mortality (n=25)	**n (%)**
Respiratory arrest	8 (32)
Cardiac-related causes	6 (24)
Anaphylactic shock	4 (16)
Hypotension	2 (8)
Bleeding varicose	2 (8)
Anesthesia	1 (4)
Cerebrovascular event	1 (4)
Pacemaker asystole	1 (4)

In India, a study reported therapeutic procedures, high-risk procedures, and patient request as patient selection criteria for sedation (13). In our study, 86 (61%) patients who refused anesthesia and 74 (52.5%) who had other diseases (cardiac, pulmonary, renal, etc.) were included in the patient group in which gastroenterology specialists did not prefer to use sedation. Both studies did not consider advanced age an important criterion for deciding on sedation. In our study, advanced age was another reason for not preferring sedation with a rate of 28%, which was consistent with the literature.

Many studies have investigated anesthetic agents used in endoscopic sedation. These studies show significant differences in drug preference according to the person responsible for the use of sedation. It is universally accepted that midazolam can be used without an anesthesiologist. However, the use of propofol without an anesthesiologist can vary between 0% and 100% depending on the country (7,8,11,15,16). Propofol has advantages in terms of shorter eye-opening and postanesthetic recovery time and higher patient and doctor satisfaction (1,22). However, its potential to cause hemodynamic and respiratory depression is a matter of concern (19). The most commonly used sedative and analgesic agents are propofol (61%) and fentanyl (36.3%) in China, midazolam (52.6%) in India, propofol (24%) in Germany, propofol alone or in combination with midazolam in Korea and Portugal (55.6%), and propofol in Greece (30.8%) (18,19-24). These differences can be explained by medical and legal concerns. Some of these countries allow non-anesthesiologists to perform sedation in gastrointestinal endoscopy. In such cases, sedation is administered by nurses, endoscopists, or other trained personnel. Surveys conducted in the USA, Italy, and Portugal showed that propofol use was almost entirely administered by anesthesiologists, whereas surveys from Germany and Spain showed that propofol was almost entirely administered by non-anesthesiologists (7,11,12,15,16). In our study, the most commonly used anesthetic agents were midazolam (92%) and propofol (75%). A higher rate of propofol use compared with the rate of having an anesthesiologist during endoscopy (53.2%) reflects the use of propofol by gastroenterology specialists. While the American Society for Gastrointestinal Endoscopy and European Society of Gastrointestinal Endoscopy have guidelines for sedation in gastrointestinal endoscopy, unfortunately, we have not found any domestic guidelines published by a relevant association, which leads to applications according to personal preferences in different regions of the country (23,24).

According to our survey results, the most common monitoring method was monitoring of peripheral oxygen saturation (SpO_2, 97%), consistent with those in several other countries (7,11,12,17,25). Despite its widespread use, the SpO_2 can show higher oxygen levels than the arterial oxygen value, even if severe alveolar hypoventilation occurs (20). Continuous capnographic monitoring is recommended by the American Society of Anesthesiologists (ASA) to evaluate the adequacy of ventilation

Table 6. Relationship between the anesthesia team and sedation practices

		An anesthesiologist is present		An anesthesia technician is present		A nurse is present	
	Top	**n (%)**	**p**	**n (%)**	**p**	**n (%)**	**p**
Anesthesia method							
Conscious sedation	107	53 (49.5)	0.088	61 (57)	0.113	66 (61.7)	**0.049**
Deep sedation	103	62 (60.2)	**0.005**	66 (64.1)	0.094	58 (56.3)	0.400
General anesthesia	20	19 (95)	**<0.001**	17 (85)	**0.011**	13 (65)	0.314
Local pharyngeal anesthesia	92	46 (50)	0.194	54 (58.7)	0.366	56 (60.9)	0.172
Anesthetic agents							
Midazolam	130	65 (50)	**0.008**	77 (59.2)	0.294	77 (59.2)	0.124
Propofol	106	61 (57.5)	0.054	76 (71.7)	**<0.001**	62 (58.5)	0.404
Ketamine	14	13 (92.9)	**0.001**	11 (78.6)	0.116	9 (64.3)	0.402
Fentanyl	33	30 (90.9)	**<0.001**	29 (87.9)	**<0.001**	19 (57.6)	0.575
Remifentanyl	8	8 (100)	**0.005**	7 (87.5)	0.103	7 (87.5)	0.076
Other	10	7 (70)	0.220	0	**<0.001**	3 (30)	0.069
Monitoring							
ECG	64	49 (76.6)	**<0.001**	44 (68.8)	**0.044**	33 (51.6)	0.132
Non-invasive blood pressure	68	51 (75)	**<0.001**	53 (77.9)	**<0.001**	38 (55.9)	0.424
Peripheral O_2 saturation	137	72 (52.6)	0.360	82 (59.9)	0.479	78 (56.9)	0.430
Capnography	0	0 (0)	-	0	-	0 (0)	-
Bispectral index	8	7 (87.5)	**0.047**	7 (87.5)	0.103	1 (12.5)	0.100
Oxygen administration							
All patients	76	43 (56.6)	0.241	50 (65.8)	0.102	46 (60.5)	0.265
Only desaturated patients	46	21 (45.7)	0.143	25 (54.3)	0.206	26 (56.5)	0.510
High-risk patient	32	19 (59.4)	0.276	15 (46.9)	0.061	14 (43.8)	0.058
None	3	2 (66.7a)	0.548	1 (33.3)	0.347	2 (66.7)	0.612
Code blue frequency							
Once a year	80	34 (42.5b)		48 (60)		56 (70.0b)	
Once a month	18	11 (61.1a)	**0.018**	11 (61.1)	0.868	9 (50.0b)	**0.002**
Once a week	2	1 (50ab)		2 (100)		0 (0.0a)	
Other	41	29 (70.7)		24 (58.5)		16 (39.0a)	

(21). However, capnographic monitoring was not performed in any center included in our survey. We believe that future guidelines will help increase its implementation with the conveyance of the importance of capnographic monitoring.

In our study, blood pressure and ECG monitoring rates were 45-48% in the follow-up of cardiac effects. Blood pressure and ECG follow-up were performed in India (42.1%), Italy (30%), and China (79.3% and 76.5%, respectively) (11,13,25). We believe that low ECG rates result from the fact that ECG monitoring requires a specific perspective and assistant health personnel trained in this regard (device setup and electrode placement). A review of competent association guides in these fields demonstrates that ECG is considered among basic monitoring methods. Despite these guidelines, a low rate of ECG monitoring applied by practitioners may also cause medicolegal problems.

In our survey, supplemental nasal oxygen administration was routinely preferred (53%). The use of supplemental oxygen has been associated with a reduced incidence of hypoxemia during moderate sedation (26-29). It is also recommended by the ASA (19). Continuous nasal oxygen is applied in China (95.5%), whereas nasal oxygen is administered in Korea (52.6%), Italy (39.3%), and USA (72.7%) (7,11,17,25). This rate was 76% in the present study.

We found that necessary emergency equipment such as oxygen supply (100%), aspirator (98%), emergency vehicle (91.5%), and monitor (90.8%) were provided at a high rate, whereas the rate of defibrillator availability (65.2%) was relatively lower. These rates were higher than those of China and Greece and similar to India (13,25,30). Generally, one should watch out for potentially fatal side effects of sedation and consider safety parameters. Emergency equipment should be provided to ensure patient safety.

A preoperative pre-anesthetic evaluation was performed by 66% of the respondents, whereas 34% did not perform a pre-anesthetic evaluation. A survey conducted in Korea with a similar rate (38.3%) found that the practitioners never used the ASA classification for preprocedural evaluation or they seldom used it (17). High ASA classification, a definite risk factor for complications, is now recommended as an important quality indicator for all gastrointestinal endoscopic procedures.

We found that anesthesia technicians (60.3%) constituted the majority of the anesthesia team, followed by nurses (57.4%) and anesthesiologists (53.2%). However, when asked about the preferences of gastroenterology specialists, the majority (86.5%) preferred an anesthesiologist. In another survey study, with regard to preference for sedation to be administered by an anesthesiologist for endoscopic procedures, the majority of the respondents (68% versus 32%) stated that they would prefer the presence of an anesthesiologist (8). The high demand for the administration of sedation by an anesthesiologist was associated with concerns regarding medicolegal and patient comfort.

The most common complication during sedation was desaturation (88.7%), and code blue occurred once yearly at 56.7% and once monthly at 12.8%. Moreover, 17.7% (n=25) of the gastroenterology specialists encountered complications that resulted in mortality. Among the causes of mortality, respiratory arrest had a rate of 32%. These results highlight the importance of close monitoring of vital signs and airway management during sedation. Necessary interventions should be performed when required. The risks for patients and physicians increase when ambient light is reduced during endoscopy procedures, the endoscopist concentrates on the procedure, and a nurse working with endoscopist's directives is present. The results of our survey also reveal the importance of such awareness.

Study Limitations

This study provides an insight into current national approaches toward sedation use in gastrointestinal endoscopy. However, this study has some considerable limitations. First, only 18.95% of the associate members responded to our survey; therefore, the results may not fully reflect the overall situation in Turkey. Second, a significant majority (53%) of the gastroenterologists responding to our survey worked in university hospitals, and a substantial portion consisted of young physicians (30-49 years old, 78.7%). Such sample heterogeneity can be considered a limiting factor in adapting our results to the whole country. Moreover, this survey type bears several well-known systematic biases, such as recall bias and self-report bias.

Conclusion

We believe that our study provides an insight into current sedation practices in endoscopy units where procedural complexity is experienced. We observed that gastroenterology specialists prefer a competent anesthetist to administer sedation during the procedure. We also determined that those without such an opportunity acted based on their personal experiences on how to proceed. We believe that it is necessary to prepare guidelines on sedation use in endoscopy units to assist care providers and health managers in providing quality service.

Ethics Committee Approval: Ethical approval for the study was obtained from Bezmialem Vakıf University Faculty of Medicine Clinical Research Ethics Committee (approval number: 21/30, date: 18.11.2015).

Informed Consent: Informed consent wasn't obtained.

Peer-review: Externally peer-reviewed.

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Appendix A. Survey form

Attitudes and behaviors of gastroenterology specialists toward sedation practices in endoscopy units in turkey: is anesthesia mandatory?

Dear Gastroenterology Specialist:

Our survey invites all gastroenterology specialists in Turkey to respond questions regarding sedation practices you apply in endoscopy units. Through this survey, we aim to determine national sedation practices and experiences and preferences of gastroenterology specialists in endoscopy units.

Thank you for participating in our 10-minute survey.

- Age:

- Gender: Female..... Male.....

- Length of experience as a gastroenterology specialist: .....

- What type of hospital are you working in? University ..... Training and Research ..... State ..... Private .....

- Province: .....

- Number of beds in the institution: .....

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1. In your endoscopy unit, do you use sedation for patients during diagnostic and/or therapeutic procedures, interventions, and operations?

a. Yes
b. No

2. If yes, how often do use it?

a. Every time
b. Usually
c. Frequently
d. Rarely

3. Is there a specific patient group for which you do not prefer to use sedation?

a. Patients who refuse sedation
b. Elderly patients
c. Patients without anxiety
d. Patients with other diseases (cardiac, pulmonary, renal etc.)
e. Other (……)

4. In which procedures and interventions is sedation used in the endoscopy unit?

a. Gastroscopy
b. Colonoscopy
c. EUS

d. ERCP

e. ESD

f. Other (……)

5. Which sedation method or methods are used in the endoscopy unit?

a. Conscious sedation

b. Deep sedation

c. General anesthesia

d. Local pharyngeal anesthesia

e. Other (……)

6. Which agent or agents do you prefer the most for patients undergoing sedoanalgesia in the endoscopy unit?

a. Midazolam

b. Propofol

c. Ketamine

d. Etomidate

e. Thiopental

f. Fentanyl

g. Alfentanyl

h. Remifentanyl

i. Other (……)

7. What facilities and equipment are available in the endoscopy unit where you apply sedation?

a. Oxygen supply

b. Aspirator

c. Anesthesia device

d. Defibrillator

e. Monitor

f. Perfusor

g. Emergency trolley

h. Appropriate area with sufficient width

8. Which monitoring methods do you use as part of your sedation practices in the endoscopy unit?

a. ECG

b. Non-invasive blood pressure

c. Invasive arterial monitoring

d. Peripheral oxygen saturation

e. Capnography

f. TOF monitoring

g. Arterial blood gas analysis

h. BIS monitoring

i. Other (……)

9. Do you apply nasal cannula oxygenation to all patients in the endoscopy unit?

a. All patients

b. Only desaturated patients

c. Only high-risk patients

d. None

10. Who among the following is included in the anesthesia team of the endoscopy unit of your current institution?

a. Anesthesiologist

b. Anesthetic technician

c. Nurse

d. Other (……)

11. Who do you think the anesthesia team should consist of?

a. Anesthesiologist

b. Anesthetic technician

c. Nurse

d. Other (……)

12. Do you perform pre-anesthesia examination by listing patients to be sedated in the endoscopy unit?

a. Yes

b. No

13.Do you receive written consent from patients you sedate in the endoscopy unit or from their legal guardians for those who are unable to give consent, and do you have written informed consent forms?

a. We have written consent forms, and I routinely ask patients to complete and sign them.

b. We have written consent forms, but I do not ask all patients to complete and sign them.

c. We do not have written consent forms, and I do not ask patients to sign them.

14. Where do you compile outpatient data who received sedation in the endoscopy unit?

a. Operation site

b. Department

c. Waiting room

d. Recovery unit

e. Other (……)

15. What is the most common intraoperative complication you encounter in the endoscopy unit?

a. Desaturation

b. Hypotension

c. Bradyarrhythmias

d. Nausea/vomiting

e. Other (……)

16. What is the frequency of code blue in the endoscopy unit?

a. Everyday
b. Once a week
c. Once every 2 weeks
d. Once a month
e. Once a year
f. Other (……)

17. Have you encountered anesthesia-related complications resulting in mortality in the endoscopy unit?

a. Yes
b. No

18. For those who responded yes to question 18, what was the cause(s) of mortality?

(……
……)

THANK YOU

EUS: Endoscopic ultrasound, ERCP: endoscopic retrograde cholangiopancreatography, ESD: endoscopic submucosal dissection, BIS: bispectral index, TOF: train-of-four

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Evaluation of Vaginal Culture Results in Recurrent Vaginitis

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ABSTRACT

Introduction: Vaginitis is one of the most common complaints of women who present to health institutions. This study aimed to evaluate the results of vaginal culture obtained from patients who were admitted to the outpatient clinic because of recurrent vaginitis.

Methods: Patient records including vaginal culture results of patients aged 18-49 years who were admitted to the gynecology outpatient clinics of the University of Health Sciences Turkey, İstanbul Training and Research Hospital between January 2018 and June 2020 with the complaint of recurrent vaginitis were analyzed retrospectively.

Results: The mean age of the 206 patients included in the study was 34.4±12.2 years. Of the 206 vaginal cultures, 124 (60,1%) were negative and 82 (39.8%) were culture positive. Thirty-four patients (16,5%) had mixt microorganisms, 22 had Candida species (10,6%) and 11 had Gardnerella vaginalis (5,3%). Various bacteria were isolated in 15 patients.

Conclusion: The rate of vaginitis recurrence and type of microorganism detected can be affected by various factors such as sociocultural structure, race, education level, and contraception method. Only a few studies examined vaginal culture results in patients with recurrent and persistent vaginitis in general and in Turkey. In this study, the contribution of vaginal culture to patient management was limited in this patient group; moreover, the incidence of recurrent vaginitis was lower in women who were using the barrier method.

Keywords: Vaginitis, Candida, *Gardnerella vaginalis*, Trichomonas

Introduction

Vaginitis is a state of vaginal infection and inflammation with symptoms such as itching, burning, dyspareunia, abnormal vaginal discharge and bad odor (1). It is one of the most common reasons for women to apply to a health institution (2). Pain and discomfort may result in significant loss of work force, absenteeism from school, and sexual dysfunction (1). In patients with vaginal symptoms, 20-25% candida, 40-50% bacterial vaginosis (BV) and 15-20% trichomonas have been found to be causative agents, but some patients may not be able to show an agent (1,3,4).

There are no symptoms that have sufficient predictive value to definitively diagnose infectious diseases, but they can help the diagnosis (3). Microscopic examination of fresh saline preparation in vaginitis is the most practical way to confirm the diagnosis (3). Because of the heterogeneity of the vaginal flora, culture is not recommended in the diagnosis of BV (1). The diagnosis of vulvovaginal candidiasis is made by detecting yeast, spores, and pseudohyphae in fresh saline preparation microscopy in patients with clinical suspicion and normal pH (sensitivity 60-70%) (1,3). In treatment planning for vulvovaginal candidiasis with negative microscopy or complicated vulvovaginal candidiasis [recurrent (4 or more attacks in 12 months), severe vulvovaginal candidiasis, suspected to be caused by non-albicans species, seen in immunocompromised patients such as pregnant, uncontrolled diabetes, human immunodeficiency virus infection] culture is preferred (1,5). Trichomonas vaginitis is diagnosed by showing motile Trichomonas vaginalis in a fresh saline preparation (sensitivity: 50-60%) or by nucleic acid amplification tests with high sensitivity (1,3). In the diagnosis of trichomonas, culture is considered less appropriate than molecular detection methods because it takes at least 5 days to result and requires special microbiological media (1).

Culture in vaginitis is a method suitable for use in selected cases. Culture seems appropriate in cases where access to other simple methods is not possible (e.g., inability to perform microscopy, lack of molecular detection methods) and in vulvovaginal candidiasis microscopy-negative and complicated cases (1,3,5,6).

In our study, we aimed to evaluate the results of vaginal cultures obtained from patients who applied to our hospital with recurrent or persistent vulvovaginitis.

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Methods

The study was carried out by retrospectively examining the files of patients aged 18-49 years who applied to the gynecology outpatient clinics of University of Health Sciences Turkey, İstanbul Training and Research Hospital, Obstetrics and Gynecology Outpatient Clinics between January 2018 and June 2020 with the complaint of recurrent or persistent vulvovaginitis and whose vaginal cultures were taken. As a result of the examination, the results of the vaginal cultures taken from the patients were evaluated and the percentage distribution of the results was obtained. In our hospital, vaginal culture samples are delivered to the University of Health Sciences Turkey, İstanbul Training and Research Hospital microbiology laboratory with Stuart transport swap and medium (BTR-Gülkimya/Ankara or Fıratmed/Ankara). Samples are inoculated on 5% blood agar, MacConkey agar and Candidal samples on Sabouraud medium. Microorganisms are identified by fresh saline preparation and gram staining after incubation. *T. vaginalis* is diagnosed by monitoring trophozoites in a fresh saline preparation. *Candida* is identified by the appearance of yeast or pseudohyphae and growth in culture. BV is diagnosed by Gram staining of coccobacilli with variable staining, visualization of epithelial cells, namely clue cells, to which these bacteria adhere, and Nugent scoring.

Inclusion criteria:

1. Persistent vaginitis: patients whose symptoms regressed after the first treatment, but who were diagnosed with vaginitis with the same symptoms in the controls within the first month.

2. Recurrent vulvovaginal candidiasis: defined as 4 or more attacks per year (7).

3. Three or more attacks in the last 12 months for recurrent BV and other vaginitis agents (8,9).

Exclusion criteria:

1. Contact dermatitis (allergic dermatitis): vaginitis caused by intravaginal pessaries and creams (10).

2. Desquamative inflammatory vaginitis: uncommon, non-infective, painful vaginitis of unknown cause, characterized by radiance, erythematous patches and/or petechiae (11).

3. Chronic drug eruption: erosive vulvovaginitis mostly associated with nonsteroidal anti-inflammatory drugs and statins.

4. Type 1 hypersensitivity reactions: itching, burning, may result from exposure to latex condoms and seminal fluids.

5. Pregnant patients, those with malignant or chronic autoimmune diseases, those who use drugs continuously for these reasons and other rare causes of vaginal symptoms.

Our study was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2468, date: 10.07.2020). Since our study was retrospective, informed consent was not obtained from the patients.

Statistical Analysis

Statistical analyzes were performed using Windows Statistical Package for the Social Sciences 15.0 software (SPSS, Chicago, IL, USA). Qualitative data were analyzed with the chi-square test. $P<0.01$ was considered statistically significant.

Results

As a result of retrospective examination of patient files, vaginal culture results of 212 patients were obtained. Four patients were excluded from the study because of continuous drug use due to various chronic diseases, and 2 patients due to antibiotic use in the last 15 days due to different focus of infection. Culture results of 206 patients with recurrent or persistent vaginitis were included in the study. The mean age of the patients included in the study was 34.4 and ±12.2. Median parity value was determined as 2 (minimum: 0 - maximum: 9). Thirty-nine patients had never given birth. The microorganisms detected in the culture results and their percentages are given in Table 1.

There was no growth in 124 (60.1%) of 206 patients. Mixed growth was observed in 34 patients (16.5%). Candida species grew in 22 (10.6%) and *Gardnerella vaginalis* in 11 (5.3%) of 48 (23.3%) patients with growth. Various bacteria grew in the remaining 15 patients (Table 1). Trichomonas vaginalis, which is one of the important vaginitis agents, could not be determined as a factor.

Twenty-five of 206 patients was using condom (barrier method) to prevent pregnancy. One hundred and seven patients were using non-barrier methods: distribution of these patients by method; 43 patients were protected with intrauterine device (IUD), 24 patients with oral contraceptive (OCS), 11 patients with monthly injectable hormone, 29 patients with tubal ligation. The remaining 44 patients were either unprotected or protected by ineffective-conventional methods (calendar method, withdrawal, etc.). Information about the method of protection could not be obtained from the files of 30 patients.

When 132 patients using any effective contraceptive method were evaluated within themselves; in 25 patients using the barrier method; there were 2 mixed growths, 2 *Candida albicans* (*C. albicans*), 2 *G. vaginalis*, 1 *Escherichia coli* (*E. coli*) growth.

Thirty-two mixed growth, 15 *Candida albicans*, 5 non-albicans *Candida* (NAC), 9 *G. vaginalis*, 7 *E. coli*, 3 *Streptococcus agalactiae*, 3 *Klebsiella*,

Table 1. Microorganisms with their percentages in vaginal culture

Cause	n=206	%
Culture negative	124	60.1
Mix reproductive	34	16.5
Candida albicans	17	8.2
Non-albicans Candida	5	2.4
Gardnerella vaginalis	11	5.3
Escherichia coli	8	3.8
Streptococcus agalactiae	3	1.4
Klebsiella pneumoniae	3	1.4
Enterococcus faecalis	1	0.4

1 *Enterococcus faecalis* were detected in 107 patients using non-barrier method.

The reproductive rate in the vaginal culture (28%) of the patients using the barrier method was found to be statistically lower than the patients using the non-barrier method (70%) (Pearson chi-square value: 14,797, p=0.0012) (Table 2).

Table 2. Vaginal culture reproductive results by protection methods

Groups	n	%	
Barrier methods	25	18%	
Non-barrier methods	107	81%	
Total	132	100%	
	Barrier methods n (%)	**Non-barrier methods n (%)**	**p-value**
Reproduction	7 (28)	75 (70)	*p=0.0012
No reproduction	18 (72)	32 (30)	*p=0.0027

*Pearson chi-square test. Significance at the 0.01 level

Discussion

Our study aims to evaluate the results of vaginal cultures obtained from patients with recurrent and persistent vaginitis in the obstetrics and gynecology outpatient clinic of our hospital over a 30-month period. From the patient files reviewed retrospectively, 206 patients treated with this diagnosis were included in the study.

Vaginal flora is colonized by a very large group of bacteria and Candida. Cultivation of these bacteria, which can be found in the normal flora, does not conclusively indicate that they are responsible for the patient's symptoms. Treatments given only based on culture may result in inadequate or inappropriate treatment (12). In the results we determined in our study, it was observed that some bacteria that can be found in the normal flora reproduce.

In our study, only 5.3% of *G. vaginalis* culture positivity was found (Table 1). In a study conducted by Thulkar et al. (13), 400 patients were examined with recurrent vaginitis and BV at a rate of 53.8% was found. In addition to the socioeconomic status of the patients and whether they comply with the hygiene rules, these authors stated that the results may be related to the contraceptive method of women (13). These authors found a higher rate of BV (70.3%) in patients protected by tubal ligation, and this rate decreased with condom use. Although Donders et al. (14) did not examine barrier methods, they showed that different contraceptive methods can affect the vaginal flora. In other studies, increased vaginal anaerobic bacteria amount and decreased *Lactobacillus* rates were shown in women using IUD with levonorgestrel and combined oral contraceptive (15,16). Haukkamaa et al. (16) showed that vaginal flora was preserved and *Lactobacillus* rates were higher in women using the barrier method compared to those using OCS and IUDs with levonorgestrel. Ceruti et al. (17), in their large study involving 2,387 patients, found less BV in patients using the barrier method (condom, diaphragm) and found a higher rate of lactobacilli in the vaginal flora in these patients (17). Kaplan (18), in their study, found that the frequency of BV increased in patients using copper IUDs. In our study, we found that the rate of growth in vaginal culture in patients using the barrier method was statistically significantly lower than the rate of growth in culture in patients using other methods.

Powell and Nyirjesy (19) reported the rate of recurrent BV as 30% in their review. [American College of Obstetricians and Gynecologists (ACOG)] does not recommend culture in the diagnosis of BV (1). Amsel criteria and gram staining with Nugent scoring are used in the diagnosis (6,20,21). In patients with BV, it was stated that 10% KOH dripping (Whiff test) and pH determination instead of culture, fresh saline preparation and microscopy with gram staining are more valuable (12).

In our study, *Candida albicans* grew in 17 patients (8.2%), while non-albicans species grew in 5 (2.4%) patients. Rosati et al. (22) reported that 75% of women in fertile age had vulvovaginal candidiasis at least once in their lifetime, and although it varies in different societies, up to 9% of them have recurrent vulvovaginal candidiasis. Our results were consistent with this, and we detected 10.6% of all candidal infections (albicans and non-albicans species). 90% of all vulvovaginal candida infections are caused by *C. albicans* (1). 60-70% of these patients can be diagnosed by microscopic examination of spores and pseudohyphae (1,3). Culture is performed only in patients with negative microscopy and in complicated cases (1,5). Vulvovaginal candida infections caused by NAC species tend to be milder than *C. albicans* infection (23). The peculiarity of NAC species is that first-line therapy results in treatment failure due to their resistance to azole antifungals or their low dose sensitivity (23). Culture and antifungal susceptibility testing may be necessary for optimal treatment of these infections. In our study, the majority of recurrent *Candida infections* were caused by albicans species. ACOG states that 150 mg weekly fluconazole treatment for 6 months prevents disease recurrence by 90% and recommends extended fluconazole treatment in this patient group (1).

In total, no Trichomonas vaginalis was detected in 206 disease groups. In these patients, it is difficult to obtain results from the culture due to the need for special media, insufficient communication between the clinician and the microbiologist, and failure to convey the suspicion of the relevant diagnosis to the microbiologist. In addition, this suggests that this patient group was effectively treated at the time of initial diagnosis. Although the possibility of detecting trichomonas with microscopy is limited, it can be successful up to 60% (1). Until the use of molecular detection methods, vaginal culture was the most sensitive and preferred method in the diagnosis of trichomonas (1). Culture is considered less appropriate than molecular detection methods, as it takes at least 5 days to result and requires special microbiological media (1). Nucleic acid amplification tests are easy, quick to diagnose, and highly sensitive (95-100%) tests (6). Commercially available DNA probe tests or PCR tests are also recommended by ACOG and (Food and Drug Administration-USA) because of their high sensitivity and easy and quick diagnosis (1,6). In Turkey, it seems more appropriate to do microscopy instead of culture, and to start using these tests in the patient group that cannot be diagnosed by microscopy. Until this is done, treatment delays may occur due to unnecessary culture taking and long waiting times for results.

The number of studies evaluating the results of vaginal culture in recurrent vaginitis is limited. Although there are valid guidelines on this subject, the rate of compliance with them is limited in general and in our clinic for various reasons. Moreover, vaginitis rates are affected by many factors such as the distribution of microorganisms in cultures taken from these patients and microorganisms detected in the normal flora, education, cultural influences, socioeconomic status, and race (13,24-26). Therefore, it may be more appropriate to localize the guides on this subject. There are also studies on vaginitis in Turkey, but the number of studies on culture results in recurrent and persistent vaginitis is limited and generally studies investigating a single microorganism (27-30). It is highly probable that the sociocultural habits of Turkish women also affect the prevalence of vaginitis, the rate of recurrence, and the rate of microorganisms produced in the culture, and more studies are needed on this subject. Our patient series has shown that, in clinical practice, taking vaginal cultures is an expensive and limited method in chronic and recurrent vaginitis. In addition to the Whiff test, pH measurement, fresh saline preparation microscopy, and gram staining opportunities for clinicians, with the introduction of trichomonas molecular detection methods into clinical practice, unnecessary cultures can be avoided and more effective treatment will be selected.

Study Limitations

Due to the retrospective nature of our study, the contraceptive method information of some patients could not be accessed from their files. Information on treatment success in subsequent follow-ups is also missing. For the same reason, it is not known for certain whether patients are given training on keeping the vaginal flora healthy, but this training is widely given in our polyclinics. Information on various behaviors that may affect the results of condom use, such as wearing the condom while close to ejaculation, is lacking. Despite these shortcomings, we think that our study will be a good contribution to the limited data on this subject.

Conclusion

Follow-up and treatment are characteristic in recurrent and persistent vaginitis. Vaginitis recurrence rate and the type of microorganism detected can be affected by many factors such as sociocultural structure, race, education level and contraception method. The number of studies on vaginal culture results in recurrent and persistent vaginitis patients in general and in the Turkish population is insufficient. In our study, we found that the contribution of vaginal culture taking to patient management was limited in this patient group and the rate of recurrent vaginitis was lower in women using the barrier method.

Ethics Committee Approval: Our study was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2468, date: 10.07.2020).

Informed Consent: Since our study was retrospective, informed consent was not obtained from the patients.

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The Effects of Depression Severity on the Stress Coping Methods of Mothers with Mentally Disabled Children

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ABSTRACT

Introduction: This study aimed to evaluate the effects of depression severity on stress coping methods of mothers with mentally disabled children.

Methods: This study included 50 mothers of children with intellectual disabilities who were admitted to the psychiatric outpatient clinic of our hospital. Sociodemographic data form, Beck Depression scale, and Stress Coping scale were applied to all participants.

Results: The mean Beck Depression score of participants was 17.42±6.32. A One-Way relationship was found between the Beck Depression score and Stress Coping scale-desperate and submissive subscales. The Stress Coping Scale-desperate approach score is higher in those with severe depression than those with mild depression, whereas the Stress Coping scale-self-confidence subscale is higher in those with severe depression. The Stress Coping scale-submissive approach score is higher in participants with moderate depression than those with mild depression ($p<0.005$).

Conclusion: Depression negatively affects the stress coping methods of mothers with children with intellectual disabilities, and psychosocial support is recommended to be provided to mothers who prefer desperate and submissive approaches to stress management methods.

Keywords: Disabled children, coping stress, submissive approach, desperate approach, depression

Introduction

Mental disability, also known as mental retardation, is a chronic problem that is observed in 2-3% of the total population and can be determined by the deterioration in various sub-dimensions of intelligence, such as cognition, language, motor, and social skills (1). It occurs in early childhood and is characterized by a decreased ability to adapt to the environment. Mental abilities, in general, are significantly below average. In most cases, intellectual disability is a very frustrating life condition with no real cure (2). The emotional burden on families begins to increase as soon as they learn that they have a child with a mental disability. A healthy child is expected; however, the birth of a child with different characteristics significantly affects the life of the family. In the first stage, families respond by ignoring and denying, and then the grieving process begins. In the grieving process, feelings of intense sadness and helplessness accompany the feelings of guilt (3). When caring for a disabled child, family problems, such as jealousy among siblings and neglect of the other child, also arise with other children in the family (4). Finally, marital relations are broken. Numerous studies revealed communication problems (5) between the presence of a disabled child in the family and the parents, thus families may experience feelings, such as anger, guilt, relationship problems, and unhappiness. In addition to family problems, social problems can be experienced, such as social problems and exclusion.

Moreover, mothers who take care of the needs of the disabled child on one hand and protect the child from dangers, on the other hand, experience increased stress levels. The mother takes care to meet the needs of both the disabled child and other family members.

Additionally, the decreased participation in social activities due to the attitudes and judgments of the society toward disability and the uncertainty of the child's present and future situation causes more anxiety in the mothers. Thoughts about the future life of children and who will take care of their children when they are unavailable increase their anxiety. Therefore, social and emotional problems, such as social isolation, depression, guilt, and anxiety, may occur in mothers of disabled children.

Especially in society, the child is considered as the personal success or failure of the mother. A sick child may be seen as a failed child, thus the mother may be blamed or even humiliated by the mother's environment. This situation affects the mother's feelings and may cause the mother

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to experience more guilt, dissatisfaction, and stress compared to other family members (6). The severity of anxiety and depression experienced by mothers can change their coping mechanisms (7). Stress coping methods also affect the child care process. Therefore, this study aimed to investigate the effects of depression on the stress coping methods of mothers with mentally retarded children.

Methods

This study included 50 mothers with mentally retarded children who agreed to participate in the study. A sociodemographic data form including age, education level, marital status, age of the mentally disabled child, and the total number of children was evaluated. Additionally, the mothers were evaluated using the Beck Depression scale (BDS) and the Stress Coping scale, Stress Coping scale subscales of mothers with high scores on the BDS were compared with the Stress Coping subscale results of mothers without depression. Approval was obtained from the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2949, date: 22.10.2021). Consent was obtained from all participants.

Stress Coping Scale

The scale consisted of 30 items, wherein the total score is not calculated, but the scores for each factor are separately calculated. The high scores obtained from the subscales indicate that the approach in that subscale is used more in coping with stress. In the evaluation of the scale, as the scores obtained from the factors of Self-Confidence, Optimism, and Seeking Social Support increase, stress coping was found effective. The increased scores obtained from the desperate approach and submissive approach factors indicate that ineffective methods are used in stress coping (8).

BDS

BDS is a self-report scale that is developed by Beck in 1961 to measure the emotional, cognitive, somatic, and motivational components. The validity and reliability of the BDS, which is used to determine the intensity of depression, was determined by Teğin (9) for the Turkish population.

Statistical Analysis

Statistical analyzes were performed using the Statistical Package for the Social Sciences version 17.0 program. The conformity of variables to the normal distribution was examined using histogram graphics and the Kolmogorov-Smirnov test. Mean, standard deviation, median, and minimum-maximum values were used while presenting descriptive analyzes. Comparisons between more than two groups were made using the Kruskal-Wallis test, and post-hoc analyzes were made using the Mann-Whitney U test. The Spearman correlation test was used in the analysis of the measurement data with each other. P-values of <0.05 were considered statistically significant.

Results

The mean age of participants in the study was 42.62±9.73 years. The minimum age was 25, and the maximum age was 59 years. Of the participants, 20 are at primary education level, 26 at high school, and 4 at the university education level. Additionally, 24 participants are working and 26 are housewives. The mean duration of marriage was 14.26±7.64 years. The mean age of the disabled child was 11.14±4.16 years and the mean number of children was 2.16±0.74. Mild Beck Depression score was determined in 25 participants, moderate in 22, and severe in 3 people. The mean Beck Depression score was 17.42±6.32. The mean Coping with Stress scale-Helpless Approach Subscale score was 17.88±5.27, Submissive Approach was 14.78±4.01, self-confidence was 16.32±3.80, Seeking Social Support Approach was 11.78±2.57, and Optimistic Approach was 10.60±2 (Table 1).

The relationship between the Beck Depression score and Coping With Stress subscales and age, duration of the marriage, age of the disabled child, and the number of children were examined. An inverse relationship was found between age and the Coping with Stress scale-Optimistic Approach subscale. As the age of the mother progresses, the optimistic approach method also decreases. A statistically significant relationship was found between the age of the disabled child and the Stress Coping scale-Social Support Seeking Approach subscale. As the age of the child increases, the help-seeking behavior also increases. A statistically significant relationship was found between the number of children and the Stress Coping scale-self-confidence subscale (Table 2). Education levels, Beck Depression score, and Coping with Stress subscales were compared and revealed no significance ($p>0.05$) (Table 3).

The relationship between the Beck Depression score and Coping with Stress subscales was investigated. A significant relationship was found

Table 1. Sociodemographic variables

		Mean ± SD/n	Median (min.-max.)-%
Age		42.62±9.73	45 (25-59)
Education	Primary school	20	(40.00)
	High school	26	(52.00)
	University	4	(8.00)
Work	House wife	26	(52.00)
	Working	24	(48.00)
Years of marriage		14.26±7.64	14.50 (1-30)
Age of disabled child		11.14±4.16	10.50 (2-22)
Number of children		2.16±0.74	2 (1-3)
Beck	Mild	25	(50.00)
	Moderate	22	(44.00)
	Severe	3	(6.00)
Beck Depression score		17.42±6.32	16 (10-33)
Coping with Stress scale - Desperate approach		17.88±5.27	17.50 (10-30)
Coping with Stress scale - Submissive approach		14.78±4.01	13.50 (10-23)
Coping with Stress scale - Self-confidence		16.32±3.80	16 (10-25)
Coping with Stress scale - Seeking Social Support		11.78±2.57	12 (5-16)
Coping with Stress scale - Optimism		10.60±2.84	10 (5-15)

SD: Standard deviation, min.: minimum, max.: maximum

between the Beck Depression score and the Stress Coping scale-Helpless Approach and Submissive Approach subscale (Table 4). This result revealed that mothers with depression prefer to use ineffective methods of coping with stress ($p<0.05$).

Coping With Stress subscales were compared according to Beck Depression Severity. Those with severe Beck Depression have a higher Coping with Stress scale-Helpless Approach subscale than those with mild Beck Depression , and a lower self-confidence subscale score than those with mild depression. Stress Coping scale-Submissive Approach subscale score was higher in those with moderate Beck Depression status than those with mild Beck Depression status (Table 5) ($p<0.05$).

Discussion

This study aimed to determine the relationships between the stress levels caused by the depression level of mothers with disabled children and the variables of coping styles, such as self-confident approach, optimistic approach, self-blaming approach, submissive approach, and social support seeking approach.

Having a child with an intellectual disability is stressful. Stress, depression, and anxiety levels of mothers were also revealed as high in many studies in the literature (10). Due to her cultural role in society, women are responsible for chores, such as housework and childcare. With the effects of this situation, the burden of mothers with a disabled child also increases compared to fathers (11). All participants in our study had depression, 50% of ratıo had at least mild depression. This result supports the results from previous studies. Many studies revealed that mothers' stress, depression, and anxiety levels are higher than fathers' (12). Therefore, mothers were preferred in our study. The relatively high level of fathers' stress can also be interpreted as a result of the economic burden caused by the disease. Some studies revealed no relationship between parental stresses (13).

Additionally, studies revealed that as the age of the disabled child increases, the depression symptoms of the parents increase, and the depression levels of the parents who have children aged 7 years and over are higher than the depression levels of the parents who have children between the ages of 0 and 6 years (14). The possible reason is that special education is taken with the advancing age, in addition to the periods that affect the family, such as adolescence, thus the burden on the family increases even more. Our study revealed no correlatıon between maternal depression and the age of children. Additıonally, the social seeking support subscale correlated as the child gets older.

Coping is an individual's response to stressful situations. Difficulties may arise with the care of the child in mental or physical developmental delays; however, appropriate coping methods are stated to play a role in protecting the parents from the effects of a challenging situation (15). Problem-focused coping methods are generally used with positive expectations.

Therefore, the subscales of the Stress Coping scale in our study revealed that as the mother's depression increased, the helpless approach

Table 2. Coping with Stress scale subscales and sociodemographic variables

		Age	Years of marriage	Age of the disabled child	Number of children
Beck Depression scores	r	0.138	0.022	0.116	-0.098
	p	0.341	0.882	0.421	0.500
Coping with Stress scale - Desperate approach	r	-0.128	-0.140	0.040	-0.228
	p	0.377	0.333	0.783	0.111
Coping with Stress scale - Submissive approach	r	-0.054	-0.048	-0.074	-0.134
	p	0.711	0.739	0.610	0.355
Coping with Stress scale - Self-confidence	r	-0.052	-0.055	0.197	0.314
	p	0.719	0.705	0.170	0.026
Coping with Stress scale - Seeking Social Support	r	-0.173	-0.098	0.326	-0.207
	p	0.228	0.499	0.021	0.149
Coping with Stress scale - Optimism	r	-0.325	-0.205	0.099	-0.031
	p	0.021	0.154	0.495	0.831

Table 4. Spearman Correlation test-Relations with Coping with Stress scale subscales and depression

Coping with Stress scale subscales	Beck Depression scale	
	r	p
Desperate approach	0.438	0.001
Submissive approach	0.462	0.001
Self-confidence	-0.243	0.089
Seeking social support	-0.144	0.319
Optimistic approach	-0.075	0.604

Table 3. Education level and depression and coping stress scale relation

	Education						p
	Primary school		High school		University		
	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	
Beck depression scores	18.30±6.39	18.50	16.96±6.48	13.00	16.00±5.83	15.50	0.628
Coping with Stress scale							
Desperate approach	18.95±5.49	19.50	16.85±4.91	15.00	19.25±6.50	21.00	0.311
Submissive approach	14.60±4.15	13.00	14.35±3.86	13.00	18.50±3.00	20.00	0.183
Self-confidence	16.40±3.94	16.00	16.12±3.40	16.00	17.25±6.34	17.00	0.906
Seeking social support	11.65±2.48	11.50	11.77±2.29	11.50	12.50±5.00	15.00	0.594
Optimism	11.05±1.79	10.50	10.00±3.09	9.00	12.25±4.86	14.50	0.088

SD: Standard deviation

Table 5. Kruskal-Wallis test, Mann-Whitney U test (for Posthoc analysis)-Relations with Coping with Stress scale subscales and Depression Severity

Coping with Stress scale subscales	Beck						p
	Mild		Moderate		Severe		
	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	
Desperate approach	15.92±4.30	15.00	18.77±4.90	19.00	27.67±2.52	28.00	0.004
Submissive approach	13.20±3.30	12.00	16.23±4.10	16.00	17.33±4.62	20.00	0.018
Self-confidence	17.32±3.67	17.00	16.00±3.45	15.50	10.33±0.58	10.00	0.022
Seeking social support	12.08±2.43	12.00	11.59±2.87	11.00	10.67±1.15	10.00	0.436
Optimistic approach	10.80±3.18	10.00	10.55±2.63	10.00	9.33±0.58	9.00	0.616
SD: Standard deviation							

and submissive approach subscale scores of the Stress Coping scale increased. This result is important in terms of showing the problems of depression in mothers in stress coping brought on by the mentally handicapped child.

Studies revealed that the family's ability to cope increases as the education level of the family increases (16). No significant difference was found between the subscales with the increased educational level in our study.

Families become inadequate in coping with the long-lasting and wearing problem and may experience various emotional and behavioral problems. The most important of these problems is depression, which significantly affects the mother's life. Supporting the mothers from a psychiatric point of view is important since this situation will complicate the care of the child, among other difficulties. Our study supports the results of previous studies.

Study Limitations

This study has a small number of mothers with mentally handicapped children since mothers undertake the care of children with disabilities alone and therefore cannot find time to apply to our polyclinic. The difficulties of the participants in finding a person to care for their children reduced the number of participants in our study and caused a decreased number of participants.

Conclusion

Our results revealed that as the age of the children with a mental disability grows, the social support seeking approach in mothers increases. Additionally, having a mentally disabled child causes anxiety for the future and depression for mothers, and causes the mother to wear out, leading to negative stress coping methods. Our study revealed the necessity of determining the severity of depression in mothers of mentally retarded children and supporting them in the psychiatric field. We recommend providing psychosocial support and applying psychiatric treatments that address the family as a whole to correct this situation.

Ethics Committee Approval: Approval was obtained from the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2949, date: 22.10.2021).

Informed Consent: Consent was obtained from all participants.

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The Relationship Between the Admission Blood Glucose Level and 90-Day Mortality in Non-Diabetic Patients with Coronavirus Disease-2019

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ABSTRACT

Introduction: The admission blood glucose (ABG) level is associated with increased mortality in non-diabetics patients with Coronavirus disease-2019 (COVID-19) in short-term follow-up studies. However, post-discharge mortality has also increased in COVID-19. Thus, this study aimed to examine the relationship between ABG and 90-day mortality including the post-discharge period.

Methods: Non-diabetic patients who are hospitalized due to COVID-19 in 2020 were evaluated. Patients were divided into groups according to the ABG level. Groups 1, 2, and 3 have ABG level of <100 mg/dL, 100-139 mg/dL, and 140-199 mg/dL, respectively. Intensive care unit admission, in-hospital mortality, and 30- and 90-day mortality rates were evaluated as outcomes. COX regression analyzes were used to assess mortality risk factors.

Results: A total of 1207 non-diabetic patients, of whom 49.2% were females, with a mean age of 65.2±13.4 years, were included in the study. The patients were followed up for a median of 153 (inter quartile range: 107.5-251, maximum: 369) days. The in-hospital and 30-day mortality of group 2 was higher than group 1 in the univariate analysis but without statistical significance in multivariate analysis. Group 3 had worse outcomes than group 1 in both univariate and multivariate analysis at all endpoints. Group 3 had 2.533 adjusted hazard ratios (95% confidence interval: 1.628-3.941, p<0.001) 90-day mortality compared with group 1.

Conclusion: Non-diabetic patients with COVID-19 with an admission glucose level of ≥140 mg/dl had 2.5-fold increased all-cause mortality at 90 days. Therefore, being more careful in treating and following non-diabetic patients with COVID-19, especially those with hyperglycemia at admission, was recommended.

Keywords: Glucose, SARS-CoV-2, COVID-19, hyperglycemia, hospitalization, intensive care units

Introduction

Hyperglycemia in hospitalized patients is an independent risk factor that is strongly associated with adverse outcomes. Hyperglycemia disrupts neutrophil functions and movements, causing adverse effects on immunity. Additionally, it causes microvascular complications with endothelial dysfunction by increasing inflammatory responses and oxidative stress (1,2).

Many associated factors with mortality have been identified in patients hospitalized due to Coronavirus disease-2019 (COVID-19). Mortality rates increased nearly 2-fold in patients with a history of diabetes (3-6). Additionally, newly detected hyperglycemia in-hospital admission, even without a known history of diabetes, has shown association with increased mortality (7,8), as well as increased intensive care unit (ICU) admissions and prolonged hospital stays. Several studies have shown that patients with hyperglycemia without a history of diabetes have an even higher risk of mortality than those with known diabetes (9).

Studies that examined the newly developed hyperglycemia at hospital admission due to COVID-19 mainly examined in-hospital and 30-day mortality rates. These studies did not evaluate the long-term mortality (7,10). However, the mortality also increased in the post-discharge period in patients with COVID-19, and this rate has been reported to be approximately 10% (11-13). This study aimed to evaluate the relationship between at least 90 days mortality and admission blood glucose (ABG) level, including the post-discharge period.

Methods

A total of 1207 hospitalized patients with COVID-19 between March 2020 and December 2020 in Çanakkale Onsekiz Mart University Hospital were retrospectively analyzed. COVID-19 diagnoses were made either by polymerase chain reaction positivity or radiological findings. Patients with compatible diabetes diagnoses from the previously given International Classification of Diseases (ICD) codes, hemoglobin A1c (HbA1c) of ≥6.5% in

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their system records, using diabetes medication before admission, under 18 years of age, pregnant, and ABG of >200 mg/dL were excluded from the study. Patients with newly diagnosed diabetes were also excluded when the HbA1c is ≥6.5% during hospitalization. Patients were divided into groups according to the ABG level. Groups 1, 2, and 3 have ABG level of <100 mg/dL (5.6 mmol/L), 100-139 mg/dL (5.6-7.7 mmol/L), and 140-199 mg/dL (7.8-11.1 mmol/L), respectively. The study was approved by the Ethics Committee of Çanakkale Onsekiz Mart University Faculty of Medicine (approval number: 2021-07, date: 20.10.2021).

Patients' mortality status was inquired via the Turkish Central Death Registry in March 2021. ICU admission, in-hospital mortality, and 30- and 90-day mortality rates were evaluated as outcomes.

Acute renal failure was diagnosed by Kidney Disease: Improving Global Outcomes criteria (14). The Chronic Kidney Disease Epidemiology Collaboration equation was used to calculate the estimated glomerular filtration rate (eGFR) (15).

Statistical Analysis

Continuous variables with normal distribution were presented as mean ± standard deviation, whereas non-normally distributed variables as the median and interquartile range [(IQR): the difference between the 25th and 75th percentiles]. Numbers and percentages were used to express categorical variables. Normal distribution was evaluated with the Kolmogorov-Smirnov test. Analysis of variance was used to compare the three groups for data with normal distribution and the Kruskal-Wallis test used for those with non-normal distribution. Homogeneity of variances was evaluated with Levene's test. Pairwise post-hoc comparisons were made with the Tukey test if the variances were homogeneous and with the Tamhane T2 test if not if a significant difference was found between the three groups. In the variables, in which the groups were evaluated with the Kruskal-Wallis test, post-hoc analyses in pairs were evaluated using the Mann-Whitney U test by Bonferroni correction. Pearson's chi-square was used to test the distribution among categorical variables. Wherein, paired post-hocs were evaluated with the Z-test, with Bonferroni correction.

COX regression analyses were used to assess the risk factors for COVID-19-associated mortality. A single variable was used to calculate the unadjusted hazard ratios (HR). Gender, age, alanine transaminase (ALT), eGFR, co-morbidities as chronic lung disease, coronary artery disease, cerebrovascular disease, hypertension, and hyperlipidemia were used in the adjusted HR (aHR) analysis. In COX regression analyses, group 1 was used as the reference group to evaluate the outcomes of groups 2 and 3.

The Statistical Package for the Social Sciences version 19 for Windows was used for statistical analysis (IBM, Armonk, NY, USA). A statistically significant p-value of 0.05 was used.

Results

A total of 1207 patients with a mean age of 65.2±13.4 years, of whom 49.2% (594) were females, were included in the study. In all study groups, the in-hospital mortality rate was 11.1% (134). The 30- and 90-day mortality rates were 12.7% (153) and 16.7% (201), respectively. Groups 1, 2, and 3 consisted of 285 (23.6%), 706 (58.5%), and 216 (17.9%) patients, respectively.

From groups 1 to 3, ICU Admission, in-hospital mortality, 30-day mortality, and 90-day mortality rates increased as blood sugar increased. In the post-hoc analysis, these differences were determined to be caused mainly by group 3. From groups 1 to 3, a decreased eGFR and a prolonged hospitalization were observed. Group 3 had higher ALT levels, hyperlipidemia history, and acute renal failure rates than other groups. Group 1 was younger and had a lower coronary artery disease rate. The general characteristics and comparisons of the groups are given in Table 1.

In-hospital mortality and 30-day mortality rates, which were significant for mortality in the univariate analysis for group 2 (ABG: 100-139 mg/dL), lost statistical significance in the multivariate analysis adjusted for multiple variables (gender, age, ALT, eGFR, and co-morbidities). In group 3, univariate analysis of 90-day mortality HR was 3.45 [95% confidence interval (CI): 2.231-5.335, p<0.001] and in the multivariate analysis of 90-day mortality aHR was 2,533 (95% CI: 1.628-3.941, p<0.001). In group 3 (ABG: 140-199 mg/dL), statistically, significant mortality increases were observed with all univariate and multivariate analysis outcomes. Univariate and multivariate HR and forest plot graphs of groups 2 and 3 according to reference group 1 are given in Figure 1 and 2, respectively.

Patients were followed up for a median of 153 (IQR: 107.5-251, minimum: 1, maximum: 369) days. The Kaplan-Meier one minus survival graph of mortality between the groups during the follow-up periods is given in Figure 3 (log-rank p<0.001). The all-cause mortality rate was the highest in group 3 during the follow-up period.

Discussion

We found that ICU admission, in-hospital, 30-day, and 90-day all-cause mortality was higher in non-diabetic patients with ABG of 140-199 mg/dL, even after correction for other factors in our study, which had a maximum follow-up period of close to 1 year. Our study is among the first reports that investigated the effects of ABG on long-term mortality in non-diabetic patients with COVID-19 (16).

Our findings are consistent with those of other studies with a short-term follow-up that found increased mortality due to hyperglycemia in non-diabetic patients with COVID-19 (7,10,17). Unlike these studies, our study showed the effect of ABG level on long-term mortality. Mortality rates for the post-discharge period in patients with COVID-19 have been reported as approximately 10% (11-13). Therefore, long-term follow-up studies of patients are also important.

Diabetes mellitus, one of the most common co-morbidities in patients with COVID-19, has been reported from 7% to 30% in studies. People with diabetes with COVID-19 have higher hospital admission rates, severe pneumonia, and higher mortality than non-diabetics (18). Hyperglycemia that occurs during acute illness, called stress hyperglycemia, is also associated with adverse outcomes (19).

Various studies before the COVID-19 era have shown that high ABG is associated with increased mortality and morbidity in patients

Table 1. General characteristics and comparisons of the admission blood glucose groups

	Group 1 ABG <100 mg/dL	Group 2 ABG 100-139 mg/dL	Group 3 ABG 140-199 mg/dL	Total	p
Number of patients	285	706	216	1207	-
Age (years)	61.0±14.7*,**	66.1±13.1	67.8±11.9	65.2±13.5	<0.001
Female (%)	142 (49.8)	343 (48.6)	109 (50.5)	594 (49.2)	0.865
Glucose (mg/dL)	91.1±6.3	116.5±10.4	160.4±16.3	118.4±24.8	<0.001
ALT [median (IQR)] (IU/L)	17 (11-30)	17 (12-27)	20.5 (14-36)**,***	18 (12-29.5)	0.01
eGFR [median (IQR)]	88.6 (72.3-101.8)*	84.9 (62.7-98)***	78.4 (49.7-95.2)**	85.6 (61-98.5)	<0.0001
Number of hospitalization days [median (IQR)]	5 (4-10)*,**	6 (5-10)	7 (4-13)	6 (4-10)	0.01
Follow-up days count [median (IQR)]	204 (130-260)*	150 (109-256)***	125.5 (32.5-228)**	153 (107.5-251)	0.01
In-hospital mortality (n, %)	16 (5.6)	73 (10.3)	45 (20.8)**	134 (11.1)	<0.0001
30-day mortality (n, %)	20 (7)	80 (11.3)	53 (24.5)**	153 (12.7)	<0.001
90-day mortality (n, %)	29 (10.2)	105 (14.9)	67 (31)**	201 (16.7)	<0.0001
ICU admission (n, %)	28 (9.8)	96 (13.6)	55 (25.5)**	179 (14.8)	<0.0001
COPD-asthma (n, %)	43 (15.1)	111 (15.7)	36 (16.7)	190 (15.7)	0.891
Hypertension (n, %)	104 (36.5)	298 (42.2)	99 (45.8)	501 (41.5)	0.09
Coronary artery disease (n, %)	37 (13)*,**	144 (20.4)	59 (27.3)	240 (19.9)	<0.0001
Hyperlipidemia (n, %)	28 (9.8)	83 (11.8)	41 (19)**,***	152 (12.6)	0.005
Acute renal failure (n, %)	41 (14.4)	11 (16)	49 (22.7)**	203 (16.8)	0.03
Chronic renal failure (n, %)	8 (2.8)	23 (3.3)	1 (5.6)	43 (3.6)	0.2
Cerebrovascular disease (n, %)	15 (5.3)	50 (7.1)	16 (7.4)	8 (6.7)	0.52
ACE/ARB usage (n, %)	74 (26)	229 (32.4)	71 (32.9)	374 (31)	0.11

ICU: Intensive care unit, ACE: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, COPD: chronic obstructive pulmonary disease, ALT: alanine aminotransferase, ABG: admission blood glucose, post-hoc tests: *p<0.05 group 1 vs group 2, **p<0.05 group 1 vs group 3, ***p<0.05 group 2 vs group 3

hospitalized for trauma, surgery, infectious diseases (sepsis and pneumonia), cardiovascular diseases, and cerebrovascular diseases (20-23). Even without a history of diabetes, the risk of mortality is higher in cases with the hyperglycemic course during hospitalization. Some studies also revealed that newly developed hyperglycemia without a history of diabetes during hospitalization was related to higher mortality than known patients with diabetes (9). Angiotensin-Converting Enzyme II (ACE-2) is one of the receptors that allow the entry of the severe acute respiratory syndrome-coronavirus-2 (SARS-COV-2) into the cell. Acute hyperglycemia increases ACE-2 expression, whereas chronic hyperglycemia decreases ACE-2 expression (24). It may explain why newly developed hyperglycemia has a worse prognosis than those with known diabetes. Additionally, patients with hyperglycemia with known diabetes are likely to be promptly treated, and the fact that hyperglycemia is a marker of critical diseases that may increase mortality may also explain this condition (25).

The relationship between long-term mortality with ABG was also investigated in cardiovascular diseases before the COVID-19 era (21,26,27). Similar to our findings, ABG was associated with increased long-term mortality.

The causes of hyperglycemia during hospitalization can be listed as treatments that contain dextrose, glucocorticoid, increased anti-insulin hormones, and increased inflammatory response (28,29). Our study was conducted according to the first ABG level groups, thus the effect of secondary hyperglycemia due to glucocorticoid treatment on the analysis was prevented (17).

Hyperglycemia induces an exaggerated inflammatory response that results in harmful microvascular complications (30). Additionally, hyperglycemia can affect multiple biochemical pathways that can facilitate many steps of SARS-CoV-2 infection. Hyperglycemia may trigger ACE-2 receptor expression, which may increase the susceptibility to COVID-19 infection and the risk of severe disease and multi-organ failure (31). The association of hyperglycemia with increased mortality is multifactorial (1).

Some differences were determined in the definition of hyperglycemia in studies that examine the effect of hyperglycemia on mortality in non-diabetics. Some studies used a definition of hyperglycemia above 140 mg/dL, thus patients with a level above 200 mg/dL were not excluded in some studies. Our study excluded the ABG of >200 mg/dL to eliminate the overlap with the diagnosis of diabetes.

Age, male gender, multiple pre-existing co-morbidities, and renal/hepatic dysfunction are critical factors that predict COVID-19 mortality (32). Therefore, a factor should be corrected in terms of the main influencing factors to correctly evaluate the relationship with mortality. Univariate analysis of ABG of 100-140 mg/dL was significant for mortality, but without significance, after the multivariate analysis was adjusted for

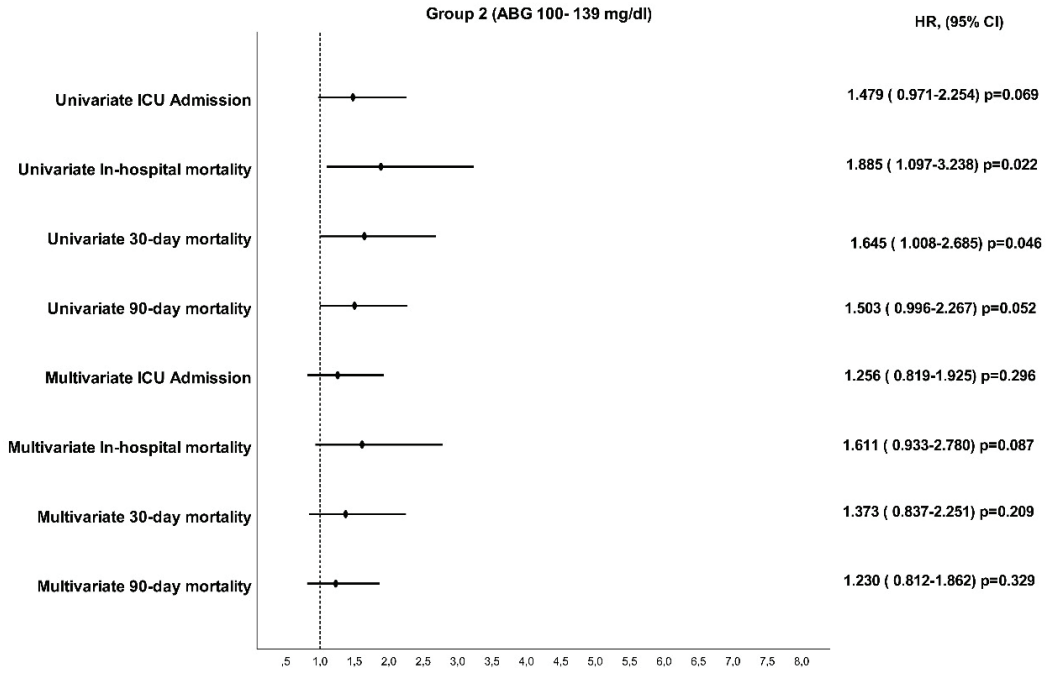

Figure 1. Univariate and multivariate hazard ratios and forest plot graph of group 2 according to the reference group 1
ABG: Admission blood glucose, HR: hazard ratios, CI: confidence interval, ICU: intensive care unit

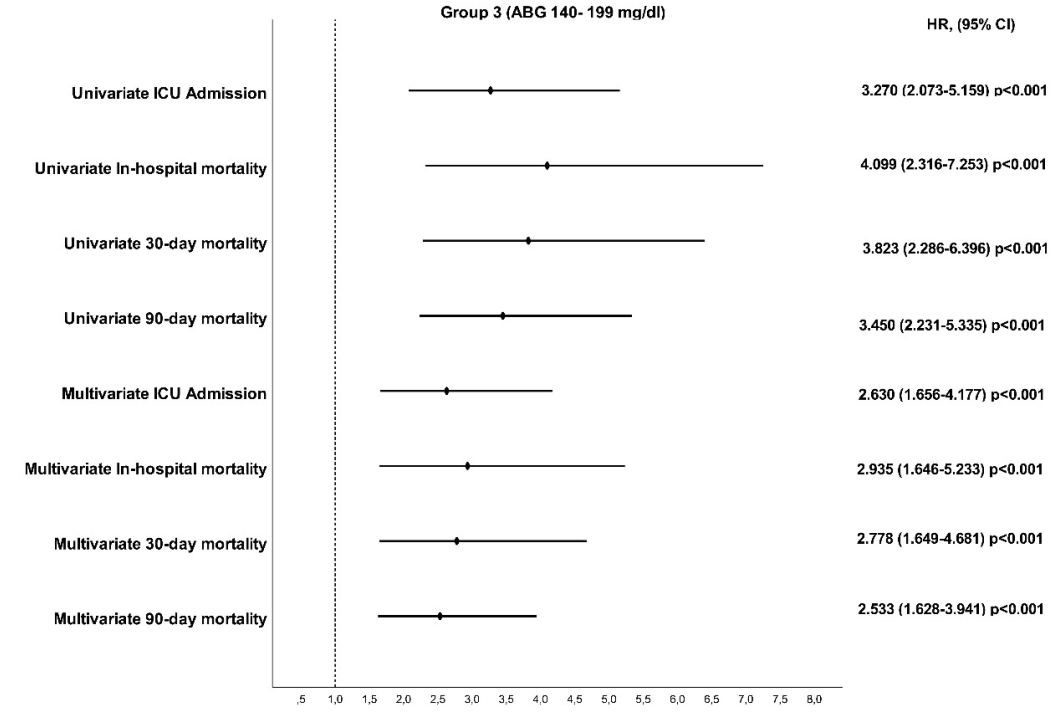

Figure 2. Univariate and multivariate hazard ratios and forest plot graph of group 3 according to the reference group 1
ABG: Admission blood glucose, HR: hazard ratios, CI: confidence interval, ICU: intensive care unit

covariates. The effect of mildly elevated blood sugar (100-140 mg/dL) on mortality can be ignored. The guidelines defined hyperglycemia as any glucose level above 140 mg/dL in hospitalized patients (33,34). Other studies revealed that blood sugar influences mortality when it is >140 mg/dL (10,21).

Study Limitations

Our study has several limitations. There may be undetected confounding factors because it is a retrospective study of data during an outbreak. Patients without diabetes-related ICD codes, medications history, and reports were selected; however, the fact that the HbA1c measurement

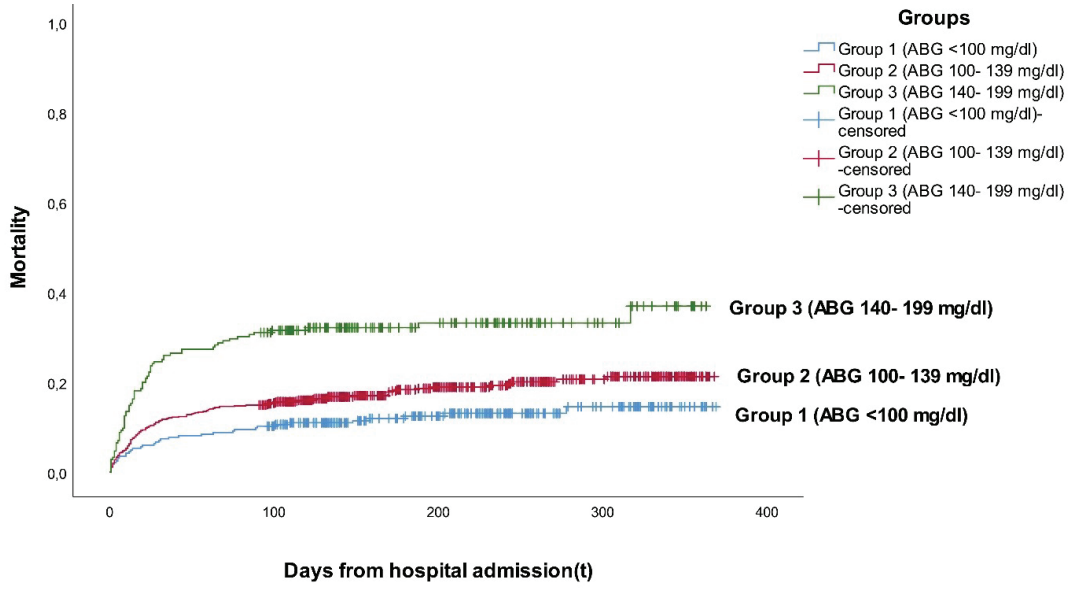

Figure 3. The Kaplan-Meier one minus survival graph of groups (log-rank p<0.001)
ABG: Admission blood glucose

was scarce among the patients is a limiting factor in excluding the history of diabetes. The ABG value taken in the fasting state or randomly could not be determined. However, our study examined the effect of ABG level on mortality rather than diagnosing new diabetes. All-cause mortality was evaluated in the analysis, thus data on exact causes of death were insufficient. The strengths of our study are the large, real-life cohort of hospitalized patients with COVID-19 and the long-term follow-up. Whether hyperglycemia treatment improves outcomes in those with high ABG levels requires a different study design. Following the guidelines, when the hospitalized patient's blood sugar levels reached >180 mg/dL, insulin was administered to lower the blood sugar level (34).

Conclusion

Non-diabetic COVID-19 patients with an admission glucose level of ≥140 mg/dL had a 2.5-fold increased all-cause mortality at 90 days. Being more careful in treating and following a non-diabetic patient with COVID-19, especially those with elevated serum glucose at admission, is recommended.

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Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept - E.S.S.; Design - E.S.S.; Data Collection or Processing - E.S.S., E.K.; Analysis or Interpretation - E.S.S., E.K.; Literature Search - E.S.S., E.K.; Writing - E.S.S., E.K.

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Breast Surgery can be Performed Safely During the COVID-19 Pandemic: A Retrospective Single-Center Analysis

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ABSTRACT

Introduction: The Coronavirus disease-2019 (COVID-19) outbreak has affected the diagnosis and treatment of various diseases including breast cancer. This study aimed to investigate whether breast surgery can be performed safely during the COVID-19 pandemic.

Methods: Patients who underwent surgery for breast cancer or suspicious breast lesions in the pre-pandemic, first wave, and second wave periods of the pandemic were evaluated retrospectively.

Results: Data of 220 patients who underwent breast surgery were analyzed. No significant difference was found between the pre-pandemic, first wave, and second wave periods of the COVID-19 pandemic in terms of patient characteristics, complications, types of complication, Clavien-Dindo classification of complications, and complications requiring intervention. No COVID-19 related complication was also observed.

Conclusion: Breast surgery can be performed safely in the COVID-19 pandemic. For safe surgery, appropriate precautionary measures against COVID-19 and COVID-19 screening should be initiated. COVID-19-free surgical pathway is also important for safe surgery. With the continuation of surgeries, fear of upstaging, subsequent requirement of more aggressive treatment for tumors, and post-pandemic overload can be prevented.

Keywords: COVID-19, breast, breast surgery, complication

Introduction

The Coronavirus disease-2019 (COVID-19) outbreak caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has spread rapidly worldwide since December 2019 and declared as a pandemic by the World Health Organization (WHO) on March 11, 2020 (1,2). With the rapid spread of the infection, various quarantine measures had to be taken.

Since the first case on March 11, 2020, additional measures were taken well and quarantine protocol were also initiated in Turkey (1,2): i.e., declaration of both state and private hospitals as pandemic hospitals, emphasizing the importance of social isolation, encouraging social isolation, and implementing curfews including people aged ≥65 years or those with comorbidities. A circular was issued by the Ministry of Health of Turkey to stop surgeries other than emergency and cancer surgeries. During this period, it was unknown how COVID-19 would affect the surgical results. Suggestions related to COVID-19 management have been reported for many malignancies, including breast cancer (1,3-5). During the pandemic, the safety of surgeries was questioned, and some authors expressed an opinion that surgeries should be delayed, if possible. On the contrary, the postponement of surgeries and a decrease in hospital admissions lead to a fear of upstaging and therefore a wider treatment requirement with enlarging tumors. However, over time, studies have started reporting that safe surgery can be performed in the pandemic period have. Thus, this study aimed to investigate whether safe breast surgery can be performed during the COVID-19 pandemic.

Methods

Based on the daily number of patients with COVID-19 taken from the website of the Ministry of Health of Turkey, the first wave of the COVID-19 pandemic was considered between April 1, 2020, and May 15, 2010, and the second wave was between November 15, 2020, and December 31, 2020 (6). Although the first case in Turkey was seen on March 11, 2020, the period between March 11 and March 31, 2020, was not included in the first wave because of the small number of COVID-19 cases.

In this study, patients who underwent upfront surgery for breast cancer or suspicious breast lesions or surgery after neoadjuvant chemotherapy

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(NACT) for breast cancer in the first and second wave of the pandemic were evaluated retrospectively. As the control group, patients who underwent surgery between December 15, 2019, and March 15, 2020, were evaluated retrospectively. The study was conducted in Acibadem Mehmet Ali Aydinlar University Research Institute of Senology (RISA).

Age, sex, tumor side, hospital stay duration, tumor type (benign, invasive, or non-invasive), type of initial treatment (upfront surgery or NACT), and number and type of surgery to the breast and axilla of each patient were recorded. Procedures were evaluated separately as upfront surgery and surgeries performed after NACT. Procedures were first evaluated in three groups as excisional biopsies, breast-conserving surgeries (BCS), and mastectomies. Subsequently, mastectomies were evaluated in separate groups as simple, skin-sparing, and nipple-sparing mastectomies (NSM). Excisional biopsies included surgeries performed for suspicious lesions in which only the lesion is excised. BCS included surgeries in which the entire breast was not removed. Simple mastectomy included mastectomies in which the nipple and skin were removed without simultaneous reconstruction. Skin-sparing mastectomies included mastectomies in which the nipple is removed, but simultaneous reconstruction is performed while preserving the breast skin. NSM included mastectomies in which both the nipple and breast skin were preserved, and simultaneous reconstructions were performed. Reconstructions were examined in two groups as reconstructions with silicone implants or autologous tissues. Axillary surgeries were examined in two groups as sentinel lymph node biopsy and axillary lymph node dissection.

Complications were evaluated according to the type of surgery to both the breast and axilla and whether they developed after upfront surgery or surgeries after NACT. The severity of the complications was evaluated according to the Clavien-Dindo classification (7). If there was more than one complication in the same patient, the patient was evaluated according to the more serious complication based on the Clavien-Dindo classification.

With the declaration of the pandemic in Turkey, RISA-affiliated hospitals were declared as pandemic hospitals. Multidisciplinary tumor meetings were conducted with the participation of doctors on-site by restricting the participation of nurses, secretaries, and allied health professionals. All patients were discussed and treatment decisions were made at the multidisciplinary tumor meetings as in the pre-pandemic period. During the pandemic, all surgeries were performed in COVID-19-free operating rooms and patients were hospitalized in COVID-19-free wards. During the pandemic period, low-dose thoracic computed tomography was taken for each patient scheduled for surgery until June 1, 2020. After this time, reverse-transcriptase polymerase chain reaction (PCR) testing for SARS-CoV-2 was used in accordance with the European guidelines (8). Surgeries of patients with positive PCR for COVID-19 were delayed for 4 weeks until having negative PCR results and disappearance of symptoms. The algorithm applied to patients before surgery is shown in Figure 1.

Patients who did not have any postoperative complaints were called for a follow-up on the 10th postoperative day to evaluate the wound site and to inform the patient about the postoperative treatment protocols. If the patient had complaints, the patient was assessed by phone. If the complication was considered as at least class 2 according to the Clavien-Dindo classification, an in-hospital appointment was planned.

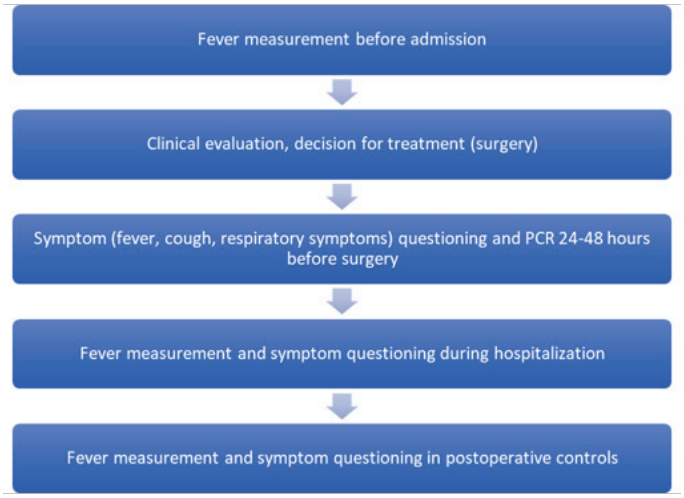

Figure 1. Algorithm applied to patients before surgery for COVID-19 screening

COVID-19: Coronavirus disease-2019, PCR: polymerase chain reaction

Ethical approval

Ethics committee approval from the Ministry of Health of Turkey was taken (file no: Akif Enes ARIKAN-2021-03-20T12_50_30) and from the Ethics Committee of Acibadem Mehmet Ali Aydinlar University (approval number: 2021-06/25, date: 24.03.2021).

Statistical Analysis

Study data were collected and managed using research electronic data capture (REDCap) tools hosted at the Acibadem Mehmet Ali Aydinlar University (9). All statistical analyses were performed using SPSS 25.0 (IBM Corp., Armonk, NY, USA). A p-value <0.05 was considered significant. Analysis of variance was performed for continuous variables, and a chi-square or Fisher's exact test was used for categorical variables. Continuous data are reported as mean ± standard deviation.

Results

Data of 220 patients who underwent breast surgery during the first and second wave of the COVID-19 pandemic and of the control group between December 15, 2019, and March 15, 2021, were retrospectively analyzed.

The COVID-19 PCR test was positive in two patients with cough during the preoperative period. Preoperative PCR test was positive for two patients without symptoms. The surgeries of these patients with positive PCR were delayed for 4 weeks after the symptoms resolved and the PCR results became negative. No COVID-19 case was detected in the first 30-day postoperatively in any of the patients, including patients with PCR-positive results preoperatively, and no COVID-19-related complications were observed. In addition, COVID-19 was not detected in healthcare personnel participating in breast surgeries. COVID-19 developed in two surgeons from the surgical team and the sources of infections were their family members.

Table 1. Characteristics of the patients

		Pre-pandemic	First wave	Second wave	Total	p
n		130	28	62	220	-
Age (years)		48.23±12.26	50.75±15.19	47.87±12.94	48.45±12.94	0.594
Hospital stay (day)		1.469±0.769	1.785±1.343	1.645±0.925	1.56±0.91	0.167
Tumor side	Left	64 (49.2%)	13 (46.4%)	35 (56.5%)	112 (50.9%)	0.567
	Right	66 (50.8%)	15 (53.6%)	27 (43.5%)	108 (49.1%)	
Sex	Male	1 (0.8%)	0 (0%)	0 (0%)	1 (0.5%)	0.706
	Female	129 (99.2%)	28 (100%)	62 (100%)	219 (99.5%)	
Tumor type	Benign	20 (15.4%)	3 (10.7%)	10 (16.1%)	33 (15%)	0.286
	In situ	12 (9.2%)	3 (10.7%)	8 (12.9%)	23 (10.5%)	
	Invasive	98 (75.4%)	22 (78.6%)	44 (71%)	164 (74.5%)	
Type of surgery to the breast	Excisional biopsy	17 (13.1%)	3 (10.7%)	10 (16.1%)	30 (13.6%)	0.139
	Breast-conserving surgery	65 (50%)	15 (53.6%)	23 (37.1%)	103 (46.8%)	
	Simple mastectomy	14 (10.8%)	3 (10.7%)	8 (12.9%)	25 (11.4%)	
	Skin-sparing mastectomy	5 (3.8%)	1 (3.6%)	0 (0%)	6 (2.7%)	
	Nipple-paring mastectomy	29 (22.3%)	6 (21.4%)	21 (33.9%)	56 (25.5%)	
Type of surgery to the axilla	None	22 (16.9%)	8 (28.6%)	10 (16.1%)	40 (18.2%)	0.47
	SLNB	76 (58.5%)	12 (42.9%)	38 (61.3%)	126 (57.3%)	
	ALND	6 (4.6%)	0 (0%)	3 (4.8%)	9 (4.1%)	
	SLNB + ALND	26 (20%)	8 (28.6%)	11 (17.7%)	45 (20.5%)	
Initial treatment	Upfront surgery	101 (77.7%)	20 (71.4%)	43 (69.4%)	164 (74.5%)	0.427
	Neoadjuvant chemotherapy	29 (22.3%)	8 (28.6%)	19 (30.6%)	56 (25.5%)	
Complication	Yes	28 (21.5%)	9 (32.1%)	9 (14.5%)	46 (20.9%)	0.157
	No	102 (78.5%)	19 (67.9%)	53 (85.5%)	174 (79.1%)	
Clavien-Dindo classification of complications	I	9 (32.1%)	1 (11.1%)	2 (22.2%)	12 (26.1%)	0.806
	II	13 (46.4%)	6 (66.7%)	6 (66.7%)	25 (54.3%)	
	IIIa	3 (10.7%)	1 (11.1%)	1 (11.1%)	5 (10.9%)	
	IIIb	3 (10.7%)	1 (11.1%)	0 (0%)	4 (8.7%)	
Complications requiring intervention	No*	22 (78.6%)	7 (77.8%)	8 (88.9%)	37 (80.4%)	0.775
	Yes**	6 (21.4%)	2 (22.2%)	1 (11.1%)	9 (19.6%)	

SLNB: Sentinel lymph node biopsy, ALND: axillary lymph node dissection, *: Clavien-Dindo class 1-2 complication, **: Clavien-Dindo class 3 complication

Table 2. Type and timing of complications after breast surgery

Complications	Period	
	Early (<30 days)	Late (>30 days)
Fibrosis	-	1 (6.3%)
Hematoma	2 (5.6%)	-
Lymphedema	-	3 (18.8%)
Necrosis (full thickness)	1 (2.8%)	-
Ischemia	2 (5.6%)	-
Capsule formation	-	3 (18.8%)
Prosthesis rejection	-	3 (18.8%)
Seroma	21 (58.3%)	5 (31.3%)
Wound infection	4 (11.1%)	-
Fever	2 (5.6%)	-
Postoperative nausea	4 (11.1%)	-
Rotation of implant	-	1 (6.3%)

No significant difference was found between the pre-pandemic, first wave, and second wave periods in terms of age, sex, hospital stay, tumor site, tumor type (benign/*in situ*/invasive), type of initial treatment, and type of surgery to the breast and axilla. The characteristics of the patients are shown in Table 1.

The types and timing (early/late period) of the complications are shown in Table 2. Clavien-Dindo classification of complications according to the type of initial treatment and pandemic period is shown in Table 3.

No significant difference was noted between the pre-pandemic, first wave, and second wave periods in terms of complication development, complication type, Clavien-Dindo classification of complications, and complications requiring intervention.

Discussion

In this single-center study of 220 patients, no complications related to COVID-19 were detected in breast surgeries performed in the first and second waves of the pandemic period. In addition, the number

Table 3. Clavien-Dindo classification of complications according to the type of initial treatment and pandemic period

Type of initial treatment	Period	Clavien-Dindo classification				Total	p
		1	2	3a	3b		
Upfront surgery	Pre-pandemic	4 (23.53%)	11 (64.71%)	1 (5.88%)	1 (5.88%)	17	0.688
	First wave	-	5 (83.33%)	1 (16.67%)	-	6	
	Second wave	2 (33.33%)	3 (50%)	1 (16.67%)	-	6	
	Total	6 (20.69%)	19 (65.52%)	3 (10.34%)	1 (3.45%)	29	
Surgery after neoadjuvant chemotherapy	Pre-pandemic	5 (45.45%)	2 (18.18%)	2 (18.18%)	2 (18.18%)	11	0.359
	First wave	1 (33.33%)	1 (33.33%)	-	1 (33.33%)	3	
	Second wave	-	3 (100%)	-	-	3	
	Total	6 (35.29%)	6 (35.29%)	2(11.76%)	3 (17.65%)	17	

of complications did not increase because of breast surgery. Our study shows that with appropriate precautions, breast surgery can be performed safely in the pandemic period.

Following the announcement of the COVID-19 pandemic by the WHO, measures have been taken in many countries. Like other countries, the government of Turkey emphasized the importance of social isolation and directed people to practice social isolation. Curfews were implemented for patients aged >65 or for those with comorbidities. Private and public hospitals were declared as pandemic hospitals, and a circular was issued by the Ministry of Health of Turkey to stop surgeries other than emergency and cancer surgeries.

The safety of surgeries was questioned in the early period of the pandemic. Studies in this period had reported high mortality and morbidity associated with surgeries, especially in patients with COVID-19 (4,10,11). In the international cohort study by the COVIDSurg group covering 1,128 patients who underwent surgery between January 1 and March 31, and 294 of whom were diagnosed with COVID preoperatively, the 30-day mortality rate was 23.8% (268 of 1,128) (10). Pulmonary complications occurred in 577 (51.2%) of 1,128 patients, and the 30-day mortality rate in these patients was 38.0% (219 of 577), accounting for 81.7% (219 of 268) of all deaths. Many authors have recommended postponement of surgeries if possible in the early period of the COVID-19 pandemic due to reasons such as the effects of COVID-19 on mortality and morbidity and the allocation of hospital beds and sources to patients with COVID-19 (1,3-5). Moreover, since COVID-19 was seen more in healthcare workers in the early pandemic period, ensuring the protection of healthcare workers had also been effective on this decision (12,13).

However, studies reporting that safe surgery can be performed in the pandemic period have started to emerge (14-23). These studies have reported that complications due to surgery do not increase during the pandemic and that COVID-19-associated complications are not high. In the present study, as there was no increase in complications during the pandemic period, no COVID-19-related complications were observed.

Although the risks associated with COVID-19 are high in patients with malignancy in the early pandemic period, there are publications that show breast cancer does not pose a high risk for COVID-19 (24,25). In the study involving 279 patients who received chemotherapy, 92 of which had breast cancer, between January 19 and April 2020, more complications were found in hematologic cancers compared than in solid tumors (24). The author reports that treatment can be applied by taking precautions in solid cancers such as breast cancer. Similarly, Zhang et al. (25) compared 35 patients with COVID-19 and breast cancer and 55 patients with COVID-19 without breast cancer and 81 patients with COVID-19 and cancer other than breast cancer as controls. They reported no differences in disease severity and outcomes between patients with COVID-19 and breast cancer and common patients with COVID-19. Moreover, the clinical characteristics of patients with breast cancer were milder than those with other types of cancers. In line with these studies, we can state that breast cancer does not pose a high risk for COVID-19, considering the short duration of hospitalizations because of breast surgery (26).

Ji et al. (16) evaluated a total of 621 patients, 141 of whom underwent breast-endocrine surgery, who underwent elective cancer surgery between 01.02.2020 and April 27, 2020. While PCR was performed in only symptomatic cases (n=40, 6.4%), COVID-19 infection was not detected in any patients postoperatively.

One of the most important studies regarding safe surgery during the COVID-19 pandemic is the study by the COVIDSurg group, which includes 9,171 patients, of which 2,140 had undergone breast surgery (17). In total, 2,481 patients received surgery following the COVID-19-free surgical pathway (i.e., complete segregation of the operating theater, critical care, and inpatient ward areas). COVID-19-free surgical pathways were followed for younger patients with less comorbidities. The postoperative SARS-CoV-2 infection rate was also lower in COVID-19-free surgical pathways. Pulmonary complication rates were lower with COVID-19-free surgical pathways (2.2% vs 4.9%). Therefore, they suggest that dedicated COVID-19-free surgical pathways should be established to provide safe elective cancer surgery in the current and before future outbreaks of SARS-CoV-2.

Another important study of Kane et al. (18) showed that elective surgeries can be performed under appropriate conditions; the study involved 557 patients between March 29 and June 12, 2020. Patients without COVID-19 symptoms were screened by oronasal swab and chest imaging (chest X-ray or computed tomography if aged ≥18 years) and preceded to surgery if negative. While 13 (2.4%) patients tested positive during screening, 7 (1.4%) tested positive for COVID-19 [1.4%, 95% confidence interval (CI): 0.7-2.8%] with one COVID-19-related death (0.2%, 95% CI: 0.0-1.1%) within 30 days.

Another issue related to the postponement of surgeries during the pandemic is the overload problem that may occur after the pandemic. The COVIDSurg group performed an estimation using a Bayesian β-regression model for 12-week cancellation in 190 countries (27). The best estimate was that 28,404,603 operations would be cancelled or postponed. If countries increased their normal surgical volume by 20% after the pandemic, a median of 45 weeks is needed to clear the backlog of operations resulting from the COVID-19 disruption. The rapid decrease in the number of patients in the early period of the pandemic supports this estimation. However, the number of operations has increased after the first wave because of reasons such as the adaptation of the clinic and patients, fluctuating course of the pandemic, and application of COVID-free protection methods throughout the country. To prevent this scenario, which the COVIDSurg group estimates, appropriate measures should be taken and the surgeries should continue. Therefore, hospitals can be made available for surgery or not every hospital is declared a pandemic, and some can be spared.

In the COVID-19 pandemic or similar pandemics that may occur in the future, precautions should be taken from the first diagnosis of the patient to the end of the treatment so that the surgeries can continue, treatments are not delayed, and post-pandemic overload can be prevented. These measures should include the following:

- Hospitals with COVID-19-free surgical pathway should be organized, and these hospitals should not be declared as pandemic hospitals and should be spared for oncological treatments.

- Patients should be questioned in terms of COVID-19 related complaints at the time of admission and follow-up.

- Symptom screening and suspicious travel questioning should be conducted at the entrance of the hospital, and patients with suspicious symptoms should be directed to the COVID-19 clinic.

- At the beginning of the treatment, in line with the guidelines of the institutions, PCR, chest radiography, or low-dose thorax CT should be performed for COVID-19.

- In the hospital, patients should wear a mask without valve.

- The number of companions should be reduced.

- To provide a social distance between patients, the space between the seats should be widened and daily magazine or tabloid magazines should be removed.

- The use of personal protective equipment by all healthcare professionals is mandatory.

- Healthcare professionals and patients should pay attention to hand hygiene.

- The number of healthcare personnel and patients in all areas within the hospital should be minimized.

- Movements of patients and healthcare personnel between departments should be minimized.

- In areas where healthcare personnel gather, such as dining halls, the sitting areas should be made sparse. Meals can be prepared in disposable containers, and the healthcare personnel can eat in the department where they work or the meals can be sent to the departments to reduce contacts between departments.

- In operating rooms, a minimum number of medical personnel should be employed.

- In case of delay or delay in elective breast cancer surgery, a metallic marker should be placed in every patient who has an image-guided biopsy if it does not contain microcalcification.

- Telemedicine can be used to reduce the number of hospital admissions (28).

Conclusion

Breast surgery can be performed safely during the COVID-19 pandemic. For safe surgery, appropriate precautions against COVID-19 should be taken and COVID-19 screening should be performed. COVID-19-free surgical pathway (i.e., complete segregation of the operating theater, critical care, and inpatient ward areas) is also important for a safe surgery. With the continuation of surgeries, our method can prevent the fear of upstaging and therefore requirement of more aggressive treatment for tumors and post-pandemic overload.

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Effect of Preoperative Trapezius Myalgia on Postoperative Pain

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ABSTRACT

Introduction: Trapezius myalgia (TM) is the chronic pain of trapezius muscle, one of the most common reasons for shoulder pain seen in a common population. The aim of our study is to determine the effects of an existence of preoperative TM to the postoperative pain in the patients, who underwent a laparoscopic cholecystectomy.

Methods: After receiving an ethical committee approval, we have included 60 ASA 1-2 patients who underwent a laparoscopic cholecystectomy surgery in the general surgery operating room in University of Health Sciences Turkey, İstanbul Training and Research Hospital between January and June 2015. The patients who were classified as ASA 3-4, had head and neck surgery or trauma, operations which had started as the laparoscopic procedures but then had to be performed as an open surgery, patients who had rheumatological and neurological diseases, tendinitis that affects the shoulder joints, and patients who had to have the emergency surgeries were excluded in this study. Patients were divided into two groups, one with (TM+) and who were not having (TM), when evaluated preoperatively. Each group had analgesia by a patient-controlled device. Using Numeral Rating scale demographical data, shoulder and umbilical pain levels were evaluated, and postoperative analgesic needs and doses were recorded in the case files.

Results: Five patients who were excluded; n=26 in TM+ group and n=29 in TM group were taken. There was no significant demographic difference found between two groups. No statistically significant difference was found between TM+ and TM- groups ($p>0.05$). While no statistically significant difference was established in the tramadol doses between two groups, a total of ten patients out of 26 TM+ had shoulder pain, and additional analgesic need was found statistically increased in TM+ group ($p<0.001$).

Conclusion: We have concluded that the existence of a preoperative TM increased the need for analgesics postoperatively, this could be important for choosing the analgesic regimen, and that the TM should be considered after a laparoscopic cholecystectomy.

Keywords: Trapezius myalgia, postoperative pain, laparoscopic cholecystectomy

Introduction

Postoperative pain is a kind of acute pain which appears to happen due to a surgical trauma, and which decreases eventually by healing of tissues. The postoperative pain severity differs from patients to patient, and it is very subjective (1,2). The curing of pain is a very important process for the patient. Although postoperative pain appears to happen less in a laparoscopic cholecystectomy in comparison to the conventional methods, it is not a pain free method either.

The pain that occurs after a laparoscopic cholecystectomy clinically consists of three components. Visceral pain (deep abdominal pain), somatic pain (incisional pain), and shoulder pain (reflexion of a visceral pain). Shoulder pain appears because of a CO_2 insufflation, depending on the diaphragmatic and phrenic nerve irritation. Shoulder pain may increase with the movements and may continue for a few days after the operation, also the insufflated gas may cause severe pain (3). The severity of the postoperative pain cannot be predicted in length, and it shows individual differences (4).

The main reason why our patients come to our hospitals, who are the majority of the population consisting of women and lower income group, is that; they suffer from a chronic pain based on the chronic muscle-skeleton system (3,5).

Trapezius myalgia (TM) is one of those pains which is basically a chronic pain of the trapezius muscle, it is not only having the multifactorial ethnology, but also forms the 10-20% of the persistent pains (6-9).

In fibromyalgia, myofascial pain syndrome and the TM (which occurs as the component of both) patients detect some stimulators as a pain, although these are just stimulators caused by the change in the processing the pain and senses. This situation may cause an increase in the using analgesic caused by a decreased sensitivity to peripheral and central sensitization (10-13). In our study, we considered this situation

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and planned to work on the effects of the existence of a chronic TM pain on a postoperative pain in laparoscopic cholecystectomy patients.

Methods

After we got the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics committee (approval number: 677, date: 03.07.2015), a total of 60 voluntary patients are chosen randomly between the dates January and June 2015, who were going to have the ASA 1-2 laparoscopic cholecystectomy operation in the University of Health Sciences Turkey, İstanbul Training and Research Hospital general surgery operating room. Their consent was taken before starting the study. Some of the patients who have ASA 3-4, neck or shoulder operation, or trauma, rheumatic diseases, and who had to have an emergency operation are excluded from the study. Patients' age, gender, height, weight, body mass index (BMI), American Society of Anesthesiologists (ASA) scores are recorded on case report forms. In preoperative period, the existence of a TM is confirmed by pressing the thumb to the middle of the trapezius muscle on both the sides with approximately 4 kg of pressure (enough to make the nails white), and the patients' sensitivity toward this examination was observed. Patients are separated into the two groups, as the ones with the TM and the ones without it. General routines on anesthesia conditions are provided, and they are operated. During the operation, general anesthesia induction is given 2 mg/kg fentanyl + 2 mg/kg propofol + 0.5 mg/kg rocuronium, and during the maintenance 50% oxygen with 50% air mixture and 2% sevoflurane is used. To the patients in both the groups 300 mg tramadol HCL/100 cc mediflex, 10 mg/h basal infusion, 10 mg bolus dose is given with the controlled analgesia device (CADD-Legacy Patient Control Analgesia device Model 6300 Ambulatory Infusion Pump Smith Medical ASD, Inc. St. PAUL mn 55112 USA) with a 15 minutes lock down period.

In a postoperative period, patients who need analgesics are given with 1 mg paracetamol intravenous. Patients are visited in the 1st, 2nd, 4th, 8th, 12th, 18th hours, and checked if they had any pain in the shoulder or in the umbilical part of their body, scaled by the Numerical Rating scale (NRS); 0=no pain, 10=severe pain) and recorded. Patients' tramadol dosage, additional analgesic need, and the dose if needed are also recorded.

Statistical Analysis

Statistical analyses are done by using the SPSS version 15 software. The suitability of the variables to a normal criteria are inspected by the visuals (histogram and probability charts) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests), descriptive analysis for abnormal variables are given using the mid and interquartile intervals. Postoperative NRS scores are compared using a Mann-Whitney U test, because NRS scores in 1st, 2nd, 4th, 8th, 12th, and 18th hours do not show normal dispersion. The cases where p-value is <0.05 are considered statistically significant.

Results

In our study, a total of 60 patients are included. In that, 30 of them with TM and 30 of them without it. Five of the patients are later excluded from the study, because their operation started as laparoscopy but then changed to open cholecystectomy. Patients' demographic data and ASA scores are shown in the Table 1.

Despite that; after the statistical analysis done, statistically significant difference is not observed between TM+ and TM groups in terms of umbilical NRS scores (Table 2).

In conclusion to the statistical comparisons, no difference is found between TM+ and TM groups in accordance with age, BMI, and ASA rates. In conclusion to a statistical analysis, additional analgesics is found to be needed for ten patients out of 26 (38.4%) in TM+ group and five patients out of 29 (17.2%) in TM group. This situation is found statistically and meaningfully high (p=0.001) (Table 3). Paracetamol 1 gram intravenous is given to the ones who needed it. When the groups are compared about the tramadol dosages, no significant difference was detected (Table 4). According to the statistical analysis done, ten patients out of 26 in TM+ group had a shoulder pain.

Table 1. Demographic data and ASA scores of the participants

	TM+	TM-	Total	p
Age *	41.3±11.4 (min.: 22; max.: 60)	45.8±11.3 (min.: 26, max.: 65)	43.9±11.7 (min.: 22, max.: 65)	0.23
BMI*	27.8±3.1	27.6±3.6	27.7±3.3	0.78
ASA**				
1	20 (76.9%)	21 (72.4%)	41 (74.5%)	0.76
2	6 (23.1%)	8 (27.6%)	14 (25.5%)	

*Student's t-test, **chi-square test, TM+: the ones with trapezius myalgia, TM: the ones without trapezius myalgia, BMI: body mass index, min.: minimum, max.: maximum, ASA: American Society of Anesthesiologists

Table 2. Comparison of TM+ and TM- groups in terms of umbilical NRS scores

	(TM+) median (min.-max.) Mean ± SD	(TM-) median (min.-max.) Mean ± SD	p
1. hour	0 (0-5) 0.6±1.3	0 (0-8) 0.6±0.9	0.42
2. hour	0 (0-3) 0.4±0.9	0 (0-8) 0.6±1.9	0.86
4. hour	0 (0-2) 0.1±0.4	0 (0-6) 0.5±1.4	0.25
8. hour	0 (0.0) 0	0 (0.4) 0.4±1.2	0.07
12. hour	0 (0.0) 0	0 (0.4) 0.2±0.9	0.14
18. hour	0 (0.0) 0	0 (0.4) 0.2±0.9	0.14

Statistically significant (p<0.05), Mann-Whitney U test, TM: Trapezius myalgia, min.: minimum, max.: maximum, SD: standard deviation, NRS: Numerical Rating scale

Table 3. Comparison of TM+ and TM groups in terms of additional need for analgesics

		Yes, (n, %)	No (n, %)	p
Additional analgesics	TM+	10 (38.4)	16 (61.6)	0.001*
	TM	5 (17.2)	24 (88.8)	

Statistically significant (p<0.05), chi-square test. TM: Trapezius myalgia

Table 4. Comparison of TM+ and TM groups in terms of tramadol usage

	TM+	TM	p
Tramadol usage doses	291.9±19.5	286.2±26.1	0.348

Student's t-test, TM: Trapezius myalgia

Discussion

In our study while there was no difference found between the TM+ and TM groups according to the tramadol dosage, ten patients out of 26 with TM had a shoulder pain, and we observed that the TM+ group needed the additional analgesics. Despite that, in terms of umbilical NRS scores, there is no statistically important difference found between the groups. In the study of Kim et al. (14) conducted in 64 patients, the postoperative pain score is noted to be the highest in the 24th hour, and patients were observed for 48 hours. But in our study we were able to observe our patients only for 18 hours, because they were given with the oral analgesics and discharged earlier.

According to a study by Avtan et al. (15) having the sample size of 72 patients in purpose of searching the pain mechanism, the reasons of the pain and curing methods after a laparoscopic cholecystectomy is observed. They detected a postoperative pain in 63 of the patients. In 43 patients, the pain is detected mostly in trocar, in 21 patients the pain is detected in the right hypochondrium and back, and in 8 patients in shoulder (15).

In another study by Joris et al. (16) on 20 patients, they compared incisional, visceral, and shoulder pain. They realized that in postoperative 48 hours, incisional and visceral pain is felt much more intensely than a shoulder pain (16). After the laparoscopic cholecystectomy operations, it is seen that the left shoulder is also affected as well as the right shoulder (16).

Another study done by Lee et al. (17) about a post laparoscopic shoulder pain incidence, they reported that after 24 hours, 33 patients (39.3) said that wound pain is more severe than the shoulder pain, 41 patients (48.8) said wound pain is less than the shoulder pain, and 10 patients (11.9) said wound pain and shoulder pain are equal. The different results between those studies and our study may be related to the existence of TM or because of the difference between our perioperative analgesic usage protocols.

In our study we thought the reason why the shoulder pain is not detected in the TM cases are because the pain was dominated by the visceral pain. While the TM patients' shoulder pain may be caused by the TM, it may also be because of the effects of this illness which causes some changes in the procession of senses and central sensitization (18).

In our study, there were no differences found between the groups in terms of tramadol usage doses, but the need of additional analgesics was higher in the TM+ group than the TM group. As the reason of this situation, we thought that chronic existence of the TM's effects on a peripheral and central sensitization, and reduced sensitivity to opioidergic effect.

Study Limitations

Because the laparoscopic cholecystectomy patients who agreed to be included in our study were all women, our study cannot be regarded as homogeneous in the aspect of gender. One of the other limitations was; while studies on this matter require 24-48 hours of acute pain follow-ups according to the literature, we were able to observe our patients just for 18 hours. This was because they were discharged prematurely due to the usage of the oral analgesics.

Conclusion

As a result, postoperative pain is unique. It may differ in the severity and it is subjective. Pain control is crucial in terms of an early discharge after operation, shortening the healing time, and reducing operational costs.

The patients who have chronic pain may sense pain because of the changes in their pain and sense process, whereas the normal people do not feel any pain at all. Peripheral sensitization, central sensitization, and reduced sensitivity to the opioidergic effect in neck neurons may cause an increase in the analgesics consumption.

In our study we took those data into consideration, and we think that the preoperative existence of TM increases the analgesic need during the postoperative period. Therefore, we came into a conclusion that, the patients who have shoulder pain after a laparoscopic cholecystectomy in postoperative period, TM should be taken into consideration and the existence of the TM is very important in the analgesics regimen planning.

Ethics Committee Approval: This study approval by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 677, date: 03.07.2015).

Informed Consent: Their consent was taken before starting the study.

Peer-review: Externally peer-reviewed.

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The Association Between Arg72Pro C>G Polymorphism in the *p53* Gene and the Risk of Obesity

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ABSTRACT

Introduction: The role of genetic factors in obesity has long been recognized, but their involved specific genes remained unidentified. The relationship between *p53* gene single nucleotide polymorphisms and the risk of obesity has been investigated in recent years. Therefore, this study aimed to investigate the association of p53 Arg72Pro C>G (rs1042522) polymorphism with the risk of obesity in our study.

Methods: This study included 52 patients with obesity (26 were females and 26 were males) and 52 normal-weight healthy controls. Genomic DNA isolation was performed from the blood samples of all participants. P53 Arg72Pro C>G (rs1042522) polymorphism was detected by real-time quantitative polymerase chain reaction from genomic DNA samples.

Results: No significant associations were identified between Arg72Pro (rs1042522) P53 polymorphism and obesity risk. Glucose levels are significantly different between the obese and control groups with the CC and CG genotypes, but without difference in the GG homozygous genotype.

Conclusion: Our study is one of the first to investigate the relationship between p53 codon 72 polymorphisms and obesity risk but revealed no correlation between them. The relatively small number of participants may limit our study. Further research is needed in a large cohort to associate the *p53* gene Arg72Pro C>G (rs1042522) variant with obesity risk.

Keywords: P53, risk of obesity, single nucleotide polymorphism

Introduction

Obesity is a disease that occurs when caloric intake and expenditure imbalance, resulting in increased visceral adiposity and systemic low-grade chronic inflammation. Obesity is caused by several factors, including metabolic, social, environmental, and genetic (1). Obesity has become a global health problem that is linked to various diseases, including diabetes mellitus, hypertension, metabolic syndrome, atherosclerosis, and cancer. Aside from the exogenous and endogenous variables, the role of genetic factors in obesity has long been recognized, but the specific genes involved have not yet been thoroughly identified (2).

One of the genes that play a central role in intracellular metabolic pathways is p53. P53, commonly known as the tumor suppressor gene, is a transcription factor that controls gene expression in the cell cycle, DNA repair, differentiation, and apoptosis (3). Furthermore, it regulates various metabolic activities, including glycolysis, glycogen synthesis, oxidative phosphorylation, and lipogenesis (4). P53 directly suppresses the expression of two glucose transporters (GLUT), GLUT1 and GLUT4 in glucose metabolism, leading to reduced glucose flux (5). P53 inhibits lipid synthesis while promoting fatty acid oxidation by inducing the expression of *carnitine acetyltransferase* genes, which transport fatty acids to the mitochondria for oxidation (6). In adipogenesis, it promotes brown adipocyte development while suppressing white adipocyte differentiation (7).

Many polymorphisms have been discovered in the *p53* gene's promoter, exon, and intron regions. P53 single nucleotide polymorphisms (SNPs) have been linked to a higher risk of cancer, autoimmune disorders, diabetes, and obesity in numerous studies (8,9). The most widely investigated p53 polymorphism is Arg72Pro C>G (rs1042522), which occurs at codon 72 and has been proven to alter p53 function (10). In 55,521 Europeans, the G allele located at p53 codon 72 was associated with an increased prevalence of type 2 diabetes (11). The Arg72 variant increases the ability of p53 to induce apoptosis, while the pro-encoding allele has a lower apoptotic activity (12). The increased apoptotic rate of pancreatic beta cells causes impaired insulin secretion, which sometimes results in elevated plasma glucose (11). A study that consist of 136 patients with obesity and 122 healthy subjects revealed the relationship between the p53 rs1042522 GG genotype and obesity risk with men with

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obesity, showing a three-fold higher risk with the GG genotype (13). No other study has yet been performed in the literature that revealed the association of p53 Arg72Pro C>G variant with obesity. With the proven effect of this SNP on obesity, its use as a biomarker may be possible. Therefore, this study aimed to investigate the association between p53 Arg72Pro C>G polymorphism and obesity risk in our study.

Methods

Study Subjects

The study included 52 patients with obese (26 females and 26 males) and 52 normal-weight healthy individuals (28 females and 24 males) between the ages of 18 and 65 years who presented to the İstanbul Aydin University VM Medical Park Florya Hospital, General Surgery Department with complaints of overweight and related symptoms. The study group was formed by calculating the body mass index (BMI) [(kg)]/height^2(m^2)]. The BMI, demographic data, and laboratory values were collected according to standard procedures (Table 1). The mean age was 36.00 (29.50-43.50) years for patients with obesity and 36.50 (32.00-43.00) years in the control group. Psychotic or bipolar disorders, eating disorders, pregnancy and lactation, and documented cancer are all exclusion factors. The study protocol complies with the 2013 Helsinki Declaration ethical guidelines and was approved by the İstanbul Aydın University Ethics Committee (approval number: B.30.2. AYD.0.00.00.050-06.04/589). The informed consent form was obtained from all participants.

DNA Extraction and Genotyping

Venous blood samples were taken from all individuals who voluntarily agreed to participate in the study. Genomic DNA isolation was performed using the spin column method following the protocol of the commercial kit (Jena, Bioscience). A nanodrop spectrophotometer was used to evaluate the purity of DNAs (Epoch, Biotek). DNA samples with an absorbance value -was detected by real-time quantitative polymerase chain reaction (qRT-PCR) from genomic DNA samples (7500 Fast RT-PCR System, Applied Biosystems). qRT-PCR was performed with a total volume of 10 µL for each sample using 2.75 µL of dH2O, 5 µL of master mix kit (TaqMan, Thermo Fisher Scientific Inc.), 0.25 µL of genotyping assay kit (TaqMan, Applied Biosystems, Waltham, MA, ABD) (Assay ID: C_2403545_10), and 2 µL DNA (10 ng/µL). The DNA sequence of the probe used to determine the changing base of the SNP is "AGGAGCTGCTGGTGCAGGGGCCCACG[C/G]GGGGAGCAGCCTCTGGCATTCTGG" (Thermo Fisher Scientific), and its luminescence in the device changes based on the allele-specific VIC/FAM fluorescent dye. qRT-PCR conditions were set as 40 cycles of 15 min at 95 °C and 1 min at 60 °C after an initial denaturation step of 10 min at 95 °C. Results were analyzed according to VIC/FAM illumination pattern.

Statistical Analysis

Study data analyses were performed using the Statistical Package for the Social Sciences version 19 (IBM Co., Ltd., Chicago, IL, USA). The Shapiro-Wilk and Levene tests were used to determine the normality and homogeneity of variances. The Mann-Whitney U test was used to compare the differences between two independent groups when the variable is continuous, but not normally distributed. The chi-square test was performed to evaluate the distribution of genotype and allele frequencies of p53 polymorphisms. A p-value of <0.05 was used to determine statistical significance.

Results

This study included 52 patients with obesity and 52 normal-weight controls. The overall clinical characteristics of all participants are

Table 1. Comparison of variables in obese and control group, as well as by gender

	Variables	**Control (n=52) Median (25-75%)**	**Obese (n=52) Median (25-75%)**	**p**
Study group	Age (year)	36.50 (32.00-43.00)	36.00 (29.50-43.50)	0.376
	BMI (kg/m^2)	22.64 (20.25-24.00)	42.25 (39.25-45.70)	0.001***
	Glucose (mg/dL)	78.00 (75.00-83.50)	103.50 (87.00-122.00)	0.001***
	HOMA-IR index	1.05 (0.74-1.17)	18.36 (11.35-21.10)	0.001***
Gender	**Variables**	**Control (n=28) Median (25-75%)**	**Obese (n=26) Median (25-75%)**	**p**
Women	Age (year)	34.50 (29.50-41.00)	35.50 (29.00-44.00)	0.924
	BMI (kg/m^2)	22.11 (19.94-23.34)	40.25 (37.50-42.67)	0.001***
	Glucose (mg/dL)	78.00 (76.50-84.00)	111.00 (85.00-119.00)	0.001***
	HOMA-IR index	1.05 (0.86-1.33)	18.36 (11.20-20.00)	0.001***
	Variables	**Control (n=24) Median (25-75%)**	**Obese (n=26) Median (25-75%)**	**p**
Men	Age (year)	42.00 (35.00-48.50)	36.00 (32.00-43.00)	0.173
	BMI (kg/m^2)	23.68 (21.95-24.33)	45.00 (41.50-46.50)	0.001***
	Glucose (mg/dL)	78.00 (74.50-78.00)	102.00 (89.00-128.00)	0.001***
	HOMA-IR index	1.05 (0.65-1.05)	18.36 (13.30-21.50)	0.001***

Mann-Whitney U; values are expressed as median (25-75%). BMI: body mass index, HOMA-IR index: Homeostatic model assessment for insulin resistance, kg: kilogram, m: meter, mg: milligram, dL: deciliter, p-value *p<0.05, **p<0.01, ***p<0.001

presented in Table 1. The mean BMI of the obese participants was 42.25 (39.25-45.70), whereas 22.64 (20.25-24.00) in the normal-weight control group. Glucose ($p<0.001$) and insulin resistance [Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) Index] ($p<0.001$) were significantly different between the two groups. Likewise, glucose ($p<0.001$) and HOMA-IR Index ($p<0.001$) were significantly different between the obese and healthy controls in males and females (Table 1).

The genotype frequencies of the P53 Arg72Pro (rs1042522) polymorphism and its associations with obesity are summarized in Table 2. The frequency of the C allele was 70 (67.3%) in the control group and 63 (60.6%) in the obese group, whereas the G allele was 34 (32.7%) in the control group and 41 (39.4%) in the obese group. No significant associations were identified between the Arg72Pro (rs1042522) P53 polymorphism and obesity risk. The distribution of Arg72Pro (rs1042522) and p53 rs1042522 variant by BMI of males and females are summarized

Table 2. Distribution of p53 genotypes in obese and control group, as well as by gender

SNP (rs1042522)	Variant	Control (n=52) (n, %)	Obese (n=52) (n, %)	OR (95% CI)	χ^2	p
	CC (Pro/Pro)	22 (42.3)	19 (36.5)	1	-	Ref
	CG (Pro/Arg)	26 (50.0)	25 (48.1)	1.113 (0.489-2.537)	0.07	0.798
	GG (Arg/Arg)	4 (7.7)	8 (15.4)	2.316 (0.601-8.916)	1.53	0.215
	Allele frequency					
	C (Pro) allele	70 (67.3)	63 (60.6)	1.340 (0.759-2.364)	1.02	0.312
	G (Arg) allele	34 (32.7)	41 (39.4)	0.746 (0.423-1.317)	1.02	0.312
	Dominant model					
	CC + CG	48 (92.3)	44 (84.6)	1	-	Ref
	GG	4 (7.7)	8 (15.4)	0.458 (0.129-1.629)	1.51	0.220
	Recessive model					
	CC	22 (42.3)	19 (36.5)	1	-	Ref
	GG + CG	30 (57.7)	33 (63.5)	1.274 (0.579-2.801)	0.36	0.547
Women	**Variant**	**Control (n, %)**	**Obese (n, %)**	**OR (95% CI)**	χ^2	**p**
	CC (Pro/Pro)	9 (32.1)	9 (34.6)	1	-	Ref
	CG (Pro/Arg)	17 (60.7)	15 (57.7)	0.882 (0.278-2.803)	0.05	0.832
	GG (Arg/Arg)	2 (7.1)	2 (7.7)	1.000 (0.115-8.730)	0.00	1.000
	Allele frequency					
	C (Pro) allele	35 (62.5)	33 (63.5)	0.960 (0.439-2.097)	0.01	0.918
	G (Arg) allele	21 (37.5)	19 (36.5)	1.042 (0.477-2.278)	0.01	0.918
	Dominant model					
	CC + CG	26 (92.8)	24 (92.3)	1	-	Ref
	GG	2 (7.2)	2 (7.7)	0.923 (0.120-7.078)	0.01	0.939
	Recessive model					
	CC	9 (32.1)	9 (34.6)	1	-	Ref
	GG + CG	19 (67.9)	17 (65.4)	0.895 (0.288-2.776)	0.04	0.847
Men	CC (Pro/Pro)	13 (54.2)	10 (38.5)	1	-	Ref
	CG (Pro/Arg)	9 (37.5)	10 (38.5)	1.444 (0.426-4.897)	0.35	0.554
	GG (Arg/Arg)	2 (8.3)	6 (23.1)	3.900 (0.645-23.598)	2.36	0.124
	Allele frequency					
	C (Pro) allele	35 (72.9)	30 (57.7)	1.974 (0.851-4.580)	2.54	0.111
	G (Arg) allele	13 (27.1)	22 (42.3)	0.506 (0.218-1.175	2.54	0.111
	Dominant model					
	CC + CG	22 (91.6)	20 (76.9)	1	-	Ref
	GG	2 (8.4)	6 (23.1)	1.891 (0.613-5.833)	2.02	0.155
	Recessive model					
	CC	13 (54.1)	10 (38.5)	1		Ref
	GG + CG	11 (45.9)	16 (61.5)	0.303 (0.055-1.677)	1.24	0.266

Chi-square test was used to evaluate the distribution of genotype and allele frequencies of p53 polymorphisms. SNP: Single nucleotide polymorphisms, OR: odds ratio, CI: confidence interval

in Table 2. The p53 polymorphism is not linked to obesity risk in either gender (Table 2).

Further, the p53 SNP rs1042522 were separately analyzed in each genotype (CC, CG, and GG) association with age, BMI, glucose, and HOMA-IR index (Table 3). Obese participants with p53 (rs1042522) CC, CG, and GG genotypes had higher BMI and HOMA-IR levels than the controls. Glucose levels are significantly different between the obese and control groups with the CC and CG genotypes but without difference in the GG homozygous genotype.

Discussion

The *p53* gene Arg72Pro C>G (rs1042522) polymorphism has been extensively studied as a risk factor in several cancer types (14). The codon 72 polymorphism, which occurs in exon 4 of p53, results in a non-conservative change of an arginine (R72) to a proline (P72) at amino acid 72 and leads to a structural change in the protein that will alter the apoptosis activity (15). Recent studies revealed that this functional change in P53 is associated with insulin resistance, diabetes, and obesity, as well as some cancer types (16).

The waist circumference of participants with the P53 rs1042522 GG genotype expands more over time than those with the CC and CG genotypes, according to a study that involves a large number of people from the Dutch and Finnish populations (17). However, the increased waist circumference has not been associated with obesity. Another study revealed that mice with the R72 variant fed a high-fat diet gained more weight and developed glucose intolerance, insulin resistance, and fatty liver disease compared to the P72 variant (18). The p53 rs1042522 GG genotype significantly increased the risk of obesity in the Saudi population. Additionally, male participants with obesity have a three-fold higher risk in the GG genotype (13). Our study is one of the first to investigate the relationship between the p53 codon 72 polymorphisms and obesity risk. No correlation was found between the p53 rs1042522 variant and obesity risk according to allele and genotype distributions. Additionally, any link between obesity risk and gender was not determined. The relatively small number of obese participants and healthy control groups may limit our study.

A study of 335 patients with type 2 diabetes and 367 healthy controls shows that the p53 codon 72 polymorphism affects insulin resistance independent of body mass in patients with type 2 diabetes. Pro/Pro genotype was associated with lower HOMA-IR values compared to Arg/Arg and Arg/Pro genotypes but without difference in the HOMA-IR between diabetic and healthy Pro/Pro genotypes (19). The p53 rs1042522 polymorphism has increased the risk of type 2 diabetes in Chinese Han (20) and Iranian populations (21). Our study revealed that obese participants with p53 (rs1042522) CC, CG, and GG genotypes had higher BMI and HOMA-IR levels than the controls. However, genotype (CC, CG, or GG) is assumed to not affect this condition because people with obesity already have a high BMI and, as a response, high HOMA-IR levels. Glucose levels are significantly different between the obese and control groups with the CC (Pro/Pro) and CG (Arg/Pro) genotypes, whereas no difference in the GG (Arg/Arg) homozygous genotype. A relationship may not be determined with glucose because the number of patients with the GG genotype is minimal in both the obese and control groups.

Study Limitations

The most important limitation of our study is the relatively small number of participants.

Conclusion

Our study found no relationship between the *p53* gene Arg72Pro C>G (rs1042522) polymorphism and the obesity risk. Further research in a large cohort is needed to associate the *p53* gene Arg72Pro C>G (rs1042522) variant with obesity risk.

Ethics Committee Approval: The study protocol complies with the 2013 Helsinki Declaration ethical guidelines and was approved by the İstanbul Aydın University Ethics Committee (approval number: B.30.2.AYD.0.00.00.050-06.04/589).

Table 3. Comparisons of variables according to genotype in obese and control groups

Variables	Genotype	Control (n=52) median (25-75%)	Genotype	Obese (n=52) median (25-75%)	p
Age (year)	CC (Pro/Pro) (n=22)	40.00 (32.00-46.00)	CC (Pro/Pro) (n=19)	39.00 (29.50-46.00)	0.719
	CG (Pro/Arg) (n=26)	35.00 (33.00-43.00)	CG (Pro/Arg) (n=25)	33.00 (29.00-43.00)	0.399
	GG (Arg/Arg) (n=4)	32.50 (25.00-52.00)	GG (Arg/Arg) (n=8)	36.00 (34.00-42.00)	0.847
BMI (kg/m^2)	CC (Pro/Pro) (n=22)	22.76 (21.47-24.22)	CC (Pro/Pro) (n=19)	42.90 (40.40-46.20)	0.001***
	CG (Pro/Arg) (n=26)	22.53 (20.25-24.00)	CG (Pro/Arg) (n=25)	42.00 (38.10-45.00)	0.001***
	GG (Arg/Arg) (n=4)	20.93 (18.16-23.97)	GG (Arg/Arg) (n=8)	43.25 (36.55-46.35)	0.01**
Glucose (mg/dL)	CC (Pro/Pro) (n=22)	78.00 (73.00-78.00)	CC (Pro/Pro) (n=19)	107.00 (88.50-117.00)	0.001***
	CG (Pro/Arg) (n=26)	78.00 (78.00-85.00)	CG (Pro/Arg) (n=25)	101.00 (86.00-128.00)	0.001***
	GG (Arg/Arg) (n=4)	76.00 (70.00-88.50)	GG (Arg/Arg) (n=8)	100.50 (87.00-141.00)	0.249
HOMA-IR index	CC (Pro/Pro) (n=22)	1.05 (0.62-1.22)	CC (Pro/Pro) (n=19)	18.36 (12.45-22.10)	0.001***
	CG (Pro/Arg) (n=26)	1.05 (0.78-1.05)	CG (Pro/Arg) (n=25)	18.36 (11.50-18.36)	0.001***
	GG (Arg/Arg) (n=4)	1.03 (0.76-1.53)	GG (Arg/Arg) (n=8)	16.60 (10.95-24.35)	0.01**

Mann-Whitney U; Values are expressed as median (25-75%). BMI: Body mass index, HOMA-IR Index: homeostatic model assessment for insulin resistance, kg: kilogram, m: meter, mg: miligram, dL: deciliter, *p*-value *p<0.05, **p<0.01, ***p<0.001

Informed Consent: The informed consent form was obtained from all participants.

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To Feed or Not to Feed? During Hemodialysis Session

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ABSTRACT

Introduction: Patients undergoing hemodialysis (HD) like to eat during HD sessions. To prevent coronavirus infection, health authorities recommended restriction of taking food and fluids. In this multicenter retrospective chart review study, we aimed to confirm the relationship between oral intake and intradialytic complications using the date before and after the restriction in a relatively large HD population.

Methods: Data of a total of 190 (47% female) patients with prevalent HD during the 3 months before and 3 months after the restriction of oral intake during HD session were collected. In patients who received HD three times a week, data on blood biochemicals and clinical parameters taken routinely at the first week of each month were recorded from the dialysis session files. Differences between the means for both periods were evaluated using the χ^2 test for categorical variables and Student's t-test for continuous variables; $p<0.05$ was considered significant between groups.

Results: The mean age was 66±11.3 (23-91) years. Of the patients, 53% had diabetes mellitus, receiving HD treatment for 65.6±55.7 months. Rates of intradialytic hypotension (IDH) and muscle cramps decreased significantly (0.075% vs 0.043%, $p<0.001$; 0.016% vs 0.008%, $p<0.05$, respectively), whereas no changes in the hypoglycemia rate were noted.

Conclusion: IDH and muscle cramps mostly attributed to splanchnic vasodilation-related digestion may be prevented by restriction of food intake during HD sessions.

Keywords: Intradialytic hypotension, hemodialysis, muscle cramps

Introduction

Patients undergoing hemodialysis (HD) may encounter problems during the intradialytic period. Although some problems are preventable or mitigable, they continue to pose significant challenges to the quality of life of patients on HD. Intradialytic hypotension (IDH) is an upsetting condition mostly accompanied by nausea, vomiting, and muscle cramps during HD sessions. IDH has varied definitions, as there is no ideal blood pressure measurement during the session. Increased mortality was associated with intradialytic systolic blood pressure (SBP) <90 mmHg, whereas the K-DOQI guideline defines it as a drop of SBP >20 mmHg with accompanying symptoms (1). Increased cardiovascular mortality, loss of residual renal function, vascular access thrombosis, and dialysis insufficiency, which are all related to IDH, are important (2,3).

In dialysis sessions, the prevalence of IDH was 11.6% if the threshold of SBP <90 mmHg is accepted for the diagnosis and 10.1% when it is defined as a >20 mmHg decrease in SBP in addition to clinical findings and interventions of position and hypertonic solutions (4).

In the normal population, post-prandial hypotension (PPH) has not been clarified yet. According to some recent theories, PPH may be secondary to a postprandial increase in the levels of vasodilatory polypeptide incretins (5) and an insufficient sympathetic response (6). Another possibility is the attenuation of the arterial baroreflex, especially in the elderly (7).

During feeding, increased splanchnic blood pooling (8) and changes in the hemodynamic response to gastric distension (9) may probably lead to hypotension.

Generally, patients on maintenance HD are allowed to eat during the session. To prevent the spread of coronavirus infection, food, and fluid intake has been restricted by health authorities in our country. In this retrospective chart review study, we aimed to confirm the relationship

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between oral intake and intradialytic complications using data before and after the restriction in a relatively large HD population.

Methods

In this descriptive chart review study, patients aged >18 years with end-stage renal disease undergoing thrice-weekly maintenance HD were enrolled retrospectively. In total, 190 (of 47% female) patients with prevalent HD every first week of three consecutive HD runs of 3 months before and after restriction of oral intake (dialysate iCa=1.25 mmol/L) were noted from the dialysis session records. The restriction of oral intake was implemented in March 2021; thus, months from December 2020 to February 2021 were taken as the 3 months before the restriction, and the months from March to May 2021 were taken as the 3 months after the restriction. The exclusion criteria were as follows: presence of a pacemaker or defibrillator, amputation, serious life-threatening comorbid situations (e.g., malignancies), uncontrollable infection, and end-stage cardiac, pulmonary, and hepatic diseases.

Intradialytic complications mainly related to hemodynamic changes (i.e., hypotension), muscle cramps, nausea, vomiting, and dizziness are common among patients with HD. An IDH episode is defined as the difference in pre-HD SBP and minimum SBP during HD of >20 mmHg and symptoms of cramping, nausea vomiting, headache, and light-headedness, which requires fluid intervention (administration of intravenous hypertonic glucose or saline solution to increase blood pressure) (10). Patients in our Hemodialysis Centers were given a meal during each HD session, usually 30-90 min after the start of each session. Patients were served breakfast (tea, bread, cheese, olive, honey, and boiled egg) during the morning session (8-12 h) and cooked meals (soup, poultry, pasta, rice, and meat with vegetables) during the afternoon (13-17 h) and evening (18-22 h) sessions.

Epidemiological data (such as age, sex, presence of diabetes, HD time, frequency and duration of dialysis, dry weight, dialysate calcium, and sodium) in the charts were recorded for each patient. Biochemical tests for hemoglobin, urea, creatinine, potassium, sodium, proteins, albumin, calcium, phosphorus, C-reactive protein (CRP), and parathyroid hormone were performed mid-week of every first week of three consecutive HD runs of the 3 months before and after restriction of oral intake. Kt/V and urea reduction ratio were calculated during this session. All patients were dialyzed on Gambro AK95 machines with bicarbonate dialysis and polysulfone membrane.

The approval form the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee was obtained (approval number: 2998, date: 24.12.2021). Informed consent was obtained from patients for the use of clinical information and results.

Statistical Analysis

Statistical analysis was performed by using SPSS 25.0 (IBM Corp., Armonk, NY, USA) program. Categorical variables are presented as number and percentage (%) and quantitative variables as mean ± standard deviation. The Levene test was used to test for the normality of variables before and after restriction of oral intake. Categorical variables (intradialytic complications such as hypotension and muscle cramp) were compared using the χ^2 test. For comparison of quantitative variables, paired Student's t-test was used for those with normal distribution, and the Wilcoxon sign test was used for those who were not normally distributed. Statistically, $p<0.05$ was considered significant.

Results

The mean age of the patients was 66±11.3 (23-91) years. Of the patients, 53% had diabetes mellitus, with an HD treatment duration of 65.6±55.7 months.

The dry weight decreased from 69.6±14.66 to 69.3±14.52 kg ($p<0.01$), and the post-HD body weight decreased from 70.0±14.77 to 69.7±14.74 kg ($p<0.05$). Ultrafiltration and post-HD diastolic blood pressure (DBP) increased from 2.36±0.91 and 72.0±5.53 to 2.51±0.87 L and 72.8±5.43 mmHg respectively ($p<0.01$) (Table 1).

The following data were obtained: hemoglobin A1c (HbA1c) levels increased from 5.94±0.67% to 6.78±1.33% ($p<0.01$), serum albumin levels from 3.67±0.32 to 3.70±0.29 g/dL ($p<0.05$), serum iron from 67.9±32.1 to 76.7±34.5 mcg/dL ($p<0.01$), serum bicarbonate levels from 22.8±2.8 to 24.4±3.8 meq/L ($p<0.01$), serum ferritin from 366.3±139.3 to 479.5±194.5 ng/mL ($p<0.01$), transferrin saturation from 33.0±16.3% to 37.3±17.6% ($p<0.01$), Kt/V from 1.64±0.23 to 1.69±0.35 ($p<0.01$) (Table 2).

Pre-HD serum creatinine levels decreased from 7.09±2.03 to 6.93±1.88 mg/dL ($p<0.05$), serum total protein levels from 6.66±0.47 to 6.59±0.44 g/dL ($p<0.01$), serum uric acid levels from 5.96±1.11 to 5.54±1.00 mg/dL ($p<0.01$), CRP from 18.9±26.4 to 12.9±19.2 mg/L ($p<0.01$), and alkaline phosphatase from 154.5±116.7 to 145.4±96.6 U/L ($p<0.05$) (Table 2).

Intradialytic complications of hypotension and muscle cramps decreased significantly (0.075% to 0.043%, $p<0.001$ and 0.016% to 0.008%, $p<0.05$, respectively), whereas no increase in hypoglycemia was noted (Figure 1).

Discussion

Volume balance is the cardinal issue in the dialysis population. Cardiac diseases, mostly left atrial dilatation and left ventricular hypertrophy, are the leading causes of mortality among patients on HD. In our previous study, a total of 431 patients with prevalent HD were followed

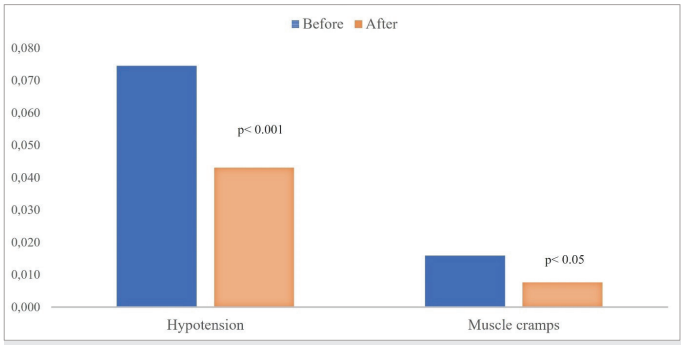

Figure 1. Intradialytic complications (p-value, results of χ^2 test)

Table 1. Hemodynamic parameters

	Meal during session	Without meal during session	p
	Mean ± SD (min.-max.)	Mean ± SD (min.-max.)	
Pre-HD body weight (kg)	72.3±15.05 (39.4-132.3)	72.2±15.04 (38.5-131.0)	0.362+
Dry weight (kg)	69.6±14.66 (38.3-125.5)	69.3±14.52 (36.0-124.0)	**0.003**+
Post-HD body weight (kg)	70.0±14.77 (38.2-128.0)	69.7±14.74 (36.9-126.6)	**0.039**+
Ultrafiltration (L)	2.36±0.91 (0.07-5.00)	2.51±0.87 (0.23-5.33)	**0.002**+
Pre-HD SBP (mmHg)	130.0±13.14 (87.8-181.1)	129.5±12.9 (98.9-168.9)	0.412+
Pre-HD DBP (mmHg)	75.6±4.67 (56.7-90.0)	76.1±6.4 (61.1-141.2)	0.228+
Post-HD SBP (mmHg)	120.6±12.98 (91.1-174.4)	121.8±12.7 (94.4-172.2)	0.059+
Post-HD DBP (mmHg)	72.0±5.53 (58.9-83.3)	72.8±5.43 (58.9-84.4)	**0.007**+

+Paired samples t-test, SD: standard deviation, min.: minimum, max. maximum, HD: hemodialysis, SBP: systolic blood pressure, DBP: diastolic blood pressure

prospectively, and hypervolemia and malnutrition were the long-term mortality indicators in patients on HD (11).

This study demonstrated that if consuming food or drinks is prevented during HD sessions, DBP, the hemodynamic parameter of post-HD, improves, facilitates sufficient ultrafiltration, and significantly decreases the dry weight. This provides adequate volume control chance, which is very important for these patients.

Although a study focused on increased albumin levels (12), in the present study, in addition to albumin, we detected increased HbA1c, serum iron, serum bicarbonate, serum ferritin, transferrin saturation, and Kt/V levels. This may be explained by the low interruption because of IDH episodes and the attainment of effective HD goals.

In the present study, levels of pre-HD serum creatinine, serum total protein, serum uric acid levels, CRP, and alkaline phosphatase decreased possibly because of fewer hypotension episodes, less tissue hypoxia, and inflammation.

Blood pressure is the product of cardiac output and vascular resistance. If any of these decreased and non-compensated by the other, hypotension would occur. During HD, plenty of blood circulates outside the body, causing decreased venous return and cardiac output, which finally results in hypotension. The reduction in myocardial contractility and heart rate in patients with cardiac disorders makes them vulnerable to IDH more than the normal population. This may explain how patients with blood volume decreases during HD are susceptible to hypotension problems.

The splanchnic region is very important for digestion. After meals, blood flows for the absorption of nutrients in the gastrointestinal system (13). Moreover, blood carries digestive enzymes to the target site. Studies have shown that postprandial celiac and superior mesenteric artery blood flow increased by 50-100% (14).

Experimental studies have shown that some vasoactive substances are secreted after consuming food, and pancreas perfusion increased in hyperglycemia and decreased in hypoglycemia (15). Blood flow is regulated by incretins in the splanchnic and systemic circulation (16).

Koffert et al. (17) demonstrated marked blood flow redistribution in the splanchnic vascular bed in response to a mixed meal because of direct chyme contact and elevations in the plasma levels of glucose and incretins, mainly glucose-dependent insulinotropic polypeptide (GIP). The putative vascular effects of glucagon-like peptide-1 and GIP are likely to be more potent during postprandial and hyperglycemic conditions (17).

Barakat et al. (18) examined the central hemodynamics of ten patients on dialysis who ingested a test meal 1 h into dialysis and were monitored by thoracic electric bioimpedance. They suggested that food ingestion during dialysis causes hypotension primarily because of decreased systemic vascular resistance (18).

According to the literature, Sherman et al. (19) analyzed postprandial blood pressure changes during HD. They found that 45 min after an intradialytic meal, the mean blood pressure dropped at 14.4 mmHg/h, significantly more than the 2.2 mmHg/h decline in the control period. DBP also decreased more rapidly after eating. The mean weight loss values per session were 2.8 and 2.5 kg in the fasting and fed periods, respectively. However, this difference was attributed to the 0.3-kg weight of the food. Similarly, the difference in weight loss was 0.82 kg/h in the fasting period and 0.73 kg/h in the feed period. The mean post-treatment weight was 0.23 kg greater in the fed period than in the fasting period. This difference could be also explained by the weight of the meal. Thirteen episodes of symptomatic hypotension were recorded in the 45-min postprandial intradialytic period compared with the two episodes during the corresponding control (fasting) period. Five of the nine patients experienced postprandial symptomatic hypotension during dialysis compared with 1 of 9 in the control period (19). Similar to the literature, the dry weight decreased from 69.6 to 69.3 kg, and the post-HD bodyweight decreased from 70.0 to 69.7 kg, ultrafiltration increased from 2.36 to 2.51 L, and post-HD DBP increased from 72 to 72.8 mmHg. Moreover, intradialytic complications of hypotension and muscle cramps were both decreased significantly, whereas no increase in hypoglycemia was noted.

Study Limitations

This study retrospectively collected data from the medical records of the patients. Prospective randomized controlled trials may be conducted in the future. In this study, we performed HD sessions every 3 months with or without meals. Longer and more comprehensive studies in the future may provide additional data. The study was performed at a few HD centers. Further studies may be performed in several HD centers

Table 2. Laboratory findings

	Meal during session	Without meal during session	
	Mean ± SD (min.-max.)	Mean ± SD (min.-max.)	p
WBC (/mm^3)	7.15±2.03 (3.40-16.75)	6.93±1.97 (2.67-15.87)	**0.020**$^+$
RBC (/mm^3)	3.79±0.48 (2.35-6.16)	3.74±0.50 (2.59-5.49)	**0.027***
Hgb (g/dL)	11.3±1.1 (7.6-13.8)	11.2±1.1 (7.9-14.6)	0.311*
HCT (%)	35.4±3.4 (24.0-45.5)	35.3±3.5 (24.7-44.3)	0.497*
PLT (/mm^3)	198.6±64.5 (63.7-605.0)	194.5±64.6 (52.7-511.3)	0.172*
MPV (fL)	0.23±0.07 (0.07-0.59)	6.85±1.70 (3.33-9.41)	**0.001***
MCV (fL)	93.8±6.3 (66.0-111.0)	94.9±6.4 (65.7-111.3)	**0.001***
MCH (pg)	29.9±2.1 (19.4-35.6)	30.2±2.2 (19.9-35.6)	**0.001***
HbA1c (%)	5.94±0.67 (4.70-7.10)	6.78±1.33 (4.60-10.10)	**0.001**$^+$
Urea pre-HD (mg/dL)	137.8±28.9 (70.7-293.7)	140.7±28.7 (69.3-240.3)	0.150$^+$
Urea post-HD (mg/dL)	36.3±10.6 (12.3-78.3)	37.0±11.2 (13.7-87.7)	0.280$^+$
Creatinine pre-HD (mg/dL)	7.09±2.03 (2.77-13.07)	6.93±1.88 (2.76-12.90)	0.102*
Creatinine post-HD (mg/dL)	2.32±0.80 (0.90-6.42)	2.27±0.74 (0.89-6.01)	0.064*
Potassium pre-HD (mg/dL)	4.89±0.56 (3.31-6.33)	4.94±0.57 (3.30-7.45)	0.170$^+$
Potassium post-HD (mg/dL)	3.33±0.29 (2.60-4.58)	3.42±0.30 (2.71-4.39)	**0.001***
Kt/V	1.64±0.23 (1.06-2.63)	1.69±0.35 (0.90-3.36)	**0.042***
Urea reduction rate (%)	73.8±4.7 (58.7-87.6)	73.8±5.1 (50.9-87.4)	0.800$^+$
Sodium (mg/dL)	136.2±2.3 (127.7-142.0)	136.5±2.3 (126.7-141.3)	**0.010**$^+$
Calcium (mg/dL)	8.60±0.55 (7.24-10.54)	8.62±0.52 (7.18-10.27)	0.520$^+$
Corrected calcium (mg/dL)	8.88±0.55 (7.34-10.65)	8.88±0.52 (7.18-10.34)	0.990$^+$
Phosphorus (mg/dL)	4.79±0.99 (2.05-7.97)	4.70±1.12 (1.18-7.48)	0.230$^+$
Ca X P (mg^2/dL^2)	42.2±9.6 (18.6-80.6)	41.7±10.5 (12.2-70.0)	0.291*
ALT (U/L)	12.8±8.0 (2.0-49.7)	13.4±8.8 (1.7-62.5)	0.395*
Glucose (mg/dL)	153.2±67.8 (75.3-362.7)	158.5±63.8 (70.3-364.0)	0.100$^+$
Total protein (g/dL)	6.66±0.47 (5.05-8.95)	6.59±0.44 (5.48-8.55)	**0.001**$^+$
Albumin (g/dL)	3.67±0.32 (2.52-4.54)	3.70±0.29 (2.51-4.37)	**0.027***
Total cholesterol (mg/dL)	154±34 (78-307)	151±37 (73-318)	NS
LDL-cholesterol (mg/dL)	82±27 (27-176)	84±26 (28-199)	NS
HDL-cholesterol (mg/dL)	43±10 (21-72)	40±9 (18-69)	NS
Triglyceride (mg/dL)	156±103 (44-633)	151±103 (45-648)	NS
Serum iron (mcg/dL)	67.9±32.1 (7.0-206.0)	76.7±34.5 (19.0-191.0)	**0.005***
SIBC (mcg/dL)	211.1±40.6 (112.0-338.0)	210.5±35.0 (136.0-389.0)	0.946*
Ferritin (ng/mL)	366.3±139.3 (39.0-1197.0)	479.5±194.5 (7.0-802.0)	**0.001***
TS (%)	33.0±16.3 (4.0-92.0)	37.3±17.6 (8.0-91.0)	**0.005***
Uric acid (mg/dL)	5.96±1.11 (2.60-9.40)	5.54±1.00 (1.60-8.10)	**0.001**$^+$
CRP (mg/L)	18.9±26.4 (0.3-149.3)	12.9±19.2 (0.4-155.3)	**0.001***
Bicarbonate (meq/L)	22.8±2.8 (14.0-31.0)	24.4±3.8 (10.0-35.0)	**0.001***
ALP (U/L)	154.5±116.7 (56.0-1308.0)	145.4±96.6 (55.0-857.0)	**0.045***
PTH (pg/dL)	364.4±320.5 (5.0-1671.0)	326.4±282.8 (1.0-1390.0)	0.418*

$^+$Paired samples t-test, *Wilcoxon sign test, min.: minimum, max.: maximum, SD: standard deviation, WBC: white blood cells, RBC: red blood cells, Hgb: hemoglobin, HCT: hematocrit, PLT: platelet, MPV: mean platelet volume, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, HbA1c: hemoglobin A1c, HD: hemodialysis, ALT: alanine aminotransferase, LDL: low-density lipoprotein, HDL: high-density lipoprotein, SIBC: serum iron binding capacity, TS: transferrin saturation, CRP: C-reactive protein, ALP: alkaline phosphatase, PTH: parathyroid hormone

with patients who have diverse dietary habits. In this study, we analyzed albumin and lipid levels for nutritional status. In further studies, anthropometric measurements and bioimpedance spectroscopy may also be performed.

Conclusion

This study analyzed whether feeding or fasting during HD treatment would be beneficial for patients on HD. Eating during treatment may be beneficial for providing protein and calorie supplementation; however, eating may cause insufficient HD application because of intradialytic hemodynamic imbalance and complications, especially hypotension and cramps. This negatively affects the adequacy of the patient's HD treatment and increases mortality and morbidity in the long term. IDH and muscle cramps, which are mostly attributed to the splanchnic vasodilatation-related digestion process, may be prevented by restriction of food intake during HD sessions. Finally, in view of these results and those of related studies, it may be practical not to give food during HD sessions, despite the nutritional benefits for most patients.

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Informed Consent: Informed consent was obtained from patients for the use of clinical information and results.

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The Role of Presepsin in Predicting Severe Coronavirus Disease-2019 Pneumonia Prognosis

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ABSTRACT

Introduction: There are several biomarkers to predict disease severity in Coronavirus disease-2019 (COVID-19); however, more precise biomarkers are still needed to evaluate the disease course. This study aimed to evaluate a potential biomarker, a soluble cluster of differentiation 14 subtype (sCD14-ST, Presepsin), to predict the disease prognosis in severe COVID-19 pneumonia.

Methods: This study included 60 randomly selected patients, whose diagnosis was confirmed with severe acute respiratory syndrome-coronavirus-2 nucleic acid reverse transcription-polymerase chain reaction and who were hospitalized with severe COVID-19 pneumonia, and 25 healthy controls. All patients' clinical and laboratory data were recorded. On day 1 after admission, venous blood samples were tested for C-reactive protein (CRP), procalcitonin, fibrinogen, hemogram, presepsin, and other laboratory tests (creatinine, aspartate aminotransferase, alanine transaminase, creatine kinase, lactate dehydrogenase, and electrolytes). Mortality rate, intubation rate, and duration of continuous O_2 treatment were recorded. Results were evaluated with Statistical Package for the Social Sciences.

Results: This study included 60 patients with COVID-19 infection as the patient group and 25 participants in the control group, with a total of 85 participants. The mean presepsin levels were significantly higher in the patient group compared to the control group (1.483±0.147 ng/mL vs 0.873±0.103 ng/mL). Presepsin levels had a weak positive correlation with CRP levels and a strong correlation with procalcitonin levels and creatinine levels. In the patient group, 53 participants have recovered and were discharged, whereas 7 died. No significant difference was found for the presepsin levels in recovering and dying patients in the patient group.

Conclusion: New biomarkers are needed to predict prognosis and mortality in severe COVID-19. Presepsin might be promising to predict disease severity in patients with severe COVID-19, especially in special groups, such as patients with chronic renal failure.

Keywords: COVID-19 pneumonia, presepsin, biomarkers of prognosis

Introduction

The infection caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), which is known as Coronavirus disease-2019 (COVID-19) started in 2019 and turned into a pandemic in a short period. It became a massive public health problem causing serious morbidity and mortality with a SARS that affects millions of people worldwide. The infection is clinically presented in different forms ranging from an asymptomatic state to fatal pneumonia that causes mortality (1). Additionally, several laboratory tests [ferritin, neutrophil-to-lymphocyte ratio, fibrinogen, D-dimer, and C-reactive protein (CRP)] are used to detect disease severity and prognosis.

Presepsin is a soluble cluster of differentiation (CD) 14 subtype in glycoprotein form that is secreted from the monocytes and macrophages. Its serum level is elevated in 2 h following infection and reaches pick concentration in 2-4 h. Its half-life is 4-6 h (2). It is a candidate biomarker for early diagnosis and prognosis prediction in systemic infections.

This study aimed to evaluate presepsin to predict the disease prognosis in severe COVID-19 pneumonia and its relationship with other known inflammatory markers.

Methods

This study includes 60 randomly selected patients, whose diagnosis was confirmed with SARS-CoV-2 nucleic acid reverse transcription-polymerase chain reaction and who met severe pneumonia criteria according to the Living guidance for clinical management of COVID-19 (3) and were hospitalized in our internal medicine clinic, and 25 age-gender matched healthy controls.

All patients' clinical and laboratory data were recorded. On day 1 after admission, venous blood samples were tested for CRP, procalcitonin, hemogram, presepsin, and other laboratory tests [creatinine, aspartate aminotransferase, alanine transaminase (ALT), creatine kinase (CK), lactate dehydrogenase (LDH), and electrolytes].

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Blood samples from the patients and controls were collected in Sarstedt S-Monovette® vacutainer tubes (Sarstedt AG & Co., Germany, Lot no: 1030421) and centrifuged at 1500 × g for 10 min. The serum was then stored at -80 °C until the laboratory analysis. Presepsin levels (ng/mL) were measured by the sandwich enzyme-linked immunoassay method using the human presepsin kit (MyBioSource, USA, Katalog No: MBS766136).

Mortality rate, intubation rate, and duration of continuous O2 treatment were recorded. Results were evaluated with SPSS.

This study was approved by the Ethics Committee of the University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2801, date: 02.04.2021). All participants provided written informed consent. All procedures performed in the study followed the 1964 Helsinki Declaration.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0. Categorical variables were defined as frequency and percentage rate, and numerical variables were determined as mean ± standard deviation. The Kolmogorov-Smirnov test assessed the normality of the distribution of the quantitative variables. The Student's t-test was performed for normally distributed numeric variables, and the Mann-Whitney U test was performed for non-normally distributed data for independent group comparison. Bivariate correlations were expressed by Pearson's or Spearman's correlation analyses when indicated. Statistically significant results were defined with a p-value of <0.05.

Results

This study included 60 patients with COVID-19 infection as a patient group [female/male (F/M): 25/35] and 25 control (F/M: 10/15) group, with a total of 85 participants. The mean age was 53.1±9.0 years in the patient group and 52.1±10.4 years in the control group. The characteristics of the patient group in terms of clinical and laboratory findings are shown in Table 1. The mean presepsin levels were significantly higher in the patient group compared to the control group (1.483±0.147 ng/mL vs 0.873±0.103 ng/mL) (p=0.006). The mean CRP, procalcitonin, and ferritin levels were significantly higher in the patient group compared to the control group. The evaluation of the correlation between presepsin levels and clinical and laboratory parameters in the patient group is summarized in Table 2. In the patient group, 53 participants have recovered and were discharged, whereas 7 died. No significant difference was found for presepsin levels in recovering and dying patients in the patient group. The duration of hospitalization was significantly shorter in the dying group compared to the recovering group. Presepsin level had a weak positive correlation with CRP levels (r=0.283, p<0.037) and strong correlation with procalcitonin levels (r=0.573, p<0.001) and creatinine levels (r=0.417, p<0.001) (Table 3) in the patient group.

Discussion

Severe COVID-19 pneumonia is a serious clinical condition with increased mortality due to respiratory failure. Severe and persistent immune activation causes the secretion of several cytokines and a

Table 1. Characteristics of patients in terms of clinical and laboratory findings in the whole study group

(n=85)	Patient group (mean ± SD or N) (n=60)	Control group (mean ± SD or N) (n=25)	p
Age (years)	53.1±9.0	52.1±10.4	NS
Female/male	25/35	10/15	NS
Recovering/exitus	53/7	-	-
Presepsin (ng/mL)	1.483±0.147	0.873±0.103	0.006
CRP (mg/L)	79.9±60.6	3.6±1.5	**<0.001**
Procalcitonin (ng/mL)	0.13±0.08	0.018±0.005	**<0.001**
WBC (10^3/uL)	6199.3±3252.2	6880.1±751.7	**<0.001**
LYM (10^3/uL)	1363.2±682.9	2226.6±264.2	**<0.001**
HGB (g/dL)	12.7±1.4	13.4±1.1	NS
Urea (mg/dL)	31.1±17.3	21.1±4.8	<0.001
Creatinine (mg/dL)	0.8±0.3	0.7±0.2	NS
AST (U/L)	44.3±30.7	39.9±14.4	NS
ALT (IU/L)	37.5±16.7	32.4±13.1	NS
LDH (U/L)	329.9±111.4	153.3±50.8	**<0.001**
CK (U/L)	246.0±463.8	116.8±68.4	**<0.001**
Ferritin (ng/mL)	374.2±358.5	60.8±37.6	**<0.001**
Hospitalization time (days) (oxygen-dependent days)	9.7±6.5		

P<0.05 statistically significant. Significant p-values are shown in bold. CRP: C-reactive protein, WBC: white blood cell, LYM: lymphocytes, HGB: hemoglobin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, CK: creatine kinase, SD: standard deviation

Table 2. Correlation between presepsin levels with clinical and laboratory parameters in the patient group

	Presepsin levels (ng/mL)	
(n=60)	r	p
Age (years)	-0.068	0.637
Male gender	-0.276	**0.041**
CRP (mg/L)	0.283	**0.037**
Procalcitonin (ng/mL)	0.573	**<0.001**
WBC (10^3/uL)	-0.158	0.249
LYM (10^3/uL)	-0.172	0.209
HGB (g/dL)	0.074	0.593
Urea (mg/dL)	0.495	**<0.001**
Creatinine (mg/dL)	0.417	**<0.001**
AST (U/L)	0.142	0.305
ALT (IU/L)	0.071	0.609
LDH (U/L)	0.192	0.165
CK (U/L)	0.060	0.668
Ferritin (ng/mL)	0.194	0.155
Hospitalization time (oxygen dependent) (days)	-0.284	**0.041**

P<0.05 statistically significant. Significant p-values are shown in bold. CRP: C-reactive protein, WBC: white blood cell, LYM: lymphocytes, HGB: hemoglobin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, CK: creatine kinase

Table 3. The comparison of the clinical and laboratory findings in patients who recovered or died

	Patients who recovered	Patients who died	
(n=60)	**(n=53)**	**(n=7)**	**p**
Age (years)	52.6±9.3	57.3±5.5	NS
Female/male	23/30	2/5	-
Presepsin (pg/mL)	1.3±0.9	2.4±2.0	NS
CRP (mg/L)	70.6±56.3	150.7±45.2	**0.001**
Procalcitonin (ng/mL)	0.12±0.07	0.15±0.10	**0.043**
WBC (10^3/uL)	6031.4±3184.1	7170.0±3741.3	NS
LYMPH (10^3/uL)	1396.8±715.8	1108.6±243.6	NS
HGB (g/dL)	12.8±1.3	11.8±2.0	NS
Urea (mg/dL)	30.2±16.8	38.4±21.1	NS
Creatinine (mg/dL)	0.8±0.3	1.0±0.4	NS
AST (U/L)	43.6±32.1	49.1±17.8	NS
ALT (IU/L)	37.2±28.1	38.9±12.3	NS
LDH (U/L)	324.8±113.5	369.0±92.8	NS
CK (U/L)	232.1±479.9	347.6±331.8	NS
Ferritin (ng/mL)	349.1±339.8	564.6±464.4	NS
Hospitalization time (days)	10.2±6.7	6.1±2.4	0.01

P<0.05 statistically significant. Significant p-values are shown in bold. CRP: C-reactive protein, WBC: white blood cell, LYMPH: lymphocytes, HGB: hemoglobin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, CK: creatine kinase

clinical condition like hemophagocytic syndrome during the infection.

Several prognostic biomarkers are offered to predict the disease prognosis, including white blood cell, lymphopenia, CRP, and some biochemical parameters such as ALT, LDH, albumin, CK, D-dimer, and troponin (4,5). However, more precise biomarkers are needed to predict morbidity and mortality earlier in patients with a serious infection.

CD14 is the receptor of lipopolysaccharide-lipopolysaccharide binding protein complexes. CD14 exists as a soluble (sCD14) and membrane-associated (mCD14) protein present on the surface of leukocytes. MCD14 is expressed on monocyte and macrophage surfaces and has a strong affinity for lipopolysaccharides (6). Soluble CD14 is found in plasma and it translates to the immune response of CD14 negative cells like the endothelium and epithelium cells (7). 13kDa N-terminal part creates CD14 subtype, which is called (sCD14-ST) presepsin (8). The role of presepsin in the human organism is yet unknown but is thought to have a contribution to an immune response with interaction with T vs B cells (2).

Studies demonstrated presepsin as a biomarker for early diagnosis and prediction of prognosis in bacterial sepsis (9-12). Additionally, clinical and experimental studies revealed that presepsin levels are elevated in non-bacterial and fungal infections (13,14).

Our study revealed a significantly higher presepsin level in the patient group than the control group. However, no statistically significant difference was found between patients who recovered and who died after the need for mechanical ventilation. This result needs to be supported with bigger studies.

Another study with a limited number of patients revealed higher levels of presepsin in patients who died in the intensive care unit and suggested its usage as a mortality predictor (15). Further, a study with a limited number of patients revealed the correlation of presepsin with disease severity in patients with COVID-19 (16). Dell'Aquila et al. (17) revealed that presepsin and troponin 1 were elevated in patients who died from COVID-19 and that it was a reliable biomarker to predict the 30-day mortality in patients with COVID-19.

Our study revealed a higher procalcitonin level in the patient group than the control group and a positive correlation with presepsin levels. Procalcitonin is elevated in serious bacterial infections and is used as a sepsis biomarker. Its biological effect is unclear; however, it has common sequence homology with tumor necrosis factor-alpha and interleukin-6 and is accepted as an inflammatory mediator (18). Procalcitonin elevation is shown in severe COVID-19 infection (19-22).

Chronic renal failure (CRF) increases mortality in severe COVID-19 infection (23). Our study revealed a strong correlation between presepsin and creatinine levels. Heart failure, renal failure, and class 3 obesity (body mass index of ≥40 kg/m^2) were related to hospital admissions and disease severity in COVID infection (24). Williamson et al. (25) searched the risk factors in COVID-19 infection in a wide range of patients and revealed that disease severity increases as the glomerular filtration rate (GFR) decrease. The mortality rate in this group was higher than the diabetic group and was correlated with GFR. The relationship between creatinine and presepsin levels in our study favors the immune dysregulation in patients with CRF.

Conclusion

New biomarkers are needed to predict the prognosis and mortality in severe COVID-19. Presepsin might be promising to predict the disease severity in patients with severe COVID-19, especially in groups with CRF.

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Ethics Committee Approval: This study was approved by the Ethics Committee of the University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2801, date: 02.04.2021).

Informed Consent: All participants provided written informed consent.

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A Retrospective Study of Patients with Diverticulitis: Does Neutrophil-to-Lymphocyte Ratio Predict Chronic Diverticulitis Disease Progression?

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ABSTRACT

Introduction: Diverticular disease is defined as the presence of an asymptomatic diverticulum in the colon, and an infected diverticulum is called diverticulitis. Among patients with diverticular disease, 10-25% experience diverticulitis at some stage in their lives. This study aimed to evaluate the neutrophil-to-lymphocyte ratio (NLR) determined by dividing the neutrophil value by the lymphocyte value by comparing the stages of the patients according to the Hinchey classification who presented to the emergency department and were diagnosed with acute diverticulitis and to make a decision whether the patient should be treated by hospitalization or in the outpatient clinic.

Methods: Patients who were admitted to the İstanbul Training and Research Hospital, between 2015 and 2019 and were diagnosed with acute diverticulitis by abdominal computed tomography were included in the study. Patients aged ≤18 years, pregnant patients, and patients with Crohn's disease, ulcerative colitis, colorectal, and/or anal cancer were excluded from the study.

Results: Age, white blood cell count, hemoglobin, hematocrit, platelet, monocyte, granulocyte, neutrophil, NLR, C-reactive protein, and procalcitonin values were compared according to their stage. The neutrophil and NLR values were lower in patients with stage 1 than in those with stages 3 and 4. Moreover, the neutrophil and NLR values were lower in stage 2 than in stage 3.

Conclusion: In our study, patients with acute diverticulum with higher NLR levels are more likely to develop complications. The combined use of NLR with physical examination, imaging, and other laboratory tests facilitates the diagnosis of complicated acute diverticulitis. However, further studies should be performed to confirm the utility of the NLR value in clinical practice.

Keywords: Diverticulitis, neutrophil/lymphocyte ratio, hynchey classification

Introduction

Diverticular disease, once rarely diagnosed, is now one of the most frequent gastrointestinal disorders among inpatients and outpatients (1-3). Painter and Burkitt first demonstrated a large increase in the prevalence of diverticular disease that began during the industrial revolution and documented differences in prevalence between Western and Eastern countries. In the last two decades, interest in diverticular disease has increased once again. Widespread use of modern imaging techniques like computed tomography (CT) (Figure 1) and colonoscopy and accurate diagnosis of diverticulitis and asymptomatic diverticular disease allow understanding their epidemiology (2).

Asymptomatic diverticular disease is often noticed during another imaging method. There is no consensus on the treatment and follow-up of the disease, as there is no clinical finding in patients without symptoms (4).

Diverticular disease is defined as the presence of an asymptomatic diverticulum in the colon, and the infection of these diverticula is called diverticulitis. Of the entire population with diverticular disease, 10-25% experience diverticulitis at some stage in their lives (4).

An inflammation of a colonic diverticulum is also considered diverticulitis. This process could be either acute or chronic (5). In its pathophysiology, the diverticulum orifice is obstructed by a plug such as fecalith. This condition may lead to variable clinical manifestations ranging from simple diverticulitis to complicated diverticulitis, such as colonic obstruction (6). Diverticulitis can be clinically classified as complicated and non-complicated. Complicated diverticulitis usually presents with abscess formation, fistula, obstruction, or perforation (6).

The decision of whether to hospitalize the patient is an important consideration in the management of diverticulitis. The American Society for Colon and Rectal Surgery stated that several factors influence

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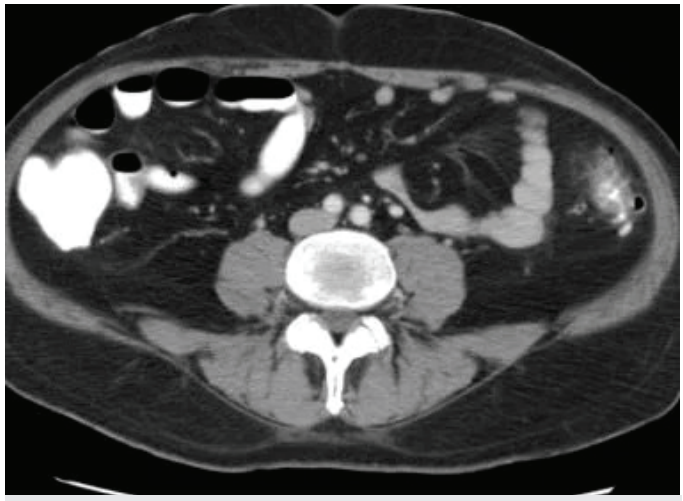

Figure 1. Diverticulitis on computed tomography

this decision, including oral intake intolerance, pain level, general comorbidities, and social support at home (7).

In recent years, its prevalence has been increasing worldwide, especially in Western countries, probably due to lifestyle changes. Although the left-sided colonic diverticular disease is more common among elderly patients, a dramatic increase has been observed in its incidence in younger age groups in recent years. Studies have shown that the lifetime risk of developing acute left-sided colonic diverticulitis in patients with diverticulosis is approximately 4%. Data from Western societies indicate that one-fifth of the patients with acute diverticulitis are under the age of 50 (8,9).

Patients with acute or chronic exacerbation of diverticulitis present with different clinical manifestations. The most common are left lower quadrant pain, nausea, vomiting, fever, and impaired oral intake. Leukocytosis, neutrophilia, and increased C-reactive protein (CRP) are observed in laboratory findings frequently. Although some patients with diverticulitis require hospitalization as has been stated above, the identification of patients who are likely to progress to complicated diverticulitis would help the clinician.

In this study, we aimed to evaluate the neutrophil-to-lymphocyte ratio (NLR), determined through dividing the neutrophil value by the lymphocyte value, by comparing the stages of the patients according to the Hinchey classification who presented to the emergency department and were diagnosed with acute diverticulitis and to make a decision whether the patient should be treated by hospitalization or in the outpatient clinic.

Methods

The patients who were admitted to the University of Health Sciences Turkey, İstanbul Training and Research Hospital, between 2015 and 2019 and were diagnosed with acute diverticulitis by abdominal CT were included in the study. Patients aged <18 years, pregnant patients, and patients with Crohn's disease, ulcerative colitis, colorectal, and/or anal cancer were excluded from the study.

The approval form the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee was obtained (approval number: 2421, date: 12.06.2020). Informed consent was obtained from each patient.

Statistical Analysis

Data were statistically analyzed using SPSS version 17.0. Histogram plots and the Kolmogorov-Smirnov test were employed to examine the conformity of the variables to the normal distribution. The descriptive analysis was presented using mean, standard deviation, median, and 25-75 percentile values. Categorical variables were compared by the Pearson chi-square test. The Kruskal-Wallis test was utilized to evaluate the differences between the stages in non-normally distributed (non-parametric) variables, and p-values <0.05 were regarded as significant. A total of 217 patients, including 122 men and 95 women, participated in the study.

Results

All patients were grouped according to the Hinchey classification based on tomographic imaging (Table 1). The examination of the Hinchey stages revealed that 176 patients were in stage 1, 22 in stage 2, 16 in stage 3, and 3 in stage 4. Moreover, 19 patients underwent surgery, 4 had drainage, 106 were hospitalized for >5 days, and 7 died (Table 2).

The mean age of the patients was 58.77±14.50 years. White blood cell count (WBC), hemoglobin (Hb), hematocrit (HCT), platelet (PLT), monocyte, granulocyte, neutrophil, NLR, CRP, and procalcitonin values are given in Table 3.

Patients were compared according to their Hinchey stages in terms of gender, surgery, drainage, hospitalization, and mortality rates (Table 4). The surgery rate was lower in patients at stage 1 than in those at stage 3. The rate of undergoing surgery was higher in stage 4 than in other stages. The drainage rate was lower in stage 1 than in stage 3. The rate of hospitalization for >5 days in stage 1 was lower than that in other

Table 1. Hinchey classification

Hinchey classification
I. Pericolic abscess or phlegmon
II. Pelvic, intraabdominal, or retroperitoneal abscess
III. Generalized purulent peritonitis
IV. Generalized fecal peritonitis

Table 2. Clinical data of the patients

	n	%
Male	122	(56.22)
Female	95	(43.78)
Stage 1	176	(81.11)
Stage 2	22	(10.14)
Stage 3	16	(7.37)
Stage 4	3	(1.38)
Operation	19	(8.76)
Drainage	4	(1.84)
>5-day hospitalization	106	(48.85)
Mortality	7	(3.23)

groups. The mortality rate was significantly lower in stage 1 than in stage 4.

Age, WBC, Hb, HCT, PLT, monocyte, granulocyte, neutrophil, NLR, CRP, and procalcitonin values of the patients were compared according to their stage (Table 5). The WBC count of patients at stage 3 was higher than those of patients at stages 1 and 2. The neutrophil and NLR values were lower in stage 1 than in stages 3 and 4. Moreover, the neutrophil and NLR values were lower in stage 2 than in stage 3. Procalcitonin levels were lower in stage 1 than in stage 3. Although a significant relationship was found between the groups in terms of Hb, PLT, and CRP values, no significant differences were found in pairwise comparisons according to the post-hoc analysis.

Table 3. Complete blood count values of the patients

	Mean	Median	P25	P75
WBC	10.79	10.40	8.10	13.27
Hb	13.07	13.30	11.80	14.40
HCT	39.03	39.90	36.30	42.50
PLT	271.85	263.00	209.00	313.00
Monocytes	0.80	0.76	0.56	1.02
Granulocyte	2.22	2.17	1.64	2.77
Neutrophil	7.56	6.90	4.79	9.44
NLR	4.33	3.04	2.12	4.80
CRP	18.30	6.00	2.60	21.00
Procalcitonin	1.68	0.50	0.01	1.60

WBC: White blood cells, Hb: hemoglobin, HCT: hematocrit, PLT: platelet, NLR: neutrophil-to-lymphocyte ratio, CRP: C-reactive protein

Discussion

In acute diverticulitis, clinical manifestations range from mild abdominal pain to hemodynamic instability and peritonitis, depending on disease severity. The most common presenting symptom is left lower quadrant pain, which typically begins 1 or 2 days earlier. As most diverticulitis occurs in the sigmoid or descending colon, the pain is in the left lower quadrant. However, diverticulitis is predominantly right-sided in Asian populations; thus, the pain is felt more on the right side (10).

Among gastrointestinal diseases, acute appendicitis, acute cholecystitis, intestinal obstruction, colon malignancy, inflammatory bowel disease, acute pancreatitis, constipation, acute gastroenteritis, and inguinal hernia are included in the differential diagnosis of diverticulitis (11).

Table 4. Gender, surgery, drainage, and mortality rates were compared according to the stage of the patients

n		Stage 1		Stage 2		Stage 3		Stage 4	
		%	n	%	n	%	n	%	
Gender	Male	99	(56.25)	12	(54.55)	8	(50.00)	3	(100.00)
	Female	77	(43.75)	10	(45.45)	8	(50.00)	0	(0.00)
Operation	No	169	(96.02)	19	(86.36)	10	(62.50)	0	(0.00)
	Yes	7	(3.98)	3	(13.64)	6	(37.50)	3	(100.00)
Drainage	No	176	(100.00)	20	(90.91)	14	(87.50)	3	(100.00)
	Yes	0	(0.00)	2	(9.09)	2	(12.50)	0	(0.00)
Hospitalization	>5 days	103	(58.52)	7	(31.82)	1	(6.25)	0	(0.00)
	<5 days	73	(41.48)	15	(68.18)	15	(93.75)	3	(100.00)
Mortality	No	173	(98.30)	21	(95.45)	14	(87.50)	2	(66.67)
	Yes	3	(1.70)	1	(4.55)	2	(12.50)	1	(33.33)

Table 5. Complete blood count values, NLR, procalcitonin, and CRP values were compared according to the stage of the patients

	Stage 1	Stage 2	Stage 3	Stage 4	p
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
	58.13±13.66	65.14±18.51	57.88±15.79	54.33±19.86	0.392
WBC	10.34±3.63	10.69±3.16	14.57±3.93	18.23±5.51	**0.000**
Hb	13.25±1.89	12.26±1.81	12.40±1.88	12.13±1.79	**0.043**
HCT	39.42±4.95	36.92±4.63	37.86±4.76	37.90±2.91	0.061
PLT	262.93±79.88	299.50±75.42	312.87±149.64	373.67±110.14	**0.006**
Monocytes	0.79±0.33	0.89±0.37	0.84±0.36	0.96±0.64	0.604
Granulocyte	2.25±0.82	2.25±0.80	1.99±1.03	1.30±0.70	0.178
Neutrophil	7.06±3.26	7.35±3.03	11.81±3.99	15.85±5.94	**0.000**
NLR	3.84±3.91	3.88±2.71	8.33±7.64	14.94±8.63	**0.000**
CRP	14.31±20.37	19.74±21.12	45.31±66.63	97.67±130.20	**0.013**
Procalcitonin	1.40±2.63	2.03±3.45	4.04±6.07	2.87±1.58	**0.001**

Kruskal-Wallis test. WBC: White blood cells, Hb: hemoglobin, HCT: hematocrit, PLT: platelet, NLR: neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, SD: standard deviation

In general, WBC counts, procalcitonin, and CRP levels are elevated in patients with diverticulitis. In one study, the combination of high WBC count and CRP value was associated with a four-fold increased likelihood of diverticulitis compared with other causes of abdominal pain (12).

Diagnosing diverticulitis by clinical examination may be difficult for patients without a previous history of diverticulitis. Previous studies have indicated that the clinical diagnosis was incorrect in 40-60% of the patients with suspected diverticulitis. Thus, various auxiliary diagnostic tests should be implemented (13).

It may be difficult to diagnose diverticulitis based solely on clinical findings. Besides, complications of diverticulitis such as abscess cannot be confirmed without imaging examination. Differentiating the complicated diverticulitis from the uncomplicated one is very important to determine the need for antibiotics, percutaneous abscess drainage, and surgery (14).

Abdominal tomography is the most preferred imaging method in the diagnosis of diverticulitis, with a sensitivity of 96% and a specificity of 95%. Abdominal ultrasonography, with sensitivity and specificity of approximately 90%, can be used in the evaluation of patients with suspected diverticulitis. Ultrasonography does not require contrast, radiation is not applied, and it can be performed at the bedside. The sensitivity and specificity of magnetic resonance imaging are also high. Plain abdominal radiography may help in the evaluation of pneumoperitoneum and exclude other diagnoses such as intestinal obstruction, but it cannot be used to confirm the diagnosis of diverticulitis or abscess (15).

In a study of 177 patients with acute cholecystitis in which NLR was used as a biomarker, as in our study, NLR values were determined to be effective in the diagnosis and determination of disease severity (16). In another study of 600 patients with acute cholecystitis, NLR was successful in the diagnosis and determination of disease severity (17).

High NLR values were reported to be associated with severe abdominal infections and worse outcomes; thus, it was used as a predictor of outcomes in patients who underwent surgery (18).

Currently, the debate on the usefulness of NLR as a predictor of complications in acute diverticulitis remains open, especially concerning disease severity, clinical impact, and the need for minimally invasive or emergency surgical procedures (19).

If the CRP value in patients with diverticulitis is >150, it is always necessary to perform CT; if <150, performing CT is decided according to the clinical condition of the patient (20).

The peripheral blood NLR has been widely reported to be associated with an inflammatory response and indicates the inflammatory state of many diseases. NLR is more significant as a biomarker than PLT and CRP, especially in advanced-stage acute diverticulitis.

Study Limitations

Patients aged <18 years, pregnant patients, and patients with Crohn's disease, ulcerative colitis, colorectal, and/or anal cancer were excluded from the study.

Conclusion

In this study, patients with acute diverticulitis with higher NLR levels are more likely to develop complications. The combined use of NLR with physical examination, imaging, and other laboratory tests facilitates the diagnosis of complicated acute diverticulitis. To confirm the utility of the NLR value in clinical practice, further studies and meta-analysis are needed.

Ethics Committee Approval: The approval form the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee was obtained (approval number: 2421, date: 12.06.2020). Informed consent was obtained from each patient.

Informed Consent: Informed consent was obtained from each patient.

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Correlation of Coronary Calcium Scores with Growth Differentiation Factor-15 Levels in Patients with Coronary Artery Disease

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ABSTRACT

Introduction: As noted in the guidelines, the efficacy of coronary artery calcium score (CACS) is remarkable in the intermediate-risk group for coronary artery disease; however, it exposes the patients to radiation. In this study, we aimed to investigate whether growth differentiation factor-15 (GDF-15) could be an alternative to CACS in patients with traditional cardiovascular risk factors.

Methods: In 2018, 86 volunteer patients (female: n=36; male: n=50) aged 25-85 years were included in the study among all patients whose CACS measurements were made in the radiology clinic. In our hospital, CACS images are obtained using 64-slice computed tomography. Serum GDF-15 levels were measured from venous blood. Participants were divided into two groups as zero and high (>0) according to the CACS. SPSS 21.0 was used for the statistical analysis.

Results: Participants were compared with zero (female: n=16; male: n=17; mean age: 53.93 years) and high (>0) (female: 20, male: 33; mean age: 58.2 years) CACS groups. Leukocytes, GDF-15 levels, and monocyte/high-density lipoprotein-cholesterol (HDL-C) ratio were significantly higher in the CACS group ($p<0.05$). Significant positive correlations were found between CACS and GDF-15 (rs=0.21), monocyte/HDL-C ratio (rs=0.29), and platelet/lymphocyte ratio (rs=0.21) ($p<0.05$).

Conclusion: In this study, GDF-15 and inflammatory markers were positively correlated with CACS. A significant difference was found in GDF-15 between patients with and without critical stenosis. Therefore, we can predict that the prognostic value of GDF-15 will be higher, especially in patients with critical stenosis. In this respect, studies with larger samples are needed.

Keywords: Coronary artery disease, coronary artery calcium score, growth differentiation factor 15

Introduction

Coronary artery disease (CAD) remains a significant public health problem in developed countries. Conditions such as industrial nutrition, sedentary life, smoking, and genetic and environmental factors that emerged after the industrial revolution negatively affect coronary vascular health.

The coronary artery calcium score (CACS) is an important prognostic marker in the moderate-risk group of CAD (1). Guidelines recommend its use for asymptomatic moderate-risk individuals with a 10-20% risk of cardiovascular (CV) events at 10 years, according to the Framingham Risk score (FRS) (1). However, the disadvantage of scanning is that healthy people are exposed to radiation. Thus, it is vital to achieve the same effect with radiation-free methods to protect healthy individuals.

Growth differentiation factor-15 (GDF-15) is a distant member of the transforming growth factor-beta superfamily, whose expression is increased under cellular stress. GDF-15 regulates biological processes involving multiple cell functions, differentiation, and regeneration of tissues (2). In CV events, GDF-15 is associated with increased mortality in people with heart failure, coronary heart disease (CHD), cardiac hypertrophy, and acute coronary syndrome (3).

In this study, we investigated whether GDF-15 could be an alternative to CACS in patients with traditional CV risk factors.

Methods

Between March and November 2018, 86 volunteer patients aged 25-85 years (female: n=36, male: n=50; mean age: 56.67 years) who applied

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to the radiology clinic for CACS screening due to traditional CV risk factors were included in the study. Patients with pregnancy, acute infection, acute vascular event, malignancy, known genetic disease, rheumatological disease, chronic renal failure, uncontrolled thyroid function tests, old stents, and inadequate cooperation and orientation were excluded from the study. All participants' anamnesis was taken, and detailed physical examinations were performed.

The approval form the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee was obtained (approval number: 1197, date: 09.03.2018). All patients have read and signed informed consent forms before participation.

Images were obtained on a 64-slice CT (Toshiba Aquilion system, Tokyo, Japan) with 400 mm rotation time and a 1 mm reconstruction device capable of descending to 0.5 sections. An automatic dose modulation system was used in the examinations. Images obtained without intravenous use of drugs using the electrocardiogram trigger feature with a 3 mm slice thickness were evaluated on the Aqua 3D workstation (Toshiba, Tokyo, Japan). Lesions with density >130 HU were marked and classified according to the Agatston technique. Percentile calculation for CACS values was performed with https://www.mesa-nhlbi.org/calcium/input.aspx.

According to the CACS, elective coronary angiography (CAG) was performed in the indicated patients, and ≥50% stenosis in a single vessel was considered critical stenosis.

Biochemistry and hemogram parameters were measured from the venous blood sample after 8h of fasting. Monocyte/high-density lipoprotein-cholesterol (HDL-C) and platelet/lymphocyte ratios, which are used as indicators of oxidative stress and systemic inflammation, were calculated from the obtained hemogram parameters. Laboratory results obtained in the routine follow-up of patients were used, and no additional expense was incurred.

In addition, extra venous blood was taken into a biochemistry tube and centrifugated. It was stored in a -80 °C cabinet until the end of the study, and serum GDF-15 levels were then measured by using the sandwich enzyme-linked immunosorbent assay (human GDF-15 ELISA Kit, Elabscience, Wuhan, China). This kit recognizes human GDF-15 in samples. It has a detection range of 23.44-1500 pg/mL, sensitivity of 14.06 pg/mL, and repeatability/coefficient of variation <10%.

Statistical Analysis

Power analysis was performed, and a sample size of 90 was determined (alpha: 0.05, power: 0.8) (4). The suitability of the quantitative variables to a normal distribution was evaluated using the Shapiro-Wilk test. Participants were evaluated as zero and high (>0) groups according to the CACS, and data were compared between the two groups. A 50% stenosis in CAG was accepted as critical stenosis. All participants who underwent CAG were regrouped according to the presence of critical stenosis, and available data were compared between the two groups. Finally, the correlations of CACS and GDF-15 with each other and with other parameters were analyzed.

In descriptive statistics, the mean and standard deviation were used in the expression of quantitative variables. Categorical variables are expressed by frequency and valid percentage. The p-value was accepted as <0.05 for significance. The results were evaluated at the 95% confidence interval. Data evaluation and analysis were performed using SPSS version 21 (IBM Corp., Armonk, NY, USA).

Results

All participants in the study (female: n=36; male: n=50; mean age: 56.67 years) were divided into two groups. Group 1 had zero CACS (female: n=16; male: n=17; mean age: 53.93 years), and group 2 had high (>0) CACS (female: n=20; male: n=33; mean age: 58.2 years). Leukocytes, GDF-15, and monocytes/HDL-C ratio of the high CACS group were higher on average, and these differences were significant (p<0.05) (Table 1). C-reactive protein and platelet/lymphocyte ratio were on average higher in the high CACS group. However, these between-group differences were not significant (p>0.05) (Table 1).

According to the CACS results, elective CAG was performed as necessary, and stenosis ≥50% in a single vessel was considered critical stenosis. Participants with critical stenosis (female: n=9; male: n=18; mean age: 64.9 years) and those without critical stenosis (female: n=26; male: n=33; mean age: 52.8 years) were compared. CACS, percentile values, GDF-15, monocyte/HDL-C ratio, and thrombocyte/lymphocyte ratio were higher in patients with critical stenosis, and this difference was significant between the two groups (p<0.05) (Table 2).

The correlation of CACS with other parameters was examined. A significantly positive correlation with GDF-15 (rs=0.21), monocyte/HDL-C (rs=0.29), and platelet/lymphocyte ratio (rs=0.21) ratios was found (p<0.05) (Table 3). When the correlation of GDF-15 with other parameters was examined, a significant positive correlation with the percentile values was noted (rs=0.34, p=0.001). However, no significant correlation was found between GDF-15 and monocyte/HDL-C and thrombocyte/lymphocyte ratios (p>0.05) (Table 3).

The receiver operating characteristics analysis was performed for CACS and GDF-15, which determine critical coronary artery stenosis. The areas

Table 1. Comparison of groups with high calcium score and zero

	CACS=0 (n=33)	CACS>0 (n=53)	p-value
Age (years)	53.93±11.42	58.2±11.31	p=0.09 T
Gender			
Female	16 (48.5)	20 (37.5)	p=1.0 χ^2
Male	17 (51.5)	33 (62.2)	
CRP (mg/L)	4.21±6.21	9.13±11.29	p=0.21 T
WBC (×10³/µL)	7.28±1.38	8.18±2.26	p=0.03 T
GDF-15 (pg/mL)	1611±712	1925±595	p=0.03 T
Monocytes/HDL-C	0.009±0.006	0.01±0.007	p=0.01 T
Platelet/lymphocyte	105.59±52.98	115.97±62.60	p=0.43 T

Student's t-test (T): mean ± standard deviation, chi-square test (χ^2): n (% valid). CACS: Coronary artery calcium score, CRP: C-reactive protein, GDF-15: growth differentiation factor-15, HDL-C: high-density lipoprotein-cholesterol, WBC: white blood cells

under the curve were 0.834 for CACS (sensitivity, 96%; specificity, 66.1%; cut-off, 69; p<0.01) and 0.389 for GDF-15 (sensitivity, 45.8%; specificity, 78.9%; cut-off, 1608.7; p=0.11) (Figure 1).

Discussion

CAD and CACS

Atherosclerosis is the main pathogenetic cause of CAD, which is a significant cause of mortality and morbidity. The atherosclerosis process begins early in life and progresses slowly (5). Vascular calcification appears as calcification or ossification at the base of advanced atherosclerotic lesions and has long been considered a natural consequence of aging. However, this is not an inevitable end and is an active pathological process (6).

CAD may be asymptomatic for a long time. Thus, it is critical to develop a screening strategy to identify those at moderate- and high-risk individuals without symptoms and to protect them from potential death and disability (7). A strong relationship was found between CV events and CACS in asymptomatic cases (8). For example, in 2004, Greenland et al. (9) evaluated whether CACS has additional prognostic significance for CHD and followed the participants for 7 years. After the study, CACS estimates individuals with a 10-year risk >10% according to FRS (9). In another study, 69% of the participants constituted a severe-risk group when assessed with FRS alone. However, this rate increased to 77% in the combined evaluation using FRS and CACS (10). In 2010, Erbel et al. (11) stated that adding CACS to traditional risk scoring improves the prediction of coronary death or non-fatal myocardial infarction.

Table 2. Comparison of groups with critical and noncritical stenosis

	Non-critical stenosis (n=59)	Critical stenosis (n=27)	p-value (T)
CACS	222±438	1074±1697	**p=0.01**
Percentile	48.6±42.5	87.70±13.47	**p<0.001**
GDF-15 (pg/mL)	1717±644	2034±683	**p=0.04**
Monocyte/HDL-C	0.010±0.007	0.014±0.006	**p=0.02**
Platelet/lymphocyte	100.5±54.3	136.9±62	p=0.007

Student's t-test (T): mean ± standard deviation.

CACS: Coronary artery calcium score, GDF-15: growth differentiation factor-15, HDL-C: high-density lipoprotein-cholesterol

CACS is highly specific for coronary atherosclerosis. The sensitivity of CACS for obstructive CAD has been reported to be between 88% and 100%. Moreover, the amount of calcium was associated with the total size of the atherosclerotic plaque (12). An autopsy study reported that coronary artery plaques show a positive correlation with CACS (13). An intracoronary ultrasound study also revealed that CACS is related to the location and grade of atherosclerotic plaques (14). As a result, the guidelines stated that CACS should be considered in CV risk assessment of moderate-risk individuals without symptoms (level of evidence class IIa, level B) (1). As regards cost-effectiveness, CACS is better than existing screening methods for intermediate-risk men (15).

CACS was first described by Agatston et al. (8) using ultrafast CT in 1990. It is used to calculate hyperdense lesions measured at ≥130 HU in the axial plane tomography sections. Individual CAD risk is determined according to the Agatston classification (16). However, some ethical issues prevail with the widespread use of CACS. CACS scanning exposes the patients to ionizing radiation and some people indicated for screening are healthy individuals (7). The effective dose for CACS using CT is 10 times the effective dose (0.7-1.8 mSv) for chest X-ray imaging (17). However, a

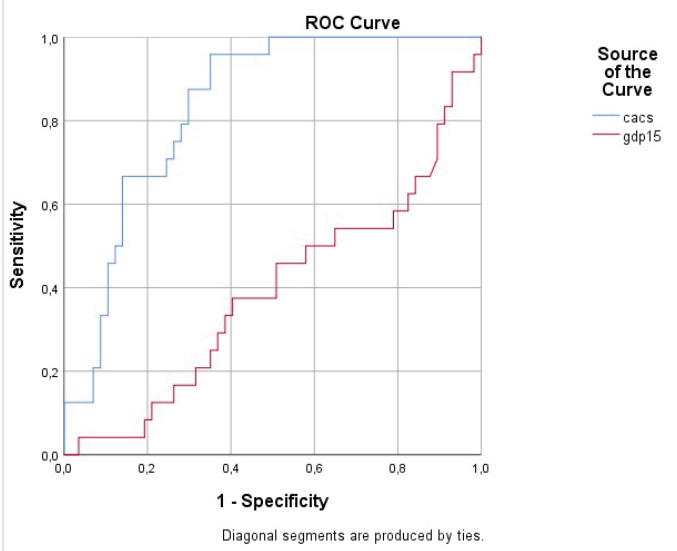

Figure 1. ROC analysis of CACS and GDF-15 to determine critical CAS

AUC: CACS=0.834, GDF-15=0.389, CACS: Coronary artery calcium score, GDF-15: growth differentiation factor-15, CAS: coronary artery stenosis, AUC: area under the curve, ROC: receiver operating characteristics

Table 3. Correlation levels

With CACS	n	r value	r^2	p value (ρ)	r s value	p value (s)
GDF-15 (pg/mL)	86	0.18	0.032	p=0.08	0.21	**p=0.04**
Monocytes/HDL-C	86	0.22	0.048	p=0.03	0.29	**p=0.005**
Platelet/lymphocyte	86	0.15	0.022	p=0.16	0.21	**p=0.04**
With GDF-15						
Percentile	86	0.33	0.108	p=0.002	0.34	**p=0.001**
Monocytes/HDL-C	86	-0.03	<0.001	p=0.72	-0.09	p=0.37
Platelet/lymphocyte	86	-0.08	0.006	p=0.43	-0.11	p=0.3

ρ: Pearson correlation analysis, s: Spearman's Rho correlation analysis.

CACS: coronary artery calcium score, GDF-15: growth differentiation factor 15, HDL-C: high-density lipoprotein-cholesterol

single moderate exposure (2.3 mSv) at age 40 years causes cancer, with a rate of 28 per 100,000 in women and 9 per 100,000 in men (18).

GDF-15 and CV Diseases

GDF-15 is one of the markers associated with cardiometabolic syndrome (19). GDF-15 regulates biological processes, including multiple cell functions, differentiation, and tissue regeneration (2). It facilitates the apoptosis of tumor cells and acts as a suppressor on metastasis (20). GDF-15 levels increase physiologically with age and during pregnancy (19,21). GDF-15 is secreted from active macrophages in human vascular smooth muscle cells, human endothelial cells, and human adipocytes, which are stimulated by proinflammatory cytokines (22). Atherosclerotic plaques also express GDF-15. Some other conditions associated with high GDF-15 levels include smoking, type 2 diabetes mellitus, metabolic syndrome, sepsis, and chronic inflammatory conditions such as rheumatoid arthritis, chronic kidney disease, anemia, solid cancers, and cachexia (23).

In CV events, studies have shown that individuals with CV risk factors or a history of CV disease have higher levels of GDF-15 than those without (24). A study reported that GDF-15 is associated with coronary artery calcification and atherosclerotic plaque burden in the coronary artery (23). In the AtheroGene study, GDF-15 was associated with CHD mortality, left ventricular ejection fraction, and number of diseased vessels independent of conventional CV risk factors (25). Furthermore, in the "Heart and Soul" study, all-cause mortality and fatal/non-fatal CV events were independently associated with GDF-15 levels (26). Therefore, high GDF-15 levels may indicate occult CV disease in healthy individuals (27). Another critical point is that a study identified GDF-15 as a cardioprotective agent (28). In a study of CHD, the animal model has shown that GDF-15 has anti-inflammatory, anti-hypertrophic, and anti-apoptotic properties that may have a protective role and improve tissue repair (3).

GDF-15 and CACS

Both CACS and GDF-15 have prognostic significance for CAD independent of traditional CV risk factors. Studies have also examined both. For example, in 2017, Martinez et al. (29), examined the correlation of GDF-15 levels and subclinical atherosclerosis with CACS in patients with stable chronic obstructive pulmonary disease. GDF-15 was associated with high CACS at high tertile compared with low tertile (29). The "Dallas Heart Study," which examined the relationship between GDF-15 and subclinical atherosclerosis, noted that GDF-15 is independently associated with subclinical coronary atherosclerosis, and the potential role of GDF-15 deserves further evaluation (22).

In our study, GDF-15 was associated with coronary atherosclerosis as determined by the CACS, similar to reports in some studies. When the participants were compared according to their CACS, a significant difference in GDF-15 was found. In addition, a positive correlation was found between CACS and GDF-15. According to CAG results, those with and without critical stenosis were compared, and a significant difference was found in GDF-15. In this respect, the prognostic value of GDF-15 will be higher, especially in patients with critical stenosis. Similarly, the monocyte/HDL-C ratio, an inflammatory marker, is also associated with coronary atherosclerosis in our study. A significant difference was found between the groups in terms of monocyte/HDL-C ratio in the evaluation with both CACS and critical stenosis.

Study Limitations

The sample size could not be expanded because of the limited number of kits and the completion of our study in a certain time. Our patient population consists of people with low socioeconomic status given our hospital's location, which reduces the diversity of our sample. Moreover, our relatively limited population reduces the statistical power. All these limit the generalization of our results.

Conclusion

The development of nonionizing and non-invasive methods is essential in identifying individuals at moderate-risk for CAD. GDF-15 and inflammatory markers appear suitable for this purpose. After our study, GDF-15 levels and monocyte/HDL-C ratio were higher in individuals with high CACS, and a significantly positive correlation was found between CACS and monocyte/HDL-C ratios and GDF-15 levels. In critical stenosis, both monocyte/HDL-C ratios and GDF-15 levels were significantly higher than non-critical stenosis. Therefore, we can predict that the prognostic value of GDF-15 will be higher, especially in those with critical stenosis. In this respect, studies with larger samples are needed.

Ethics Committee Approval: The approval form the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee was obtained (approval number: 1197, date: 09.03.2018).

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