MIDDLE BLACK SEA JOURNAL OF HEALTH SCIENCE

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EDITORIAL

Despite all the difficulties…

Thanks to all the healthcare professionals who work devotedly at the forefront of the struggle during these months when the COVID-19 pandemic was most intense ... Thanks to all the authors, knowing the importance of the articles on both the pandemic and other fields ... We are happy to be in the literature in our new issue with special studies,

Hope to meet in other issues ...

PhD, Assoc. Prof. Ülkü KARAMAN

Editor

RESEARCH ARTICLE

The Effect of Different Filling Materials Used on Immature Maxillary Central Teeth with Different Apical Diameters on Fracture Resistance

Leyla Benan Ayranci[1](ID), Ahmet Cetinkaya[1](ID), Alper Ozdogan[2](ID), Serkan Ozkan[3](ID),

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Abstract

Objective: This study aims to investigate the effect of different treatment options on immature maxillary central teeth simulated with two different apical diameters on fracture resistance.

Methods: Forty-eight maxillary central teeth with a singular root canal were collected for this in-vitro study. The specimens were decoronated to $17\pm0,12$ mm long for ensuring standardization. All samples were randomly divided into two groups: 1,2mm group (G1) prepared with No. 4 Peaso Reamer and 1.8mm group (G2) prepared with No. 6 Peaso Reamer. Each parent group is divided into 4 subgroups (n=6) to form treatment groups. The positive control group was prepared without the access cavity to simulate the immature tooth (P) and negative control (N) group was prepared and filled calcium hydroxide. In group 3 MTA was condensed with a hand plugger to obtain a 3mm thick apical plug and remaining parts of the canals were filled with Guttaflow Bioseal cold filling system (G). In group 4, simulated immature roots were filled completely MTA (M). All samples were kept at 37° C and % 100 humidity for four weeks. Fracture test was performed by applying a load at an angle 135 degrees to the long axis of the teeth until a fracture occured using a universal test device.

Results: There was a statistically significant interaction between apical enlargement diameter and fill type on fracture resistance (p<0,05). The fracture resistances of the negative control groups in both of group 1 and group 2 were significantly different from those of the other groups (p<0,05). There was no statistically significant difference in fracture resistance according to filling type in 1,2mm apical diameter groups (p>0,05). GuttaFlow (G) group in the 1,8mm apical diameter group has the highest fracture resistance while the MTA (M) group has the closest fracture resistance to the negative control group.

Conclusion: Despite the restrictions in our study, the backfilling with GuttaFlow Bioseal in large apical diameter teeth may be beneficial in terms of fracture resistance.

Key words: Immature teeth, fracture resistance, MTA

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Introduction

In childhood age traumatic dental injuries usually occur and most effected teeth are maxillary central incisors. Especially if pulp necrosis develops due to traumas occurring before completing the root development, effects such as stopping root development and apical closure cannot be achieved (1). Root canal treatments of immature teeth have been a problem due to the open apex, thin dentin wall and wide canal. These teeth are very susceptible to fracture (2).

Due to the incomplete root development in immature teeth, it makes it difficult for the root canal filling to provide an effective plug in the apical third (3). Various treatment techniques have been presented to solve the problem of apical patency in immature teeth. Among these techniques, the apexification technique offered by a researcher was the most preferred application (4). Calcium hydroxide (Ca(OH)2) has been widely accepted for the development of root apex in the treatment of apexification (5). Although used effectively, it has disadvantages such as patient compliance and multiple visits, the risk of re-infection and predisposition to fracture of the tooth (6). In situations like this, regenerative endodontic treatment options should be considered by the clinician to restore the vitality of the tooth and create an apical barrier.

Apexification treatment is used when the regenerative method is not generally considered an option or when regenerative therapy fails (7). In recent years, tricalcium silicate involving cements such as Mineral Trioxide Aggregate (MTA), Biodentin are widely used in endodontics rather than traditional calcium hydroxide. It is the most accepted materials due to its ability to be applied in single visit, superior sealing properties, high biocompatibility and antibacterial effects (8,9). In the use of tricalcium-based materials such as MTA, a strict plug is compresed into the apical third of the root that stimulate a calcified barrier formation in the periapical zone. However, the average MTA thickness used as the apical plug is an argumental treatment procedure, and the risk of fracture remains as the dentin wall thickness is still thin. In order to use the various advantages of MTA and increase the fracture resistance of the tooth, the rest portion of the root canal can be filled with gutta-percha or similar materials after the apical plug with optimum thickness is formed (10).

Silicon-based endodontic sealers stand out with their biocompatible properties (11). These sealers include specifically Guttaflow(Coltene Whaledent, GmbH + Co KG, Langenau, Switzerland), a combination of gutta-perka powder, polydimethylsiloxane and added nanometer-sized silver particles for antibacterial features (12). GuttaFlow2 (Coltene Whaledent, GmbH + Co KG) is a cold flowable system that combines the gutta-perka powder form with a particle size and sealing element of less than 30 μm and is the enhanced version of its predecessor guttaflow (13). GuttaFlowBioseal (coltene/whaledent AG, Altstatten, Switzerland) was developed as a new material by adding calcium silicate particles into the mixture of Gutta-percha powder and polydimethylsiloxane and aimed at low cytotoxicity and high cell viability (14). There is no study on the stress generated by Guttaflow Bioseal sealing agent in the canal and the resistance of the root canal to fracture. Therefore, the objective of the present investigation is to assess the difference in fracture resistance values of simulated immature teeth with different MTA thickness and different filling materials. One null hypothesis was that root canal obturation procedures would affect the fracture resistance values of simulated immature teeth and it is hypothesized that different apical diameters would differ the fracture resistance values.

Methods

One hundred human maxillary central teeth with noncarious, approximately similar buccolingual and mesiodistal dimensions and extracted for periodontal reasons were collected from Ordu University Oral and Maxillofacial Surgery. The roots were metered with a digital caliper (Teknikel, Istanbul, Turkey) in three root regions. For standardization similar forty-eight teeth with a size of $17 \pm 0,12mm$ were regulated. For avoiding calsification, resorptive defects and extra canals, periapical radiographs were taken for mesio-distal and bucco-lingual directions. Fourty eight teeth randomly seperated into two main groups based on the apical diameter. Each group were randomly divided into four subgroups (n=6). Positive control groups were prepared without any access cavity preparation for simulating immature teeth (P). In the positive control groups the specimens were standardized using peeso reamers from in the way of apical to the coronal. The apical 2mm of each root for 1,2mm diameter groups (G1) and 2mm of each root for 1,8 mm diameter groups (G2) was removed using low speed diamond saw (Diamond Disc Superflex 910S/220, North Bel, Italy). For simulate immature roots, canals were instrumented until 4 Peeso reamer (Mani inc, Tochigi, Japan) reached the apex in Group 1. In Group 2, the root canals were instrumented until 6 peeso reamer reached the apex. Then apical diameters were checked by digital calippers. If the

specimens have less than 1,2 mm and 1,8 mm apical diameters, extra enlarging with K-Files (Dentsply Maillefer, Ballaigues, Switzerland) were performed until obtained necessary wideness. Each root canal was irrigated with 3ml 2,5% sodium hypochlorite and 3ml distilled water after the instrumentation. The root canals belonging to the negative control groups were filled with calcium hydroxide (Calcicur; Voco,Cuxhaven, Germany) dispensed through a syringe tip and sealed with temporary filling material (Cavit; 3M ESPE, Germany). After these prosedures the specimens were stored in 100% humidity at temperature of 37ºC for 4 weeks. In Group 3, MTA (Angelus, Londrina, PR, Brazil) was prepared according to the manufacturers'instructions and to form a 3 mm thick apical plug MTA was positioned in the simulated immature roots with a hand plugger from the coronal access. Then the rest of the root canals were filled with Guttaflow Bioseal (coltene / whaledent AG, Altstatten, Switzerland) cold filling system until the cementoenamel junction. In group 4, MTA was completely obturated into the simulated immature roots to the semento-enamel junction. For confirming the root canal obturation and apical plug quality periapical radiographs were taken in both mesio-distal and bucco-lingual directions (Figure 1). All samples were placed in an incubator to supply the environment at 37 ° C and 100% humidity for 24 hours. Resin composite (3M ESPE, St Paul, MN) restorations were applied to the access cavities of the specimens and at 37 ° C and 100% moisture for 4 weeks.
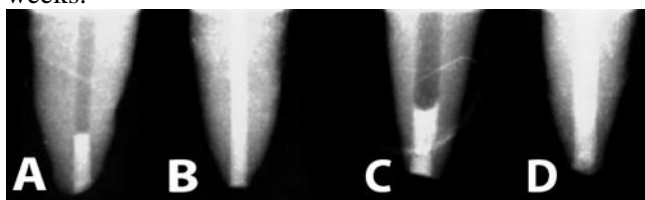
Figure 1. A: 3mm apical plug in 1.2 mm apical diameter group B: Complete obturation with MTA in 1.2 mm apical diameter group C: 3mm apical plug in 1.8 mm apical diameter group D: Complete obturation with MTA in 1.8 mm apical diameter group

Fracture Testing
The roots of all samples were dipped into the wax 0,2-0,3 mm thick and 2,0 mm below the semento-enamel junction point for simulation of periodontal ligament thickness. The prepared samples were embedded in autopolymerizing acrylic block at a 45 degree angle and removed after polymerization and purified from wax with hot water. Acrylic resin blocks were sealed with C-type silicone based impresson material (Zeta Plus, Zhermack, Bada Polesne Rovigo, Italy) for simulation PDL and teeth were re-placed in resin blocks. The samples were stored in a humid towel to prohibit desiccation until they entered the cracking test. The force was applied to the long axis of the teeth at 1350 at 1mm/min with a universal test machine until the fracture occured. Values were recorded in Newton units at the time of fracture.

Statistical analysis
A two-way ANOVA was carried out to invastigate the effects of apical enlargement diameter and fill type on fracture resistance. Data are mean ± standard deviation, unless otherwise stated. Outliers were evaluated by examination of a boxplot, normality was assigned using Shapiro-Wilk's normality test for each cell of the design and homogeneity of variances was assessed by Levene's test. All pairwise comparisons were run for each simple main effect with reported 95% reliance intervals and p-values Bonferroni-adjusted within each simple main effect. Tukey test was performed to make a pairwise comparisons as there are differences in the fracture resistance between the subgroups in Group 2. All statistical analyses were exerted by the SPSS software (SPSS, Inc., Chicago, IL, USA).

Results
The mean fracture resistances values and standard deviation of the groups are summarized in table 1.

Table 1. Mean "Fracture resistance" scores for positive, negative, guttaflow bioseal and MTA fillapex filled 1,2mm and 1,8mm apical diameter groups

	P(positive)	N(negative)	G(GBioseal)	M(MTA)	p value
1.2mm Apical Diameter	1127,07 ± 230,28	841,9 ± 215,87	1017,77 ± 173,78	1070,58 ± 230,78	0.067
1.8mm Apical Diameter	1180,35 ± 136,66	603,21 ± 105,1	1274,82 ± 24.,92	886,82 ± 106,91	<0.001
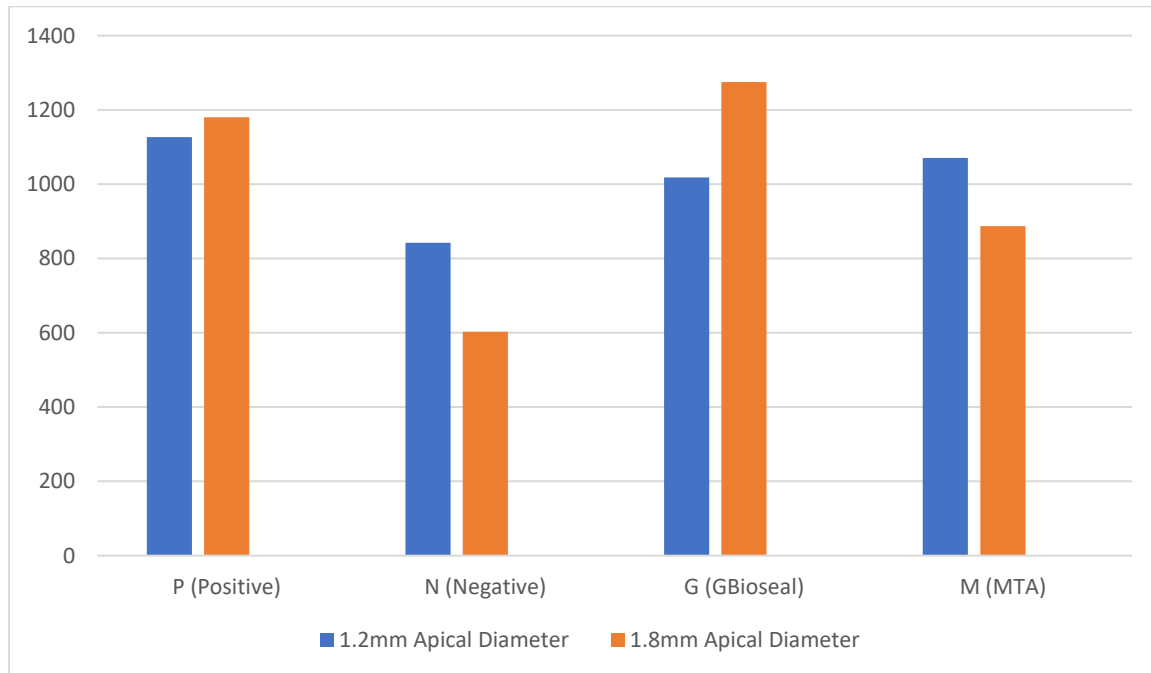
Figure 2. Bar graphics of mean fracture resistance values of groups

A statistically significant difference was reported between different apical diameters (p=0,009). Negative control groups had the lowest fracture resistance among all subgroups in both main apical diameter groups. The difference between the negative control group and the other subgroups in Group 1 was not statistically significant (p>0,05), while Group 2 also had a statistically significant difference (p<0,05). There was no statistically significant difference in fracture resistance in 1,2 mm apical diameter specimens by filling type. Tukey test was performed to make a pairwise comparisons as there are differences in the fracture resistance between the subgroups in Group 2 (p<0,05). The fracture resistance value of possitive control group was higher than negative control group and showed a statistically significant difference (p < 0,05). GuttaFlow Bioseal group mean "fracture resistance" value was higher than negative control group in Group 2, the difference is statistically significant (p < 0,05). Statistically significant difference was found between GuttaFlow Bioseal group and MTA Fillapex groups in group G2 (p = ,006). However, there was no statistically difference between the filling type groups in Group 1(p>0,05). In pairwise comparison analysis there was statistically difference between the filling types of groups (p<0,05).

Discussion

In the present study we searched the effect of different apical diameters on the fracture resistance of simulated immature teeth. Different obturation procedures effected the bond strength values in only 1,8 mm apical diameter simulated group significantly. This hypothesis was partially refused. However, the other hypothesis was accepted, we reported that different apical diameters effected the fracture resistance values significantly

When the pulp is exposed to necrosis as a result of caries or trauma before root growth and development is completed, the apex remains broadly described as open. In this study, the maxillary central teeth were chosen for the experiment because they are more susceptible to external effects and trauma due to their localization (1). Teeth with similar sizes at buccolingual and mesiodistal were included in the

experimental procedure to provide standardization. In our study, to simulate the immature teeth, the root canals were prepared using sizes 4 and 6 Peeso reamers to mimic Cvek's stage 3 and 4 root development (15). These root development groups have been referenced as representing the most commonly treated immature teeth (16). Prepared samples in this study only take on immature teeth morphologically but not in terms of physiological properties. To test the fracture resistance, simulated immature teeth were buried into acrylic resin block and periodontal membrane simulation was made using a polyether impression material to simulate the clinical situations (17). In addition, the angle between the maxillary and mandibular incisors is 135 degrees in class 1 occlusion, the applied force was loaded on the long axis of the tooth at this angle (18).

Immature teeth are poor in root dentin thickness compared to teeth that have completed root development. The need for restorative materials is increasing as less dentin wall thickness reduces fracture resistance(19). Preceding investigations have appraised the fracture resistance that used diverse root canal filling materials, such as gutta-percha, fiber post or fully MTA in immature teeth (20–22). In many studies, Ca (OH)2 apexification significantly increases the risk of root fracture. As a result of denaturation and hydrolysis that occurs in the organic matrix, debilitated dentin can be related with this situation. The risk of fracture becomes more dramatic when root development is incomplete (6, 23). In our study, the lowest fracture resistance was observed in negative control groups.

In the literature there are searches about fracture resistance of MTA thickness used in apexification of immature teeth. Bortoluzzi noted that MTA, which is used as an obturation material for immature teeth, increases resistance to root fracture (24). However, there were controversial conclusions about the situation. Cicek et al. (10) reported that the fracture resistance of root canal was completely filled with MTA was lower than the apical 3mm plug group. Considering these varied results, the present study compared the complete root canal obturation using MTA or apexification MTA with backfilling with GuttaFlow Bioseal. In this study, different MTA thicknesses were tested on both simulated immatur teeth with an apical diameter of 1,2 mm-1,8 mm and GuttaFlow Bioseal was used for backfilling in 3mm apical plug groups.

GuttaFlow Bioseal is a new biocompatible material containing calcium silicate and guttaperka particles. GuttaFlow has apatite forming and bioactive abilities due to its low solubility, good alkalizing activity combined with light calcium release (25). This silicone-based endodontic sealer material has been investigated for its effect on fracture resistance by using it as backfilling after the MTA apical plug. While Guttaflow Bioseal has the highest fracture resistance in the 1,8mm apical diameter group, it makes no significant difference in the 1,2mm apical diameter group. Difference between the different filling materials and techniques in the 1,2mm apical diameter group was not significant this can be because the dentine amount is higher than the 1,8mm apical diameter group (19). Especially teeth with wide-apex, it has been observed that using an elastic material after apical plug instead of completely filling the root canal with MTA increases fracture resistance.

Conclusion

GuttaFlow Bioseal can be an alternative backfilling material after apical plug with MTA to enhance fracture resistance in wide apex teeth such as Cvek's stage III. Our study showed that CaOH is the worst option in terms of fracture resistance.

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RESEARCH ARTICLE

Determining of Health Literacy Level in Elderly: An Example of Eastern Turkey

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Abstract

Objective: Knowing the health literacy levels of the elderly is important for better health care. The aim of this study was to determine health literacy level of the elderly.

Methods: This descriptive cross-sectional study was conducted between April 2018 and November 2018. The study population comprised individuals aged over 65 years living in the eastern province, who applied to Family Health Centers for any reason between April 2018 and November 2018 and accepted to participate in the study (983 individuals). Personal information form and Health Literacy Scale were used to collect data Institutional and ethical approvals for the study were obtained. The number, percentage, mean, parametric and nonparametric tests and Pearson correlation test were used to evaluate the data.

Results: The mean Health Literacy Scale total score of the participants was 44.00 ± 9.10. A statistically significant difference was found between the mean Health Literacy Scale total score of participants and the marital status, social security, chronic disease status, type of chronic disease and regular drug use. A weak negative correlation was found between the mean Health Literacy Scale scores of the elderly and age.

Conclusion: As a result of our research, the health literacy level of the elderly is moderate and needs to be improved further. To increase the health literacy level of the elderly, local governments, health institutions and health workers should take the necessary measures.

Key words: Elderly, Health Literacy, Health Promotion, Turkey.

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Introduction

Health literacy defined as "the ability of the individual to reach, understand and use health information for the preservation and maintenance of health" (1). For the elderly, Health literacy is a replaceable factor affecting self-management and health outcomes (2). With the rapid increase in the ratio of the elderly population among the dependent population in recent years, improving the health of the elderly, increasing the level of welfare and reducing health inequalities have gained importance in terms of elderly welfare. According to the projections of the United Nations, the ratio of the elderly population is estimated to reach 21% of the world population by

2050 (3). According to the Turkey Statistical Institute data, elderly population in Turkey is approximately 6 million and constitutes 7.7% of the total population (4). It is estimated that this ratio will reach 20.8% in 2050.

This rapid progress of the elderly population in aggregate increases the importance of health literacy for the elderly and social welfare (1). It is proposed that the level of health literacy among the elderly is lower than that among individuals in other age groups, especially because of the increase in chronic diseases, decline of cognitive and physical abilities and reduced social and economic support (1,2). Thus, it can be argued that ageing is one of the major factors affecting health literacy (4,5). It was reported in a study that individuals over 65 years constituted the most risky groups in terms of low health literacy level (1). In other words, the level of health literacy decreases with ageing (1,5). In the study by Bozkurt and Demirci in Turkey, it was found that 85.1% of elderly individuals over 65 years had inadequate or problematic health literacy levels (6). In a study conducted in the America, a one-point decrease in functional health literacy level was observed for each year of increasing age (7).

It is noted that chronic diseases are more common in the elderly population, and these chronic diseases are concomitant with other diseases. It is emphasized that health literacy rate is low among individuals over 60 years of age, and elderly individuals have problems filling forms in hospitals and answering questions. It is also reported that individuals in this age group occasionally fail to ask important questions regarding their health (5-7). In a study conducted by Von Wagner et al. on individuals aged 18–90 years, it was found that health literacy levels of the elderly, undereducated, male and low-income individuals were low (8).

Nurses can support increased health literacy by using similar examples based on previous life experiences of the elderly (9). Nurses' relationship with the elderly evolves over time, individuals may be willing to ask what feeling the lack of health literacy more comfortable express or understand and understand the health information provided by the clinician (10).

In this context, in elderly individuals, who are considered to constitute a fragile group in terms of life period, accessing accurate health information, being able to comment this knowledge and apply it in their everyday lives and being able to receive the necessary services, that is, being health literate individuals, are important in terms of elderly health and quality of life. However, this situation should be evaluated in

terms of its contribution to active ageing (1,3). As noted by the World Health Organization, active ageing is associated with the elderly people's ability to benefit from opportunities such as health, safety, and participation in society at an adequate level in order to increase the quality of life (2,4). From this point of view, the purpose of this study was to determine the health literacy level of the elderly and factors affecting it and discuss these factors in light of the literature.

Methods

Study Design
This study was designed as a descriptive cross-sectional study. The study was carried out at Family Health Centers located in the eastern province center between April 2018 and November 2018.

Study population consisted of individuals aged over 65 years. The sample of study consisted of 983 individuals who consulted to Family Health Centers in the eastern province for any reason and accepted to participate in the study.

After explaining the purpose of the research by the researcher to the individuals who applied to Family Health Centers for any reason between April 2018 and November 2018. Following that, the questionnaires were applied based on voluntariness, and the data were collected (10–15 min in average).

Personal information form and Health Literacy Scale (HLS) were used to collect data.

1. *Personal Information Form:* This form is prepared by the researcher in accordance with the literature and consists of 10 questions related to personal and professional characteristics**.**
2. *The 14-item Health Literacy Scale (HLS-14):* HLS was developed by Suka et al. in Japan to measure the health literacy level of adults (11). The Cronbach alpha value of the scale was found to be 0.81. Consisting of 14 items, the scale has the following three sub-dimensions: functional health literacy, interactive health literacy and critical health literacy. The validity and reliability study of the Turkish version was performed by Turkoglu and Kilic and the Cronbach alpha value was found to be 0.85 (12). In our study, the Cronbach alpha value was 0.88. 'Functional health literacy sub-dimension': It demonstrates the basic literacy skills of individuals. This sub-dimension comprises five items, which are associated with health risks or how to use the health system and the ability to read basic health education materials (reading prescriptions, reading prospectuses and reading and understanding the

information necessary for care). These are items 1, 2, 3, 4 and 5. The Cronbach alpha value of this sub-dimension was found to be 0.83, whereas it was 0.89 in our study.

'Interactive health literacy sub-dimension': It includes advanced cognitive, literacy and social skills. This sub-dimension is defined as the patient exhibiting independent behavior, being able to make decisions about their own health status and communicating effectively with healthcare professionals. This sub-dimension consists of five items (items 6, 7, 8, 9 and 10). The Cronbach alpha value of this sub-dimension was found to be 0.85, whereas it was 0.80 in our study.

'Critical health literacy sub-dimension': This sub-dimension, which covers advanced cognitive and social skills to be used in the critical analysis of health-related information and making health decisions, consists of four items. These are items 11, 12, 13 and 14. The Cronbach alpha value of this sub-dimension was found to be 0.76, whereas it was 0.80 in our study.

The scale items are scored between 1 and 5 points. Each item of the scale is graded as a 5-point Likert-type item between 'strongly disagree' (1 point) and 'strongly agree' (5 points). The total score that can be obtained from the scale ranges between 14 and 70 points. Higher scores indicate a higher health literacy level

Statistical analysis

The analysis of the data was done on the computer using the Statistical Package for the Social Sciences (SPSS-22) statistical software. Frequency, descriptive, percentage, mean, standard deviation, explore and normality plots with tests were used as descriptive statistical methods. Kolmogorov – Smirnov test was used to test normality distribution with analytical tests. Mann-Whitney U test was used for data that is not normally distributed for binary groups. Kruskal-Wallis test was used for data that is not normally distributed for groups more than two. Spearman correlation test was used to determine whether there is a linear relationship between the two numerical measurements, the direction and severity of this relationship, if any. In our study (p <0.05), it was accepted as statistically significant difference.

Results

The mean age of the participants was 73.74 ± 6.66 years. Of the participants, 61.7% were women, 52.7% were married, 64.2% were primary school graduates,

81.8% were insured, 47.1% had income equal to their expenses and 90.6% had chronic diseases. 20.7 % of the participants had diabetes, 28.2% had hypertension, 12.2% cholesterol, 14.0% osteoporosis, and 15.6% other diseases. Of the elderly, 81.3% had family history of chronic disease, and 89.3% regularly used medication (Table 1).

As shown in Table 2, no statistically significant difference was found between the HLS mean scores of participants based on gender, income status and family history of chronic diseases (p> 0.05). Based on the marital status, the difference between the HLS mean scores of elderly individuals was statistically significant (p< 0.05). Single individuals had a higher mean score than married individuals. Based on the educational status, the difference between the HLS mean scores of elderly individuals was statistically significant (p< 0.05). University graduates had a higher mean score. Based on social security, the difference between the HLS mean scores of elderly individuals was statistically significant (p< 0.05). Individuals with social security had a higher mean score. Based on the chronic disease status, the difference between the HLS mean scores of elderly individuals was statistically significant (p< 0.05). Individuals with a chronic disease had a higher mean score. Based on the type of chronic disease, the difference between the HLS mean scores of elderly individuals was statistically significant (p< 0.05). In the post hoc (Dunn) analysis, the difference was found to be caused by osteoporosis and hypertension. The HLS score mean of individuals with hypertension was found to be higher.

Based on regular drug use, the difference between the HLS mean scores of elderly individuals was statistically significant (p< 0.05). Individuals with regular drug use had a higher mean score.

As shown in Table 3, the functional health literacy sub-dimension mean score of the participants was 15.616 ± 4.72, interactive health literacy sub-dimension mean score was 15.866 ± 3.70, critical health literacy sub-dimension mean score was 12.829 ± 3.11 and the mean total score was 44.00 ± 9.10. As shown in Table 4, there was a statistically significant and weak negative correlation between the mean HLS total score and age of elderly people (p< 0.05).

Table 1. Demographic characteristics of the elderly (N=983)

Variables		n	%
Gender	Male	376	38.3
	Female	607	61.7
Marital Status	Married	518	52.7
	Single	465	47.3
Educational Status	Primary school graduate	631	64.2
	Secondary school graduate	224	22.8
	High school graduate	120	12.2
	University graduate	8	0.8
Social Security	Yes	804	81.8
	No	179	18.2
Levels of income	Less income than expenditure	431	43.8
	Equal income and expenditure	463	47.1
	More income than expenditure	89	9.1
Chronic Disease Status	Yes	891	90.6
	No	92	9.4
Type of Chronic Disease	Diabetes	203	20.7
	Hypertension	277	28.2
	Cholesterol	120	12.2
	Osteoporosis	138	14.0
	Other	153	15.6
Chronic Disease Status in Family	Yes	799	81.3
	No	184	18.7
Regular Drug Use Status	Yes	878	89.3
	No	105	10.7
		$\overline{X} \pm SD$	
Age (years)		73.74 ± 6.66	
	(min. 65, max. 82)		

Table 2. Comparison of demographic characteristics and health literacy scale mean scores

Variables		n	Mean ± SD	Statistic
Gender	Male	376	44.047±9.44	U=113607.00
	Female	607	44.476±8.89	p=0.906
Marital Status	Married	518	42.602±9.31	U=93692.50
	Single	465	46.217±8.46	**p= 0.000**
	Primary school	631	44.600±9.676	
Educational Status	Secondary school	224	43.116±8.252	KW=10.334
	High school	120	44.625±7.130	**p=0.016**
	University graduate	8	50.375±8.087	
Social Security	Yes	804	44.782±8.752	U=61498.00
	No	179	42.201±10.296	**p= 0.002**
	Less income than expenditure Equal	431	44.937±9.407	KW= 3.282
Levels of income	income and expenditure	463	43.933±9.062	p= 0.194
	More income than expenditure	89	43.258±7.559	
Chronic Disease	Yes	891	44.791±8.805	U=29708,00
Status	No	92	39.673±10.569	**p=0.000**
Type of Chronic	Diabetes	203	45.064±8.273	
Disease	Hypertension	277	45.909±7.860	KW=9.674
	Cholesterol	120	44.300±10.489	**p= 0.046**
	Osteoporosis	138	43.898±8.312	
	Other	153	43.594±9.885	
Chronic Disease	Yes	799	44.533±8.420	U= 71778.00
Status in Family	No	184	43.353±11.587	p=0.618
Regular Drug Use	Yes	878	44.797±8.745	U= 36235.00
Status	No	105	40.257±10.901	**p=0.000**

Table 3. Health literacy scale sub-dimension mean scores and total scale mean score

	Mean ± SD	Min- Max
Functional Health Literacy Sub-Dimensions	15.616±4.72	5.00-25.00
Interactive Health Literacy Sub-Dimension	15.866±3.70	5.00-25.00
Critical Health Literacy Sub-Dimension	12.829±3.11	4.00-20.00
Health Literacy Scale Mean Total Score	44.00±9.10	14.00-68.00

Table 4. The correlation between health literacy scale mean total score and age

	Age (Years)	
	r	p
Health Literacy Scale Mean Total Score	-0.092	**0.004**

Discussion

The findings of this study carried out to determine the health literacy of elderly individuals are discussed in the following section.

The mean HLS score of the participants was 44.00 ± 9.10. The mean HLS score of the elderly individuals obtained in this study was moderate, and it was lower than the mean scores obtained in studies on adults. In other studies that used different measurement tools on elderly individuals, the health literacy levels were found to be moderate and significantly lower than those of adults (1,13). In the studies conducted by

Ugurlu and by Cimen and Temel in Turkey, the health literacy level of elderly individuals was found to be close to moderate (14,15). It is considered that the effects of the natural ageing process, differences in interest level, interaction with environmental stimuli, dependence on others, insufficient perception, attention deficit and functional decline have an effect in the low scores of health literacy of the participants in the older age group (1,16). In addition, it is considered that the decrease in the level of education in Turkey may be a factor affecting the decrease in the health literacy levels of the elderly compared with

those of adults (17). In fact, in the systematic review of Paasche-Orlow and Wolf, it was reported that low health literacy level is related to education level (18). When the studies conducted in Turkey are examined, it can be seen that low education level, literacy-related activities and mean health literacy scores affect each other (14,15).

Health literacy is examined in three important dimensions: functional, interactive (communicative) and critical (19). Functional health literacy is based on basic reading and writing ability, and people at this level can read health education materials. The mean functional health literacy sub-dimension score of elderly participants was 15.616 ± 4.72. Similar results have been obtained in the studies conducted (19, 20). Interactive health literacy means that people have social and cognitive skills in communicating with health providers. Individuals at this level can benefit from different health activities and can easily use their knowledge in changing health conditions (19). In our study, the mean interactive health literacy sub-dimension score was 15.866 ± 3.70. Similar results were obtained in studies conducted in other countries (19, 20). Critical health literacy requires improved cognitive, social skills and critical thinking capability. Thus, individuals can critically evaluate health information; improve their capacities and understand and interpret the social, political and economic dimensions of health (20). The mean critical health literacy sub-dimension score was 12.829 ± 3.11 in our study. Similar to our study, the mean critical health literacy score was found to be lower than that of other sub-dimensions in other studies (9, 19-21). This situation is considered to be owing to the decrease in the cognitive and social abilities of the individuals as they age, and insufficient internalisation of the information received. In addition, owing to the respect for elderly people in Turkish culture, all the needs of the elderly regarding healthcare are provided by family members (usually, by their children). As a result, the elderly leaves all decisions regarding their health to their family members; retain the information they receive at a lexical level and do not test its reliability and cannot interpret the social, political and economic dimensions of health (14, 15).

There was a statistically significant difference between the mean HLS score of the elderly and marital status (p< 0.05). Single participants had a higher mean score than married individuals. When we look at the literature, although some studies did not reveal any difference, other studies reported that the mean scores of married individuals were higher than those of single individuals (6, 14, 15, 22). In our

study, it was determined that the mean score of singles was higher. This difference was attributed to the region where the study was conducted and the fact that divorced or widowed individuals were evaluated in a single category.

There was a statistically significant difference between the mean HLS score of the elderly and social security status (p< 0.05). Individuals with social security had a higher mean score than those who did not. Similarly, a significant difference was also found in the study conducted by Cimen and Temel (15).

There was a statistically significant difference between the mean HLS score of the elderly and chronic disease status (p< 0.05). Similar results were obtained in the study by Ugurlu (14). Conversely, Cimen and Temel found no significant difference between the number of chronic diseases and mean score of health literacy (15). This difference between the studies is considered to be caused by the different regions in which the studies are conducted. Furthermore, this situation is considered to be owing to the necessity of individuals with chronic diseases receiving more health services and paying attention to their treatment.

Based on the type of chronic disease, the difference between the HLS mean scores of elderly individuals was statistically significant (p< 0.05). In the post hoc (Dunn) analysis, the difference was found to be caused by osteoporosis and hypertension. The HLS score mean of individuals with hypertension was found to be higher. This result suggests that the daily follow-up of individuals with hypertension is relatively higher than those with osteoporosis and that the elderly people's health literacy levels have increased due to blood pressure monitoring. In a study conducted in China, the HLS score mean of individuals who had blood pressure control was found to be higher (23).

There was a statistically significant difference between the mean HLS score of the elderly and regular drug use (p< 0.05). The health literacy levels of drug users were higher. Similarly, a significant difference was found in other studies (13, 14). It is considered that this may be due to the fact that individuals who regularly use drugs have more knowledge about how, when and how the drug should be used, and their awareness levels are higher.

There was a weak negative correlation between the HLS mean score of the elderly and age (r= −0.096) (p< 0.05). While age increased, the mean health literacy scores of elderly individuals decreased. According to the studies conducted, it was found that individuals aged over 65 years were lower compared with those of individuals in other age

groups (14,24-26). It can be said that ageing is one of the major elements affecting health literacy. The low health literacy among the elderly affects the individual and the country negatively in many ways. Baker et al. determined that inadequate health literacy skills were independently associated with an increased mortality risk among the elderly in a community (13). In a systematic review, the effects of low health literacy on health were evaluated, and it was found to be associated with more hospitalizations, more use of emergency services, receiving less protective health care, inability to use medicines properly, poor understanding of health-related messages and particularly poor health and higher mortality in the elderly (1). Therefore, health literacy has become an important matter in Turkey, which has an increasing elderly population.

Limitations of the Study

This study was limited to individuals aged over 65 years admitted to Family Health Centres affiliated to the Provincial Health Directorate.

Conclusion

As a result of our research, the health literacy of elderly individuals was found to be at a moderate level, and this needs to be further improved. Today, owing to the change in the provision of health services, the responsibilities of the elderly towards their own health have increased. Since the incidence of chronic diseases is high, elderly people are expected to be more active in taking responsibility for their treatment and care. In this respect, it is important to increase the health literacy level of elderly people. To increase the health literacy level of elderly people, local governments, health institutions and health workers should take the necessary measures. It is recommended that health personnel, especially public health nurses, use special methods, a simpler language and materials in health education programmes and receive feedback from elderly individuals.

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Investigation of the Motivation of Nurses Working in a Mental Health and Psychiatry Hospital to Approach or Avoid Emotion Inducing Situations in Terms of Some Parameters

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Abstract
Objective: This study aims to investigate the motivation of nurses, who are working in a mental health and illness hospital, to approach or avoid emotion inducing situations in terms of some parameters.
Methods: This descriptive study was conducted with 101 nurses who worked in Samsun Mental Health and Illness Hospital between June 2017 and July 2017 and met the inclusion criteria. In the study, the "Demographic Information Sheet" and "Need for Affect Scale" were used as a data collection tool.
Results: The nurses who thought that they were capable of recognizing their feelings had a low score from the avoidance sub-scale (p<0.05). The nurses who thought that they were capable of expressing their feelings had a high score from the approach sub-scale but a low score from the avoidance sub-scale (p<0.05). The nurses, who expressed that they partially abstain from participating in emotionally intense environments in their social lives, had a higher score from the avoidance sub-scale (p<0.05).
Conclusion: It was concluded that for the nurses working in the mental health and illness hospital where the study was conducted, the parameter of thinking to be capable of expressing their feelings affected the motivation to approach emotion-inducing situations; while the parameters of thinking to be capable of recognizing feelings, of abstaining from participating in emotionally intense environments in social life, of thinking that individuals with mental illness are dangerous and having difficulty when working with them affected the avoidance motivation.
Key words: Need for Affect, Nurse, Psychiatric Nurse.

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Introduction

Emotion is "fluctuations in a person's inner world with the effect of thoughts" (1). Emotion is the "feeling" aspect of consciousness and is characterized by three elements: These include certain physical arousal, certain behavior that reveals the emotion to the outside world, and an inner awareness of feelings (2). Emotions send fast and powerful physical messages, enabling respond to the environment.

Thus, they allow us to communicate with the environment, whether willingly or unwillingly (3). According to Maio and Esses (2001), emotions often arise from some specific cognitive states, and cognitive tasks often involve some emotion (4).

People have differences in participating in and abstaining from emotion-inducing activities. This is directly explained by their need for affect. The need for affect is defined as the general motivation level of people for participating in or abstaining from situations and activities containing various emotions for themselves and others (4). Emotional approach and emotional avoidance originate from our different experiences. People often have higher motivation towards emotional approach then emotional avoidance. Because the approach motivation provides higher intrinsic satisfaction (5). In other words, since having emotional experience provides intrinsic motivation in at least one level as well as emotions promote motivational behavior and guide justifications, the motivation to approach emotions becomes high (4). Individuals who like having emotional experiences further tend to have extreme opinions regarding controversial topics and to discuss with others about them, because extreme opinions and discussions give people the opportunity to experience strong emotions. This makes individuals with a high need for affect more open and willing to learn new and different new topics. Individuals with high need for affect want to engage in emotionally intense activities such as watching theatre, reading a novel or poem or watching a horror movie, while those with a low need for affect tend to abstain from such activities. Such behaviors and tendencies are associated with the need for affect, they are also associated with personal characteristics, which are one of the main determinants of such behaviors (6).

Nursing is a profession that requires working with healthy individuals/patients and their families mostly in emotionally charged environments and activities (7). Especially nurses working in psychiatric clinics more often encounter with emotionally charged environments since they provide care for individuals with a mental disorder (8). Since nurses providing care for individuals with a mental disorder are the group that spends the most time with the patient, they are the manager, coordinator as well as user of the environment when creating the therapeutic environment. Nurses working in psychiatric clinics are also expected to use therapeutic communication techniques when communicating with patients (9). For a therapeutic patient-nurse communication, the nurse should be highly motivated to approach the emotionally charged relationship with the patient (4)

using several therapeutic techniques such as expressing observations about patient-nurse communication, encouraging for conversation, being acquiescent, exploring, concentrating on emotions and reflecting emotions (9). It is thought that many parameters have effect on the motivation of nurses to approach and avoid emotionally charged environments. Nurses are adversely affected by various situations such as the chronic and long-term nature of the mental illness, having difficulties with communication and relationships with the patient and his/her relatives, working with aggressive patients, very stressed patients (10). On the other hand, the parameters related to the working environment of nurses are also important. A study found that 72.2% of nurses worked at both day and night, 38.9% of them were subjected to physical violence, and 85.7% of those being subjected to physical violence worked in psychiatric clinics (11). A study performed by Dil and Aykanat (12) with students taking mental health and illness nursing course found that the "motivation to approach emotions" was significantly increased and positive changes occurred in the "motivation to avoid emotions" after taking the course.

No study was found in the literature, where the motivation of nurses working in psychiatric clinics to approach and avoid emotionally charged environments was investigated in terms of personal and professional parameters. This study aims to investigate the motivation of nurses, who are working in a mental health and illness hospital, to approach or avoid emotion-inducing situations in terms of some parameters.

In the study, the following questions were sought:
• What are the parameters affecting the motivation of nurses working in a mental health and illness hospital to approach emotionally charged environments?
• What are the parameters affecting the motivation of nurses working in a mental health and illness hospital to avoid emotionally charged environments?

Methods

Study Design and Setting
This study is descriptive. The study universe consisted of 119 nurses who worked in Mental Health and Illness Hospital between June 2017 and July 2017; the study sample consisted of 101 nurses who met the inclusion criteria. The sample was determined based on the study performed by Süt in 2011 (13). Before starting the study, the sample size was determined by power analysis, and it was found that at least 101 nurses should be included in the study for

a 95% confidence interval and an 89% power. The nurses who have permanently worked in the Mental Health and Illness Hospital and volunteered to participate in the study were included in the study.

Ethical issues

To conduct the study, permission was obtained from Mental Health and Illness Hospital and affiliated institutions (Number: 61646299/044; Date: 26.10.2017); ethics committee approval was obtained from the Clinical Researches Ethics Committee of the university in the city where the study was conducted (Number: B.30B2BDM.0.20.08/1029; Date: 23.06.2017), and permission to use scale was obtained from Prof. Dr. Veli Duyan who prepared the Turkish Version of the "Need for Affect Scale" used in the study. The nurses were informed about the study, and their written and verbal consents were obtained.

Instruments

Nurse Demographic Information Sheet: This sheet that was prepared by the researcher based on the literature (4, 12, 14, 15) consists of a total of 13 questions. This sheet contains 5 questions on sociodemographic characteristics of nurses, 4 questions on their emotional characteristics, and 4 questions on emotional characteristics for working with individuals with mental illness.

Need for Affect Scale (NAS): It was developed by Maio and Esses in 2001 to evaluate the needs for people (4). The Turkish version of this scale was prepared by Duyan et al. in 2011 (14). The Need for Affect Scale (NAS) is a self-measure scale to evaluate the motivation of individuals to approach and avoid emotional environments. The scale has a total of 26 items: 13 in the emotional approach sub-scale and 13 in the emotional avoidance sub-scale. The individuals are asked for expressing their opinions about the items on the 7-point scale, ranging from "strongly disagree -3" to "strongly agree +3". The score from each subscale ranges from -39 to +39. The overall score from the need for affect scale ranges from -78 to +78. A high score from the inventory means that the participant has a high motivation to approach emotions, while a low score means that the participant has low motivation to approach emotions. The reliability analysis of the scale used in the study

showed that the approach sub-scale is reliable, and the avoidance sub-scale is highly reliable. In the study, the Cronbach's alpha coefficient of the Need for Affect Scale was found 0.751

Statistical analysis

The data were evaluated using SPSS 21.00 program. The statistical evaluation was performed based on descriptive statistics, independent t-test, ANOVA, Pearson correlation analysis. In the study, the significance level was taken as $p<0.05$.

Results

The demographic information of the nurses included in the study is given in Table 1. Of the nurses participating in the study, 70.3% were women, 77.2% were married and 71.3% had a bachelor's degree. 70.3% of the nurses worked in inpatient ward, and 84.2% received education on approach to individuals with mental illness (Table 1).

The distribution of the emotional characteristics of the nurses is given in Table 2. 39.6% of the nurses included in the study stated that they receive support from their colleagues when they are emotionally charged. 48.5% of the nurses stated that they are capable of recognizing their emotions, 47.5% stated that they are partially capable of expressing their emotions, and 52.5% stated that they partially abstain from participating in emotionally intense environments in their social lives (Table 2).

The distribution of the emotional characteristics of the participating nurses regarding working with individuals with mental illness is given in Table 3. 34.7% of the nurses answered the question "What do you have emotional difficulties with when working with individuals with mental illness?" as "patient behaviors", while 28.7% of the nurses answered the question "What emotion do you experience most often when working with individuals with mental illness?" as "all emotions", and 28.7% of them answered the same question as "sadness". 55.4% of the nurses answered the questions "Do you think that you are capable of managing various emotional situations seen in individuals with mental illness?" and "Do you think that individuals with mental illness are dangerous?" as "partially" (Table 3).

Table 1. Distribution of nurses by their demographic characteristics

Characteristics		Number	%
Sex	Women	71	70.3
	Men	30	29.7
Marital Status	Married	78	77.2
	Single	23	22.8
Educational Status	High-school	3	3.0
	Undergraduate	18	17.8
	Bachelor's Degree	72	71.3
	Master's Degree	8	7.9
Department	Inpatient Wards	71	70.3
	Emergency Room	7	6.9
	AMATEM	5	5.0
	Forensic Ward	7	6.9
	Other	11	10.9
Having Education on Approach to Individuals with Mental Illness	Yes	85	84.2
	No	16	15.8
Total		101	100

%: Percentage

Table 2. Distribution of emotional characteristics of nurses

Characteristics		Number	%
Persons from Whom Support is Received When Being Emotionally Charged	Family	30	29.7
	Relative	5	5.0
	Friend	40	39.6
	Mental Health Specialist	18	17.8
	Other	8	7.9
Thinking to be Capable of Recognizing Emotions	Yes	49	48.5
	No	5	5.0
	Partially	47	46.5
Thinking to be Capable of Expressing Emotions	Yes	43	42.6
	No	10	9.9
	Partially	48	47.5
Abstaining from Participating in Emotionally Intense Environments in Social Life	Yes	18	17.8
	No	30	29.7
	Partially	53	52.5
Total		101	100

%: Percentage

Table 3. Distribution of the emotional characteristics of the nurses regarding working with individuals with mental illness

Characteristics		Number	%
Issues That They Have Emotional Difficulties When Working with Individuals with Mental Illness	Patient Behaviors	35	34.7
	Histories of Patients	31	30.7
	Emotional Burdens of Patients	31	30.7
	Other Characteristics of Patients	4	4.0
Emotion Most Often Experienced When Working with Individuals with Mental Illness	Anger	6	5.9
	Fear	10	9.9
	Sadness	29	28.7
	Pity	13	12.9
	Shame	4	4.0
	Discomfort	7	6.9
	All Emotions	29	28.7
	Other	3	3.0
Thinking to be Capable of Managing Various Emotional Situations Seen in Individuals with Mental Illness	Yes	25	24.8
	No	20	19.8
	Partially	56	55.4
Thinking that Individuals with Mental Illness are Dangerous	Yes	21	20.8
	No	24	23.8
	Partially	56	55.4
Total		101	100

The average score of the nurses from the "Approach" sub-scale of the NAS was 5.52±8.77; the average score of them from the "Avoidance" sub-scale was -7.54±13.36.

The scores of the nurses from the NAS approach and avoidance sub-scales by their emotional characteristics were examined and given in Table 4. No statistically significant difference was found between the scores of the nurses from the NAS approach and avoidance sub-scales by persons from whom they receive support when they are emotionally charged (p>0.05). The nurses, who thought that they were capable of recognizing emotions, received significantly low scores from the avoidance sub-scale (p<0.05); no statistically significant difference was found between the scores from the approach sub-scale in terms of this parameter (p>0.05). The nurses, who thought that they were capable of expressing their emotions, received significantly low scores from the avoidance sub-scale (p<0.05); no statistically significant difference was found between the scores from the approach sub-scale (p>0.05). The nurses, who stated that they abstained from participating in emotionally intense environments in their social lives, received significantly high scores from the avoidance sub-scale (p<0.05); no statistically significant difference was found between the scores from the approach sub-scale in terms of this parameter (p>0.05; Table 4).

In the study, the distribution of the scores of the nurses from the NAS approach and avoidance sub-scales in terms of some parameters regarding working with individuals with mental illness was examined and given in Table 5. It was found that the nurses, who answered the question "What do you have emotional difficulties with when working with individuals with mental illness?" as "Emotional burdens of patients" and the question "Do you think that individuals with mental illness are dangerous?" as "Yes", had significantly higher scores from the avoidance sub-scale (p<0.05). No statistically significant difference was found between the scores from the NAS approach and avoidance sub-scales in terms of other parameters (p>0.05; Table 5).

Table 4. Distribution of the scores of nurses from NAS approach and avoidance sub-scales by emotional characteristics

Characteristics		Approach Avg.± SD	Test and p	Avoidance Avg.± SD	Test and p
Persons From Whom Support is Received When Being Emotionally Charged	Family	6.86±6.39	F=0,500 p=0.776	-8.86±14.39	F=0.971 p=0.440
	Relative	3.2±12.04		-3.2±17.23	
	Friend	5.58±8.09		-9.28±13.09	
	Mental Health Specialist	8.29±7.12		-3.66±10.85	
	Other Persons	5.62±13.5		-3.62±15.84	
Thinking to be Capable of Recognizing Emotions	Yes	9.80±6.83	F=0.955 p=0.418	-14.30±11.60	F=9.724 *p<0.001
	No	4.13±8.90		6.80±6.97	
	Partially	6.39±9.00		-2.74±12.39	
Thinking to be Capable of Expressing Emotions	Yes	7.47±8.36	F= 2.518 p=0.086	-12.48±13.30	F=7.021 *p=0.001
	No	0.62±10.23		-12.00±13.59	
	Partially	4.66±8.68		-2.81±11.83	
Abstaining from Participating in Emotionally Intense Environments in Social Life	Yes	5.10±9.77	F=0,290 p=0.749	-8.81±12.38	F=6,114 *p=0,003
	No	7.12±8.46		-13.56±13.46	
	Partially	5.68±7.92		-3.41±12.40	

*F: ANOVA, *p<0.05*

Table 5. The Distribution of the scores of the nurses from the NAS approach and avoidance sub-scales in terms of some parameters regarding working with individuals with mental illness

Characteristics		Approach		Avoidance	
		Avg.± SD	Test and p	Avg.± SD	Test and p
Issues That They Have Emotional Difficulties When Working with Individuals with Mental Illness	Patient Behaviors	5.00±9.66	F=1,152	-14.06±12.15	F=5,659
	Histories of Patients	7.00±6.71		-7.36±13.87	
	Emotional Burdens of Patients	3.72±9.75	p=0.333	-0.72±11.67	*p=0,001
	Other characteristics of patients	10.50±5.00		-9.00±10.86	
Emotion Most Often Experienced When Working with Individuals with Mental Illness	Anger	3.50±9.95	F=0,590	-2.00±14.46	F=1,628
	Fear	5.44±7.33		-10.22±11.15	
	Sadness	5.36±11.61		-11.32±13.79	
	Pity	2.07±8.33		-7.15±10.66	
	Shame	7.75±3.40		3.00±9.55	
	Discomfort	5.00±7.64	p=0.762	-3.66±14.09	p=0.138
	All emotions	7.44±6.40		8.33±10.40	
	Other	8.33±15.50		-6.75±13.25	
Thinking to be Capable of Managing Various Emotional Situations Seen in Individuals with Mental Illness	Yes	8.45±7.02	F= 1,600	-12.95±11.84	F=1,636
	No	3.73±9.85		-5.73±13.49	
	Partially	5.18±8.94	p=0.195	-6.44±13.39	p=0.186
Thinking that Individuals with Mental Illness are Dangerous	Yes	3.40±10.68	F= 0,955	-0.08±10.970	F=0,389
			p=0.389	-11.60±12.11	*p=0,006
	No	7.08±5.78			
	Partially	5.64±9.05		-9.18±13.69	

F: ANOVA, *p<0,05

Discussion

The results obtained from the study conducted to investigate the motivations of nurses, who work in a mental health and illness hospital, to approach and avoid emotion-inducing situations in terms of some parameters were discussed in this section.

When the scores of nurses, who work in mental health hospital, from the NAS sub-scales were examined, it was found that the average score from the "Approach" sub-scale was 5.52±8.77, and the average score from the "Avoidance" sub-scale was -7.54±13.36. When these values were evaluated in terms of the lowest and highest scores from the scale, it was found that the approach motivation was partially higher, while the avoidance motivation was partially lower. In a study conducted with students taking Mental Health and Illnesses Nursing course, the average pre-test score from the NAS emotional approach sub-scale was found 16.52±8.9, and the average score from the NAS emotional avoidance sub-scale was found -7.00±12.33 (15). In another study investigating the effect of the "Mental Health and Illnesses Nursing" course on the emotional approach and avoidance motivation levels of students, the average pre-test score from the NAS "emotional approach" sub-scale was found 15.62±9.89, while the average post-test score was

found 27.17±10.91. In the same study, the average pre-test score from the "emotional avoidance" sub-scale was found 9.77±11.32 and the average post-test score was found 8.40±12.65 (12). A study conducted with pediatric nurses found that the average approach sub-size score of nurses was 7.31±12.62 and the average avoidance sub-size score was -8.85±11.50 (16). In another study with university students, the average score from the approach sub-scale was found 8.70±12,.03, while the average score from the avoidance sub-scale was found -4.18±12.42 (17). When the study results were compared with the literature, it can be said that the motivation of the nurses to approach emotional situations was low. Some study results showed that the avoidance motivation was lower.

It was found that the nurses in the study, who thought that they were capable of recognizing their emotions, had low motivation to avoid emotional situations (p<0.05; Table 4); although they had high approach motivation, the difference was not statistically significant (p>0.05; Table 4). It was found that the nurses, who thought that they were capable of expressing their emotions, had low motivation to avoid emotional situations (p<0.05; Table 4); although they had high approach motivation, the difference was not statistically

significant (p>0.05; Table 4). It was reported that nurses, who can recognize and manage their feelings, empathize, direct their relationship and realize themselves, can protect the mental health of themselves as well as thus provide better care to healthy individuals/patients, contributing to the protection of mental health of the society (18, 19). In the literature, it was reported that nurses, who are open to understanding their own emotions, can know how to respond to patient and how to be perceived; and a nurse can understand the emotions of others only if he/she can recognize their own emotions and thoughts and control and manage them (20). Rime and Zech (21) reported that people need to express their emotional experiences and mutual communication has an important role in meeting this need. Studies show that people should express their emotional experiences and mutual communication has an important role in meeting this need (12, 21). A study by Dil and Aykanat (12) found that after Mental Health and Illnesses Nursing training and practices, the emotional approach behaviors of students improved and the emotional avoidance behaviors reduced, although not statistically significant. Another study by Âsik and Albayrak (15) found that Mental Health and Illnesses Nursing course improved the emotional awareness of students and was effective in emotional needs such as "emotional approach" and "emotional avoidance". In the study, it was found that 84.2% of nurses received training on approach to individuals with mental illness. The fact that 71.3% of the nurses in the study had a bachelor's degree is important for them to have psychiatric nursing knowledge and skills. It is thought that these characteristics of the nurses in the study play a role in the fact that they have low motivation to avoid emotional situations.

The study found that the nurses, who expressed that they abstain from participating in emotionally intense environments in their social lives, had high avoidance motivation (p<0.05; Table 4). According to Maio and Esses (4), when people have an emotional experience, they need to understand the emotions of both themselves and others. This leads to the motivation to approach or avoid emotions. If people are discomfort about the emotions they experience, they do not attempt to experience them and to understand the emotions of others. People may have differences in participating in and abstaining from emotionally intense activities. This is directly related to their need for emotion. Since the majority of the nurses in the study received undergraduate education, they were equipped with both professional and life skills. On the other hand, the majority of the

nurses stated that they received specific education on approach to individuals with mental illness. The studies with students receiving mental health and illness nursing course showed that the course affects the emotional needs (12, 15). It was also reported that the "Self-Recognition and Assertiveness" course given in nursing undergraduate education improved assertiveness skills including the ability to show emotions easily (22). It is thought that all these factors affect the study results.

It was found that the nurses, who answered the question "What do you have emotional difficulties with when working with individuals with mental illness?" as "Emotional Burdens of Patients" had a high avoidance motivation (p<0.05; Table 5). Nurses are one of the healthcare professionals who most often communicate with individuals with a mental problem during the hospitalization period (23). The need for approach to emotions increases participation in emotionally intense activities and ensures to show a tendency to experience emotions (4). However, it is thought that there are factors affecting the motivation to approach emotionally charged situations because the place where this need is to be met is a hospital environment. Nursing knowledge and skills, which need to be free from personal curiosity and to interact with the individual they care for, with the aim of help and with their authentic existence, must also be included in the process. A study reported that student nurses have experienced ambivalence about the competence of their skills in helping with the psychiatric patient (24). The fact that the time allocated for theory and practice during the education process is insufficient also plays a role in nurses' failure to overcome negative attitudes towards mental illnesses (25). Another factor is the belief systems towards individuals with mental illness. It was found that the nurses answered the question "Do you think that individuals with mental illness are dangerous?" as "Yes" had a high avoidance motivation (p<0.05; Table 5). Believing that individuals with mental illness are dangerous prepares the ground for attributing negative emotions towards such individuals. To cope with these negative emotions, social stigmatizing behaviors arise. One of them is avoidance (26). "Sadness" is one of the emotions which the nurses in the study most often experienced when working with individuals with mental illness. It is thought that the belief system towards psychology patient/illness played a role in the avoidance motivation of the nurses, who stated that they had difficulties with the emotional burdens of patients when working with individuals with mental illness and thought that such individuals are dangerous.

Limitations of the Study

This research it was conducted among working nurses at a mental health and diseases hospital in Turkey. The results obtained from the research can be generalized to this hospital.

Conclusion

The results and recommendations obtained from the study conducted to investigate the motivations of nurses, who work in a mental health and illness hospital, to approach and avoid emotion-inducing situations in terms of some parameters were given in this section.

The results of the study are as follows:

- The motivation of the nurses to approach emotional situations was above medium level, while their avoidance motivation was below medium level,
- The nurses who thought that they were capable of recognizing their emotions had a significantly low score from the avoidance sub-scale,
- The nurses who thought that they were capable of expressing their emotions had a significantly low score from the avoidance sub-scale,
- The nurses, who expressed that they abstain from participating in emotionally intense environments in their social lives, had a significantly high score from the avoidance sub-scale,
- The nurses, who stated that they had difficulties with the emotional burdens of patients when working with individuals with mental illness, had significantly high scores from the avoidance sub-scale,
- The nurses, who thought that individuals with mental illness were dangerous, had significantly high scores from the avoidance sub-scale.

Based on the study results, it is recommended;

- to increase the number of courses to be conducted by the "Department of Psychiatric Nursing" in the curriculum of the Nursing Undergraduate Programs of universities,
- to make arrangements and improvements to reach the targeted skills in Mental Health and Illnesses Nursing courses in the Nursing Undergraduate Program,
- to create an education program to increase the motivation of nurses working in psychiatric clinics to approach emotional situations,
- to perform intervention studies in this regard.

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Effect of Postpartum Depression in Mothers With 0–1-Year-Old Infants on Father–Infant Attachment

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Abstract
Objective: This analytical, cross-sectional study was designed to determine the effect of postpartum depression in mothers with 0–1 year old infant on father–infant attachment.
Methods: The study included 207 mothers and 207 fathers with 0–12-month-old infants. The data were collected using the Introductory Information Form, Edinburgh Postpartum Depression Scale (EPDS), and Father–Infant Attachment Scale (FIAS). The data were analyzed using standard deviation, arithmetic mean, Mann–Whitney U test, and correlation analysis.
Results: Total 18.3% of the mothers were at risk of postpartum depression, and the mean total EPDS score was 7.19 ± 5.17. The mean total FIAS score was 74.95 ± 6.21. There was no statistically significant difference between the mean sub-scale and total FIAS scores and the mean EPDS scores ($p > 0.05$). There was a significant, weak, and negative correlation ($r = -0.15$; $r = -0.181$) between the EPDS scores and the sub-scale and total FIAS scores ($p < 0.05$).
Conclusion: We concluded that postpartum depression (PPD) in mothers has a negative effect on father–infant attachment. The primary responsibilities of midwives should include determining the factors affecting parent–infant attachment and providing training and consultancy to establish parent–infant communication. A secure father–infant attachment can be achieved by ensuring the participation of fathers during the pregnancy, delivery, and postpartum periods and careful evaluation of mothers in terms of PPD.
Key words: Postpartum depression, Attachment, Father–infant attachment, Midwifery

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Introduction

Postpartum Depression (PPD) is a common affective disorder that manifests with a decrease in interest and pleasure, loss of energy, changes in sleeping patterns, weight reduction, impaired thinking process and concentration, feelings of worthlessness, a sense of guilt, and suicidal thoughts (1-4). Its prevalence is reported to be 3.5%–63.3% worldwide and 3.5%–58% in Turkey (1,4-7). PPD can negatively affect the development of infants, reducing the quality of life of mothers and even leading to commit suicide and harm to their infants. In addition, it may also affect the attachment to the

infant that plays an important role in establishing a family order with mothers and infants (6).

Attachment is referred to as unique love relation that begins in the first days of life, develops over time between parents and infants, and has an impact on all relationships throughout life (8). PPD may negatively affect mother-infant attachment, compatibility with maternal roles, and mother-infant interaction (9-11). This mental issue affects not only mother-infant attachment, but also father–infant attachment (12).

PPD directly affects the mother infant and indirectly impacts the father and family; it is a condition that should be considered to enable early detection and the timely management using an appropriate approach (9). In this regard, midwives who are in direct interaction with the mother, father, infant, and family play critical roles. Midwives play a key role in monitoring mothers carefully in terms of PPD symptoms during pregnancy, delivery, and postpartum periods in order to ensure early diagnosis and intervention (13,14). The mothers should be interviewed in the postpartum period using the Edinburgh Postpartum Depression Scale (EPDS) that is deemed necessary by the Ministry of Health. In this way, the EPDS can help early detection of PPD in mothers, enabling timely intervention and prevention of problems associated with PPD (14,15). In addition to improving the mother's physical health, such intervention can also ensure the involvement of fathers in the prenatal care process to increase the positive communication between the mother and father and facilitate father–infant attachment. Midwives can help fathers build a secure attachment with their infants and strengthen it by providing training and social support to the fathers (16).

In this regard, we believe that the study will provide significant insights that would benefit the society by determining the extent of the effect of PPD on father–infant attachment, leading to the prevention of negative father–infant attachment via appropriate intervention and improved health protection. Midwives who are primarily responsible for maintaining the parent–infant relationship are aware of the factors affecting the parent–infant attachment that contribute to the health of individuals, families, and therefore the community. Few studies have investigated this issue (12,17) and the present study is a subjective study that is considered to provide significant contribution. The purpose of this study was to determine the effect of postpartum depression in mothers with 0-1 year old infants on father–infant attachment. The first hypothesis of our study was that PPD has an effect on father–infant attachment, and the second was that PPD has no effect on father–infant attachment.

Methods

Study type
Descriptive, cross-sectional study.

Study population and samples
The study population included mothers and fathers of 781 infants (0-1 year old) who resided in a district in the north of Turkey and were registered in one of 4 family health centers between January 01 and January 31, 2018.

For sample size calculation, when the prevalence of PPD in Turkey was assumed to be 14% (7,18-23) a power of 80%, a margin of error of 5% and an effect size of 0.07 were calculated for a population size of 781 samples in the G*Power (version 3.1.2) analysis. Based on the analysis, the sample size was determined to be 182 mothers and 182 fathers with 0-1 year old infants. The study was performed on 207 mothers and 207 fathers with 0-1 year old between February 01, 2018, and August 01, 2018.

Data Collection Tools
The data were collected using the Socio-Demographic Data Form, EPDS, and Father–Infant Attachment Scale (FIAS).

Socio-Demographic Data Form
The Socio-Demographic Data Form was created by the researchers following a literature review (16,24-26). This form consists of 14 questions regarding the baseline characteristics of mothers and fathers (age, marital status, employment status, income status etc.).

Edinburgh Postpartum Depression Scale
The EPDS is a self-assessment scale designed to determine the risk of depression, degree of depression, and change of violence in the postpartum period. The scale was adapted to Turkish by Engindeniz et al. (27) and includes 10 questions. Each question provides a 4-point likert-type measurement. The lowest score that can be obtained from the scale is 0, and the highest score is 30. The coefficient of consistence of EPDS (Cronbach's Alpha) is 0.79, and the cut-off score is 12/13). In the present study, the cut-off point of the scale was 12, and the Cronbach's Alpha value was 0.81.

Father–Infant Attachment Scale

The FIAS was designed by Condon et al. (2008) to evaluate the postpartum father–infant attachment and consists of 19 items. The scale was adapted to Turkish by Gulec (28). It has three sub-scales: patience and tolerance, pleasure in interaction, and love and pride. Each item is scored between 1 and 5, with higher scores indicating higher attachment (item 16 was removed from the scale following further analysis). The Cronbach's Alpha value of the FIAS was calculated to be 0.76. The Cronbach's Alpha value of the present study was highly reliable (0.75).

Statistical analysis

The data were analyzed using SPSS 25.0 package software. Continuous variables are expressed as mean, standard deviation, and median (minimum–maximum) values, and categorical variables are expressed as numbers and percentages. The normal distribution of the data was examined using Shapiro–Wilk and Kolmogorov–Smirnov tests. When parametric test assumptions were met, independent t-test and one-way analysis of variance were used for the comparison of the differences between independent groups. When the parametric test assumptions were not met, Mann–Whitney U test was used in comparison of independent group differences. Logistic Regression analysis was used to determine the risk factors affecting the dependent variable. In all analyzes, $p<0.05$ was considered statistically significant.

Ethics of the Study

The study was approved by the Gaziosmanpaşa University, Non-Interventional Ethics Committee (18-KAEK-053) and the institutions where the study was conducted. The purpose of the study was explained to the participants, and the participants were assured that their responses would be anonymous and would be used only in scientific research; they were also informed that they could withdraw at any point during the interview. Verbal and written consents were obtained from the participants. The study was performed as per the "Informed Consent, Confidentiality and Protection of Privacy and Respect for Autonomy" principles and the Helsinki Declaration. The required permissions were obtained from those who confirmed the validity and reliability of the Turkish version of the scale. The data were collected within 30 minutes via face-to-face interviews. The parents were interviewed in different environments to prevent influence from each other.

Results

The distribution of the socio-demographic characteristics of the parents who were involved in the study is shown in Table 1.

The postpartum depression risk levels in mothers based on the EPDS cut-off point were determined to be 18.3% (Table 2).

In the study, the mean "patience" sub-scale score was 32.8 ± 2.95, the mean "pleasure" sub-scale score was 27.86 ± 3.67, the mean "love" sub-scale score was 14.29 ± 1.2, and the mean total attachment score was 74.95 ± 6.21 (Table 3).

The comparison of the mean FIAS sub-scale and total attachment scores with the mean EPDS scores revealed no significant difference between them ($p > 0.05$). However, although not statistically significant, the total attachment scores in the spouses of mothers with EPDS scores ≥ 12 were lower than those in spouses of mothers with EPDS scores ≤ 11 (Table 4).

The examination of correlation between the EPDS scores and the sub-scale and total FIAS scores revealed a weak, significant ($p < 0.05$) and negative correlation ($r = -0.15$; $r = -0.181$) between the total FIAS scores and the patience and tolerance sub-scale scores upon the manifestation of PPD symptoms in mothers. In addition, there was a significant correlation between the total FIAS scores and FIAS sub-scale scores ($p < 0.05$). There was a strong positive correlation between the patience and tolerance sub-scales and pleasure in interaction sub-scales ($r = 0.814$; $r = 0.874$) and a moderate positive correlation with the love and pride sub-scales ($r = 0.555$) (Table 5). The correlations among the sub-scales were significant ($p < 0.05$). There was a moderate positive correlation between the patience and tolerance sub-scales and pleasure in interaction sub-scales ($r = 0.506$) and a weak positive correlation with the love and pride sub-scales ($r = 0.398$). There was a weak positive correlation between the pleasure in interaction sub-scales and love and pride sub-scales ($r = 0.35$) (Table5).

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Table 1. Distribution of the socio-demographic characteristics of parents

Characteristics		X̄ ± SD	Min–max	
Mean age of mothers (n = 207)		29.02 ± 4.87 (years)	19–41	
Mean age of fathers (n = 207)		32.87 ± 5.29 (years)	23–48	
			No (n)	**Percentage**
Marital Status	Married		206	99.5
	Divorced/widowed		1	0.5
Consanguineous marriage	Yes		14	6.8
	No		193	93.2
Marriage style	Companionate		170	82.1
	Prearranged		37	17.9
Age at the time of marriage	≤ 20 years		58	28.0
	20–30 years		141	68.1
	≥ 30 years		8	3.9
Duration of marriage	≤ 1 year		27	13.0
	2–5 years		85	41.1
	≥ 5 years		95	45.9
Educational level	Primary school		30	14.5
	Secondary school		57	27.5
	High School		62	30.0
	University		58	28.0
Employment status	Employed		44	21.3
	Unemployed		163	78.7
Family type	Nuclear family		162	78.3
	Extended family		45	21.7
Father's educational level	Primary school		33	15.9
	Secondary school		42	20.3
	High school		66	31.9
	University		66	31.9
Father's occupation	Unemployed		12	5.8
	Officer		43	20.8
	Worker		63	30.4
	Self-employment		89	43.0
Family income	Income less than expense		58	28.0
	Income equal to expense		119	57.5
	Income more than expense		30	14.5
Father's age at the time of marriage	≤ 20 years		15	7.2
	20–30 years		161	77.8
	≥ 30 years		31	15.0

X̄: Arithmetic mean; SD: Standard Deviation

Table 2. The postpartum depression risk levels in mothers based on the mean EPDS score and cut-off point (n = 207)

Mean EPDS Score	X̄ ± SD	Min–max
	7.19 ± 5.17	0–23
EPDS Cut-off Point	**No (n)**	**Percentage**
≥ 12	38	18.3
≤ 11	169	81.6
Total	207	100

X̄: Arithmetic mean; SD: Standard Deviation
EPDS: Edinburgh Postpartum Depression Scale

Table 3. Distribution of total FIAS and FIAS sub-scale scores (n = 207)

FIAS Sub-Scales	X̄ ± SD	Min–max
Patience and tolerance	32.8 ± 2.95	34–36
Pleasure in interaction	27.86 ± 3.67	15–35
Love and pride	14.29 ± 1.2	9–15
Total	74.95 ± 6.21	55–85

X̄: Arithmetic mean; SD: Standard Deviation
FIAS: Infant Attachment Scale

Table 4. Comparison of mothers' mean EPDS scores with mean FIAS sub-scale and total scores

FIAS Sub-Scales	EPDS Cut-off Point		Test and p value
	≤ 11	≥ 12	
	X̄ ± SD	X̄ ± SD	
Patience and tolerance	32.94 ± 2.96	32.18 ± 2.88	p = 0.082 z = −1.73
Pleasure in interaction	27.93 ± 3.68	27.53 ± 3.67	p = 0.631 z = −0.48
Love	14.38 ± 1.07	13.92 ± 1.63	p = 0.185 z = −1.32
Total	75.25 ± 6.03	73.63 ± 6.9	p = 0.177 z = −1.35

*$p < 0.05$ was considered statistically significant; X̄: Arithmetic mean; SD: Standard Deviation; z: Mann–Whitney U test
EPDS:Edinburgh Postpartum Depression Scale
FIAS: Infant Attachment Scale

Table 5. Correlation of mothers' EPDS scores with FIAS sub-scale and total FIAS scores

		Total EPDS	Total attachment	Patience and tolerance	Pleasure in interaction	Love and pride
Total EPDS	r	1	−0.15	−0.181	−0.181	−0.05
	p		0.031*	0.009*	0.091	0.471
Total attachment	r		1	0.814	0.874	0.555
	p			00001*	00001*	00001*
Patience and tolerance	r			1	0.506	0.398
	p				00001*	00001*
Pleasure in interaction	r				1	0.35
	p					00001*
Love and pride	r					1
	p					

*$p < 0.05$ - statistically significant correlation; Spearman Correlation Analysis; r: Correlation Coefficient (r value ranges: 0–0.199 very weak, 0.2–0.399 weak, 0.4–0.699 moderate, 0.7–0.899 strong, 0.9–1 very strong)
EPDS: Edinburgh Postpartum Depression Scale
FIAS: Infant Attachment Scale

Discussion

In the present study, the mean total EPDS score of mothers was 7.19 ± 5.17. Based on the cut-off point of the scale, it was determined that 18.3% of mothers had PPD risk (Table 2). Considering the maximum and minimum scores obtained in the scale (minimum value: 0 maximum value: 30) and the cut-off point of the scale, it can be suggested that mothers have a low risk of PPD. Previous studies that have used the same scale as that used in the present study have shown that the risk level of PPD in mothers was 9.58 ± 5.10 in the study by Aslan and Ege (29), 8.3 ± 4.6 in that by

Ngo et al. (30), and 7.26 ± 3.94 in the trial by Brown et al. (31). The findings of these studies are similar to our results. In other studies, conducted in the provinces in Turkey, PPD risk levels are at rates changed between 14% and 34.4%. (7,14,19,23,24,32-35). In a study on 2,259 mothers in 2017 in Brazil, the risk level of PPD was 12%; the risk level was 16% in Zimbabwe, 22% in Jordan and 34.7% in South Africa (7). Given the findings in studies conducted in Turkey and worldwide, it can be suggested that PPD is a very common condition. Further, the incidence rate may vary, depending on the diagnostic tools used, the cut-off point used for screening, the duration of the postpartum period, and the cultural and socio-demographic characteristics of the country and region (4,36).

In the study, the mean "patience" sub-scale score was 32.8 ± 2.95, the mean "pleasure" sub-scale score was 27.86 ± 3.67, the mean "love" sub-scale score was 14.29 ± 1.2, and the mean total attachment score was 74.95 ± 6.21 (Table 3). A literature review has revealed that in the study by Gulec (28) that examined the validity and reliability of the Turkish version of scale, the mean patience and tolerance sub-scale score was 36.05 ± 3.51, the mean pleasure in interaction score was 27.60 ± 4.11, the mean love and pride score was 19.22 ± 1.43; the mean total score was 82.88 ± 7.39. Condon (2008) who developed the original scale found that the mean total attachment score was 79.2 ± 9.0, mean patience and tolerance sub-scale score was 34.9 ± 3.8, the mean pleasure in interaction score was 26.2 ± 4.0, and the mean love and pride score was 19.3 ± 1.4. The present findings are similar to those reported by Condon and Gulec (28), and the FIAS scores were higher. In the study by Dinc (37) who used this scale in Turkey, the mean patience and tolerance sub-scale score was 32.86 ± 4.27, the mean pleasure in interaction score was 24.84 ± 5.31, the mean love and pride score was 18.03 ± 2.03, and the mean total score was 75.73 ± 10.64. The mean total FIAS score was 73 ± 9.1 in the study by Kilan (25) and 55.6 ± 10.2 in the study by Evcili et al. (38) It is considered that the differences in the scale scores in the studies may result from the timing of application of the scales, the regional and cultural characteristics, or the characteristics of fathers and infants.

The comparison of the mean total and sub-scale FIAS scores with the mean EPDS scores in the present study revealed no statistically difference between the scale scores ($p > 0.05$) (Table 4). However, although not statistically significant, the total attachment scores in spouses of mothers with EPDS scores ≥ 12 were lower than those in spouses of mothers with EPDS scores ≤ 11. This may be associated with the low mean depression risk levels in the mothers and mild depression symptoms. Previous studies have shown that maternal and paternal depression are interrelated and negatively affected by each other. It has been reported that fetal attachment and depression in mothers are the most significant factors for father–infant attachment (26,39).

Considering the correlation between postpartum depression and father–infant attachment, there was a significant correlation between the EPDS scores and the total and sub-scale FIAS scores ($p < 0.05$) (Table 5). There was a very weak negative correlation between the total EPDS score and total FIAS score ($r = 0.15$; $p = 0.003$). With an increase in the EPDS score increased, the mean FIAS scores decreased. These results confirm the assumption of the study that "PPD has an effect on father–infant attachment".

To our knowledge, no previous study has investigated the effect of postpartum depression on father–infant attachment. Therefore, the present results have been compared with studies examining the effect of postpartum depression on maternal attachment. In the study by Cankaya et al. (9), there was a moderately negative correlation between postpartum depression and maternal attachment, similar to our findings. Contrary to these studies, the study by Karabulut (40) showed a positive significant correlation between the first-month maternal attachment and the EPDS score.

Limitations
The results of the present study are applicable to only the study group and may not be generalized to the general population. The fact that the characteristics of the region where the study was conducted have caused a low risk level of depression may have influenced the study results. Another limitation may be the inability to contact both the parents simultaneously due to employment of fathers.

Conclusions
In conclusion, PPD has a negative impact on father–infant attachment. Care practices should not be limited to the physical health of the mother, but it should also extend to fathers. Therefore, it is recommended to carefully follow mothers for PPD symptoms, to interview mothers routinely using EPDS to ensure early diagnosis and intervention, ensure that fathers are involved in the care of infants through a midwife family-centered healthcare approach, to include fathers in the mother-baby-friendly hospital and health policies, and to conduct studies consisting of wider populations to determine

the effect of PPD in mothers on father–infant attachment.

Ethics Committee Approval: Appropriate permission for the study was obtained from the Committee of Ethics of Gazioamanpasa University (approval no: 20.02.2018; 2018/03-18-KAEK-053).
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RESEARCH ARTICLE

Urinary Incontinence in Women Living in Rural Areas and Reflections on Quality of Life

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Abstract
Objective: Urinary incontinence (UI) is a health problem affecting women's quality of life. Since it is not a life-threatening disease, women with urinary incontinence usually do not seek treatment in this regard. This causes them not to benefit from treatment opportunities that will improve their lives. The study aims to investigate the UI status in women living in rural areas and to determine its reflection on the quality of life.
Methods: A total of 589 patients were included in the study. The data was collected with a questionnaire including socio-demographic characteristics questions along with the Urogenital Distress Inventory (UDI-6) scale and the Incontinence Impact Questionnaire (IIQ-7).
Results: 157 (26.7%) patients who participated in our study suffered from UI. 70 (44.6%) of these patients suffered from stress incontinence (SUI), 40 (25.5%) were urge incontinence (UUI) and 47 (29.9%) were mixed incontinence (MUI). BMI, constipation, and menopause were found to be aggravating factors for incontinence (p<0,001). According to the UDI-6 scale; MUI significantly impacts a woman's life quality followed by urge or stress incontinence (p<0,001). Stress incontinence decreases life quality more than urge incontinence (p<0,001) based on the IIQ-7 scale.
Conclusion: Despite the high frequency of female urinary incontinence, many patients cannot easily express this distress. Family physicians to whom the patient applies most frequently should question their patients about UI and direct their patients to appropriate treatment.
Key words: Urinary incontinence, UDI-6, IIQ-7, Quality of life, Womens' health

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Introduction

Physicians with a high level of awareness may unveil several diseases that adversely affect the quality of life. One of these diseases is urinary incontinence and it can be diagnosed early by a family physician. Urinary incontinence (UI), according to the definition of the International Community of Incontinence, is defined as "involuntary urinary incontinence that can be shown objectively" (1). Although many prospective longitudinal studies have examined UI in women, either in the general population or focused on pregnancy, menopause, or

old age, it is a disease that affects female patients that can be seen at every age (2,3). In social studies, 20-30% of women are affected by UI, but it is estimated that only 7-12% of them perceive it as a health problem (3). The prevalence of UI according to some studies performed in our country, is in a various range; 21-37% (4,5). The reason for such difference in the prevalence of is explained as the diversity of the studied societies; differences in the definition of urinary incontinence and the number of clinical trials (6). Many factors have been described increasing the reasons and prevalence of urinary incontinence. Risk factors for UI; advanced age, hormonal disorders, obesity, birth trauma, genetic disorders, recurrent urinary tract infections, chronic constipation, smoking, gynecological surgery, diabetes, lung diseases, and neurological diseases (7,8). Although UI is not a life-threatening disease, individuals suffering from this disease have complaints about social and physical activities, hence the quality of their life decreases (9). Today, UI can be treated with various treatment options, but patients who cannot mention their ailments easily are deprived of these treatments. It is recommended that clinicians also question incontinence in their medical history from female patients so that patients can benefit from advanced treatments (10,11).

In this study, ıt was aimed to determine the prevalence of UI that restricts the lives of women registered in our family health center and to observe how UI affects their life quality. Providing appropriate treatment and counseling services for UI patients identified as a result of interviews with patients was another of our study goals.

Methods

The study was planned as a cross-sectional study in a family health center. The region where the family health center is located in a rural area. There are 756 women over the age of 18 registered in the family physician's health system. All-female patients who were subjected to care by family health centers over the age of 18 were informed about the purpose of this study. The volunteer women were interviewed face-to-face in the study. In order to gather information, we used a questionnaire that included 26 questions regarding the socio-demographic and obstetric history of the women. Also, it was determined whether it was difficult to visit a doctor because of urinary incontinence, and a few questions to evaluate the association among chronic diseases, constipation, smoking, and daily tea consumption and UI symptoms were also listed in the questionnaire.

All participants were asked if they had UI symptoms or not. A distinctive question was asked in terms of clinical typing of urinary incontinence, including conditions such as coughing and laughing that cause intra-abdominal pressure. In this regard, the stress suffering from this complaint was considered the user interface (SUI). If a patient wets before she can reach the toilet, it is considered as urge urinary incontinence (UUI) and in the presence of both complaints were evaluated as mixed urinary incontinence (MUI). Participants with UI symptoms were examined in terms of the effects of UI symptoms on quality of life. In order to determine the quality of life, Incontinence Effect Questionnaire (IIQ-7) and the Urogenital Discomfort Scale (UDI-6) were used among patients with UI symptoms. Both were developed to assess the effects of quality of life regarding urinary incontinence and validated in many languages (12, 13). The UDI-6 is composed of six items with three subscales. The subscales are; irritative, stress, and obstructive symptoms. IIQ-7 is composed of seven items with four subscales. These subscales include physical activity, travel, social, and emotional health. Each subscale is formed as a Likert scale and ranges from slight to moderate and great. The higher scores show the reduced quality of life and the severity of symptoms.

Statistical analysis

All analyses were carried out using SPSS v.22 software. Numerical variables are expressed as mean±SD and categorical variables as frequency and percentage. Numerical data was checked for normal distribution. The Student-t test and One-Way ANOVA followed by Tukey post hoc test, and were used for group comparisons. Pearson Chi-Square test was used for categorical variables, and Bonferroni adjusted method was used where column proportions are different. Pearson correlation analysis was performed to investigate the correlation between numerical data. The significance level was considered as $p < 0.05$.

Results

In total, 589 patients were included in the study. The mean age of the patients participating in the study was 47.47±14.09 years. Of these patients, 26.7% (n= 157) reported complaints of UI, while 73.3% (n=432) said they did not have UI symptoms. In total, 25.5% (n=40) patients were diagnosed with UUI. 44.6% (n=70) patients were diagnosed with SUI and 29.9% (n=47) patients were diagnosed with MUI. When it is examined from the point of view of applying and requesting for treatment, it has been detected that in

total, 43.3% (n=68) of patients referred to their physicians for UI symptoms and requested treatment.

Pearson correlation analyses showed a significant and positive correlation between body mass index and UI (r=0.255, p<0.001). Complaints of UI were significantly higher with the presence of incontinence in the family (p<0.001). UI was significantly more frequent in patients with constipation (p<0.001). The presence of recurrent urinary tract infections also makes UI significantly higher (p<0.001). A significant increase in UI was observed as the number of pregnancies increased (r=0.365, p<0.001). UI was significantly higher when the age of gestation was below 18 years (p<0.001). UI was more common among participants who had a history of vaginal delivery (p<0.005). The details of comparisons of participants with and without UI can be seen in Table 1.

According to the analysis of the subgroups; with increasing age, MUI is more common than the other subgroups. Compared with frequent urinary tract infections and the SUI/UUI/ MUI subgroup, MUI and SUI showed more association than UUI. (Table 2).

The participants with UI were evaluated in terms of quality of life. Comparisons of the participants with different types of UI are presented in Table 3. Mixed incontinence patients exhibited the least satisfaction in quality of life compared to both urge and stress incontinence in our study. According to UDI-6 total and subscale scores, patients with stress incontinence were in more discomfort than patients with urge incontinence. The same results were obtained with IIQ-7 total and subscales (Table 3).

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Table 1. Comparisons of participants with UI (+) and UI (-)

Characteristics		UI (+) (n=157)	UI (-) (n=432)	p value
Age (years)		56.61±11.69	44.14±13.40	*<0.001*
UI in the family n(%)	Yes	82(52.2)	46(10.6)	*<0.001*
	No	75(47.8)	386(89.4)	
Constipation n(%)	Yes	73(46.5)	136(31.5)	*<0.001*
	No	84(53.5)	296(68.5)	
Type of delivery n(%)	Vaginal delivery	142(92.2)	292(82.7)	*0.005*
	Caesarean section	12(7.8)	61(17.3)	
Menopause n(%)	Yes	119(75.8)	142(32.9)	*<0.001*
	No	38(24.2)	290(67.1)	
Urinary infection in a year n(%)	1 time	51(39.5)	137(52.1)	*<0.001*
	2 times	62(48.1)	119(45.2)	
	>3 times	16(12.4)	7(2.7)	
The first delivery age (years) n(%)	<18	83(53.9)	79(22.4)	*<0.001*
	18-34	70(45.5)	265(75.1)	
	>34	1(0.6)	9(2.5)	
BMI (kg/m²)		30.85±4.58	28.15±4.52	*<0.001*

Table 2. Comparisons of participants with SUI, UUI and MUI

		UUI (n=40)	SUI (n=70)	MUI (n=47)	p value
Age		51.20±10.85[a]	56.10±11.18[a]	61.96±11.03[b]	*<0.001*
BMI		30.51±3.93	30.80±4.68	31.21±5.01	0.773
Menopause, n(%)	Yes	25 (62.5)	55 (78.6)	39 (83.0)	0.065
	No	15 (37.5)	15 (21.4)	8 (17.0)	
Urinary infection, n(%)	Yes	19 (47.5)[a]	56 (80.0)[b]	41 (87.2)[b]	*<0.001*
	No	21 (52.5)	14 (20.0)	6 (12.8)	

Each superscript letter denotes difference between groups significantly from each other at the 0.05 level. (b>a).

Table 3. Quality rates of SUI, UUI and MUI

	UUI (n=40)	SUI (n=70)	MUI (n=47)	p value
UDI-6 total	10.85±2.66[a]	11.49±2.18[a]	13.43±1.90[b]	*<0.001*
Irritative	3.73±1.26[a]	4.59±1.06[b]	4.66±0.76[b]	*<0.001*
Stress	4.05±0.99[b]	3.43±1.07[a]	4.34±1.07[b]	*<0.001*
Obstructive	3.08±1.23[a]	3.49±1.06[a]	4.43±1.04[b]	*<0.001*
IIQ-7 total	11.45±3.92[a]	13.26±2.60[b]	16.06±2.44[c]	*<0.001*
Physical activity	3.40±1.37[a]	3.81±0.84[a]	4.66±1.01[b]	*<0.001*
Travel	2.63±0.63[a]	2.89±0.36[b]	2.96±0.20[b]	*<0.001*
Social	2.60±1.15[a]	3.19±0.94[b]	4.04±1.06[c]	*<0.001*
Emotional	2.80±1.24[a]	3.36±1.06[b]	4.36±0.92[c]	*<0.001*

Each superscript letter denotes difference between groups significantly from each other at the 0.05 level. (c>b>a).

Discussion

The results of the study showed that UI negatively affects the quality of life of women, although it is quite common. It also made us realize that they did not consult a doctor for this problem, which has an effective treatment. In the study, the prevalence of UI, risk factors and quality of life were evaluated according to UI types.

According to the study results, UI was detected in one third of the women in the family health center. This rate is quite variable in studies. In a previous cross-sectional study, it was shown lower prevalence among reproductive age women who had been admitted to an outpatient clinic with UI (14). Relatively high prevalence of UI was documented as 38.4% in a population-based study in Iran (15). The frequency of UI can vary greatly depending on where the study was performed, the region studied, and the participants. In a cross-sectional study performed by Danforth et al, a high prevalence of UI with increasing age was found (16). In a study performed in Norway, the prevalence among the 20-24 and 25-29 year old age groups was 10% and 14%, respectively (17). In similar to the literature, increased age was positively correlated with the presence of UI, in the present study.

In the study, less than half of patients referred to the doctor for this discomfort and requested treatment. Other patients with incontinence either do not mention these complaints to the doctor because they are embarrassed, or they consider it is normal at that age. In a study that focuses on how women feel in reality with the focus group study, it was observed that women developed strategies to cope on their own with reactions from their spouses and the environment (18). Shyness and cultural retreat play an important role in this and also with the belief that UI is a normal situation caused by increasing age. In a large multi-centered study, only one third of women had consulted a doctor about their UI symptoms (19). Ueda et al. states that only 3% of patients had ever consulted doctors because of their urinary complaints while one fourth determined their condition as a disease (20).

In our study, it was found a positive correlation between UI and weight, a young age with the first pregnancy, constipation, type of delivery, UTI's, presence of family incontinence history, and menopause. Studies performed in such centers reported that obesity (21), positive family history, and vaginal delivery (22), UTI's (23), constipation and menopause (24) were associated with UI as risk factors.

It was determined that SUI was more common than other types of UI in the study. In such studies, SUI was also determined as the most common type of UI (25, 26, 27). There are also publications in the literature observing MUI and UUI incontinence is seen more (28, 29). The reason for this difference may be the age ranges in the studies.

In the present study, UDI-6 and IIQ-7 scores were higher in the SUI group when compared to the UUI group. Both the UDI-6 and IIQ-7 scores were significantly higher in the MUI group than both SUI and UUI. Similarly, Dooley et al found that women with MUI reported greater incontinence than women with either pure stress or UI (30). Coyne et al reported no significant difference according to quality of life measures, between the three incontinence groups UUI, SUI, and MUI, but also added that because of the lower rates of incontinence episodes, patients with SUI can adapt their lifestyles by avoiding heavy lifting and exercising, and thus prevent situations that lead to involuntary loss of urine (28). Lasserre et al (14) stated that longer duration of symptoms cause higher frequency of comorbid urinary symptoms among women with MUI.

Limitations

The present study has a limitation that determining the type of UI in patients was based on their answers to questions about the symptoms of UI. Despite the

questionnaire used for this study was clinically valid and consistent with the definitions declared in the International Continence Society, no urodynamic test was carried out on the participants to verify the type of UI. Another limitation of the study is that the results cannot be generalized.

Conclusions

In conclusion, the incidence of urinary incontinence in our study was consistent with the ranges reported in the literature. In our study, we have observed that SUI makes life more difficult than UUI, besides; MUI have worst life impact on the quality of life than the other two types. It is thought that physicians should question this issue more carefully when taking anamnesis due to the low rate of the patients' help-seeking behaviors. First of all family physicians (FP) should encourage the patients' to share all their complaints and discomforts easily. The incidence of UI may be greater in the outpatient clinics than previously thought and FP's should be aware of this uncomfortable condition in their patients.

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Childhood Absence Epilepsy in the Middle Black Sea Region

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Abstract
Objective: The aim of this study was to evaluate chilhood absence epilepsy in the Middle Black Sea Region.
Methods: 14 pediatric patients who treated absence epilepsy between May 2018 and May 2020, and had adequate follow-up were included in the study. Medical record datas were reviewed age, gender, etiology, features of family, treatment, and results.
Results: 10 (71%) of the patients were female and 4 (29%) were male. Their average age was 9 years (6-15). Valproate was started in all patients at the time of diagnosis. In the controls 15 days later, no seizure was detected by the family of 5 patients. 5 patients stated that their seizures decreased but continued. In 4 patients, the family did not notice a decrease in seizure frequency. Ethosuximide was added to 9 patients who said that their seizures were still continuing. In the controls 15 days later, 6 patients were found to be cured. However, it was stated that 3 patients had intermittent seizures although they decreased. Lamutrigine was added as the third drug after checking the valproate drug level to these 3 patients, whose treatment was still unsuccessful. 3 patients still have electroencephalography disorder and seizures recognized by the family. With our treatment management, 11 of 14 patients were found to be seizure free.
Conclusion: We achieved high success with valproate and ethosuximide in the treatment management of pediatric absence epilepsy.
Key words: Absence; epilepsy; childhood; treatment

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Introduction

Epilepsy is the most common neurological disease of childhood. Absence epilepsies, on the other hand, constitute 10-17% of childhood epilepsies (1). It is frequently seen between the ages of 4 and 10. Its etiology is unknown, and the genetic basis is thought to be more common than other epilepsies (2). It usually presents as sudden hesitation and freezing. It is defined as loss of consciousness with sudden onset and sudden end (3). The diagnosis is made by clinical and electroencephalography (EEG).

In the treatment, there is a high rate of response to medical treatment. Three drugs come to the fore in the treatment of this disease. These are ethosuximide, valproate and lamotrigine (4). Ethosuximide is used

in the first stage, valproate and lamuthrigine are used in the second stage (1,4). But we can not get ethosuximide easily in Turkey. So, we have to use the others.

In this article, we aimed to evaluate 14 patients who presented to our hospital with absence epilepsy. In addition, we wanted to present our treatment method in terms of its effectiveness.

Methods

14 patients who applied to Ordu University Trainind and Research Hospital with absence epilepsy between May 2018 and May 2020 were retrospectively analyzed. Ethics committee approval at Ordu University (ODU KAEK 2020/19/181) was obtained for the study, and the medical records of the cases were examined. Informed consent was waived. All patients were questioned about own/family history, status, additional disease, and medications were evaluated. Since we could not reach ethosuximide, which is the first choice in absence epilepsy at the time of diagnosis, valproate, which is the second choice, was started in all patients. Overseas drug request was made for ethosuximide. Ethosuximide was added to the treatment after 15 days in patients who could not be controlled with valproate. Lamutrigine was added as the third drug to the patients who could not be controlled with the combination of valproate and ethosuximide. The patients were followed by the same pediatric neurologist. Patients who were re-evaluated clinically after one year were included in the study. Patients with insufficient follow-up period were exclusioned in the study

Statistical analysis

IBM SPSS (Statistical Package for the Social Sciences) Statistics for Windows, version 21.0, was used for analyzing of datas. While evaluating the study dates; caterogical variables were expressed as n (%), normally distributed continuous variables as mean±standard deviation, and non-normally distributed continuous variables, as median and minimum-maximum

Results

10 (71%) of 14 cases were female and 4 (29%) were male. Average age was 9 (6-15). It was learned from the families that patients have between 3 to 5 seizure in a day. Since we could not reach ethosuximide, which is the first choice in absence epilepsy, at the time of diagnosis, valproate, the second choice, was started in all patients. A foreign request was made for ethosuximide. In the controls 15

days later, no seizure was detected by the family of 5 patients. 5 patients stated that their seizures decreased but continued. In 4 patients, the family did not notice a decrease in seizure frequency. Ethosuximide was added to the treatment of 9 patients who said that their seizures continued. At the control 15 days later, 3 patients stated that they had intermittent seizures but that they had decreased. Lamigdal was added to the treatment of these 3 patients, whose treatment management was still unsuccessful, after checking the valproate drug level. 3 patients still have EEG disorder and seizures recognized by the family, EEG findings showed 3-hertz spike wave activities lasting 8-10 seconds. In our treatment management, 11 out of 14 patients (78%) were found to be seizure free. Patients who were re-evaluated clinically after one year were included in the study. No other accompanying seizure type was observed during the follow-up. Tandem MS and blood amino acids were sent to all patients for additional metabolic disease and no pathology was detected. Since the patients recovered completely during our follow-up period, there was no patient we terminated the drug treatment.

Discussion

Epilepsy is one of the most common neurological disorders of childhood. Epilepsy disorders occur at a rate of approximately 40-50/100,000 per year. The risk of seizure is highest in the first year of life. Approximately 20-25% of all epilepsies are resistant to drug therapy. Childhood absence epilepsy is a well-known type of epilepsy that is common in childhood and covers 10-17% of childhood epilepsies (1).

Childhood absence epilepsy appears as a form of idiopathic generalized epilepsies (2). It occurs in developing children between the ages of 4-10. It peaks between the ages of 7-8 (4). The rate of occurrence in girls is higher than in boys. Girls (71%) made up the majority of the cases in our study, too.

Genetic basis is thought to be more common than other epilepsies (2). It usually presents as sudden hesitation and freezing. Eye blinking or motor automatisms may accompany this condition (4). Typical absence epilepsies happen as often as 10-20 times a day, lasting seconds. It is defined as loss of consciousness with sudden onset and sudden end (5). While myoclonias are observed on one side of the eyelids of the face, myoclonus is rarely observed in the limbs. Usually lasts 9-10 seconds, hyperventilation and photic stimulation are sensitive. In some patients, seizures can be triggered by these warnings (6).

Absence epilepsies are divided into 2 main groups. These are childhood absence epilepsy, which starts around the age of 6, and juvenile absence epilepsy that begins at the age of 12 (7). In childhood absence epilepsy, upward sliding of the eyes may generally accompany (5). In juvenile absence epilepsies, loss of consciousness is less than childhood absence epilepsy and myoclonias may accompany with a higher rate than childhood absence epilepsy (8). In our age group, there were cases from the youngest to the age of 6 years and the oldest to 15 years old, and we had cases that we considered as both childhood and juvenile absence epilepsy.

The clinic is often noticed by a teacher or an attentive family member. It is typical to have a sudden pause during normal work. It is short term and lasts within seconds. The diagnosis can be made by a good history, hyperventilation test or typical EEG findings (9). Age group should be considered as diagnosis. For example, glut-1 deficiency should be excluded in a patient with absence epilepsy that started before the age of 4. Because glut-1 deficiency can also come with these findings and its treatment is different (10).

The centrotemporal spike wavy epilepsy of childhood (BECTS) covers 8-20% of all childhood epilepsies and can be seen with a high rate of childhood absence epilepsy. There are many studies showing their association (3). The mechanism of these two types of epilepsy is thought to be the same (3). At the same time, it has been shown that absence epilepsies may be associated with panayaotoplus, idiopathic and gestaut type occipital epilepsy, myoclonic epilepsy of infancy, juvenile myoclonic epilepsy, lgs, West syndrome (5). In our 1-year follow-up, we did not detect any other seizure type in any of our patients.

Most absence epilepsies respond to medication. Three drugs come to the fore in the treatment of this disease. These are ethosuximide, valproate and lamutrigine. Ethosuximide is used in the first stage, valproate and lamuthrigine are used in the second stage. Etosuximide has been used clinically since 1958. However, its effectiveness has been demonstrated only in absence epilepsy. Genaralized tonic is not effective in clonic or focal motor seizures (4). It is rapidly absorbed from the gastrointestinal tract. Its half-life is approximately 30-40 hours. It reaches its peak value 4 hours after ingestion and provides stable plasma concentration within 7-10 days (11). Ethosuximide can cause nausea, sedation, diarrhea, ataxia, and extrapyramidal symptoms. Rarely, it has psychological effects such as psychosis and depression. Valproate, on the other hand, is preferred in cases where absence epilepsy is accompanied by generalized tonic-clonic seizures (4). Valproate increases the amount of gaba in the brain. Closes the Na-gated voltage channels. However, it is still unclear how it affects absence epilepsy. It has been observed that ethosuximide and valproate, which are used as monotherapy in the treatment of absence epilepsy, are superior to lamutrigen. Since ethoxuximide preserves attention better than valproate, it would be more appropriate to choose this treatment at the first stage (12).

Treatment success depends on the type of absence epilepsy of the patient and the patient. Remissions generally occur between the ages of 10-14 and sometimes they can be seen at earlier ages (4,13,14).

Seizure free is achieved with drugs in 70% of absence epilepsies. In accordance with the literature, we achieved seizure free in 78% of 14 of our patients. It was observed that there was no motor automatism, clinics with pause/gaze and eye involvement were more difficult to control (15). If the EEGs are normal and there is no seizure within 1-2 years after the start of treatment, the drug is tapered and discontinued. In our 1-year follow-up period, the medical treatment of all our patients with absence epilepsy continues. Even if absence epilepsy is diagnosed and treated in a short time, its social and behavioral effects have been mentioned in adulthood (12).

There are also drugs that can aggravate the seizure. Because tiagabine, carbamezapine, oxcarbamezapine, vigabatrin and possibly phenytoin increases absence seizures, it should be avoided from these drugs

Conclusions

As a result, absence epilepsy is common in the society, especially in the childhood age group. Because it takes a short time, its diagnosis can be delayed. Early recognition and treatment of absence epilepsy cases that respond to medical treatment is very important in children...

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Definition of the Total Antioxidant Capacity and Vitamin D Levels in Professional Athletes Who Play Football in Giresunspor

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Abstract

Objective: A sufficient amount of vitamin D levels; while protein synthesis, muscle strength, jumping height, speed, exercise capacity, and physical performance increase; stress fractures cause a decrease in the rates of injury, fall, muscle relaxation, muscle pain, and weakness. Serum 25-hydroxy vitamin D (25(OH)D) levels are very important for maintaining and improving optimal performance in football players. The formation of free radicals and oxidative stress during exercise is known to affect optimal performance and recovery period after exercise. The aim of the study was to determine serum 25(OH)D and total antioxidant capacity of professional football players.

Methods: The study group consists of 56 professional football players (26 players from the first team, 30 players from the academy team) playing in Giresunspor Football Club. The control group consisted of 30 volunteer healthy male subjects. The SPSS 21 package program was used to calculate and interpret the survey data applied face to face to the study group. In addition, the body composition of the players was determined by the InBody 230 device which works with the principle of bioelectric impedance analysis (BIA). Serum 25(OH)D levels of the football players were compared with reference values (≥30 ng / mL). Serum 25(OH)D levels were determined by immunoassay method on the Roche Cobas e411 branded test analyzer. Serum total antioxidant capacity was compared with 30 healthy volunteers in the control group. Total antioxidant capacity measurements were studied with the ready-to-use kit. The method previously described for the kit has been applied to Architect c8000 clinical chemistry autoanalyzer.

Results: As a result of the study, mean serum 25(OH)D levels of the players were determined as 31.68 ng / mL. The mean serum antioxidant capacity of the participants was found to be 1.97 mmol Trolox Equiv/L. The mean serum antioxidant capacity of the control group was 1.94 mmol Trolox Equiv/L.

Conclusion: Mean serum 25(OH)D levels of the players were within the reference range (≥30 ng/mL). There is an increase in metabolic rate during training, which leads to a rapid release of free radicals. Despite this thought, there was no significant difference in serum total antioxidant capacity between the study and control groups.

Key words: Football players, antioxidants, vitamin D

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Introduction

Nutrition, health protection, growth, the use of nutrients for the continuity of life are among the priorities of human needs (1).

When nutritioning of athletes is mentioned, firstly athletes who train regularly are considered. Since these individuals use their physical powers at maximum level, they constitute a field of study for researchers. In most sports, there is an important relationship between nutrition and performance. Nutrition is extremely important for maximal performance. However, the diet varies greatly according to the athlete and the sports branch. Many genetic and environmental factors affect the athlete's performance. However, it is very difficult for the athlete to reach maximal potential without the necessary nutrition; performance cannot be elevated, training cannot be done adequately, the athlete becomes more susceptible to infection and disability (2).

Developments in industry and technology have resulted in people spending a significant portion of their time in buildings, cars, and sun-protected spaces. Vitamin D deficiency is now a worldwide problem and is referred to as a pandemic (3).

The effect of total antioxidant capacity on the healthy and long life of people has started to be examined in recent studies. Radicals are also products produced as a result of metabolism, including secretions by the cell-based defense system such as medicines and chemicals taken. The best-known feature of these products is their extremely reactive properties. They can react with any substance (especially in living tissue) (4).

Free radicals damage the cell membrane, proteins, lipids, DNA and nucleic acids in the cell structure; as a result, it causes many diseases such as cancer, diabetes, coronary diseases, liver damage, and cataracts. The organism has antioxidant defense mechanisms against free radical damage caused by endogenous or exogenous sources. These mechanisms inhibit the reaction caused by free radicals (4).

The aim of this study is to determine the serum 25(OH)D levels of the football players living here due to lack of sun's rays the climatic conditions of Giresun, a province located in the Black Sea Region in Turkey. Also, based on the idea that regular training of football players can produce more oxidants than normal healthy individuals, it is important to determine their total antioxidant capacity in their biological systems. Thus, with the data obtained, football players and normal healthy individuals were compared.

Vitamin D

95% of the vitamin D requirement is met by the effect of ultraviolet rays on the skin. The form of Vitamin D synthesized in the skin is cholecalciferol (Vitamin D3) and the diet is taken from ergocalciferol (Vitamin D2).

Vitamin D is a very important molecule, also called hormone, which regulates many mechanisms in the organism. Fat-soluble sterol structure that acts directly or indirectly in many mechanisms supporting bone and muscle development in the body (5). Vitamin D intake is limited. Mostly found in oily fish such as salmon, mackerel, sardine and egg yolk (6).

Serum 25 (OH) D level should be performed to determine whether the vitamin D level is normal, low or high in individuals.

Serum 25(OH)D Levels (7);

$\leq$10 ng/mL; significant deficiency,

10-20 ng/mL; lack,

20-30 ng/mL; moderate deficiency or inadequacy,

$\geq$30 ng/mL; enough,

40-50 ng/mL; ideal,

> 150 ng/mL; toxic.

Antioxidants

Antioxidants are known as molecules that directly affect oxidant molecules that exceed a certain level and neutralize them. The organism protects itself against oxidative damage by enzymatic (superoxide dismutase (SOD), catalase and glutathione peroxidase (GSH-Px), etc.) and non-enzymatic (vitamin C, vitamin E, flavonoids and coenzyme Q10, etc.) antioxidant systems (8).

Many factors such as exercise and aging affect the oxidative stress and antioxidant defense system (9-11).

Methods

The study group consists of 56 professional football players (26 players from the first team, 30 players from the academy team) playing in Giresunspor Football Club. A survey including general characteristics (age, gender, educational status, illness, etc.), cigarette/alcohol use and nutritional supplement use was applied to the participants. The control group consisted of 30 male volunteers who were matched with the study group in terms of age and gender and without any diagnosis of chronic disease (diabetes, hypertension, ulcerative colitis, etc.). Samples of this study were collected between August 2017 and November 2017.

Blood samples were collected after 12-hour fasting to determine the serum 25-hydroxy vitamin D (25(OH)D) level of the players and the serum total

antioxidant capacity analysis of the players and the control group. Serum 25(OH)D levels were not measured in the control group, serum 25(OH)D levels of the players were compared with reference values (≥30 ng/mL) and total antioxidant capacity was compared with healthy individuals in the control group. In addition, some anthropometric measurements were taken from football players. Body composition was determined by the InBody 230 device, which operates on the BIA principle.

All participants informed and signed a voluntary consent form.

For the sample size, according to the mean and standard deviation obtained by taking the average values of the 3 studies taken as basis, it was determined that 56 individuals were sufficient according to the 85% test power and 5% error value.

This study was approved by Ordu University Ethics Committee on 05.04.2018 in line with the decision numbered 2018-63.

Biochemical Analysis

Serum 25(OH)D levels were determined by immunoassay method on the Roche Cobas e411 branded test analyzer. The principle of this test is the competition principle.

Total antioxidant capacity (TAS) was evaluated on the basis of the conversion of the antioxidants in the sample to the colorless reduced ABTS form of the radical blue-green 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) cation (ABTS * +). The sample TAS level is related to the absorbance change at 660 nm. For calibration, a vitamin E analogue (±) -6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid (Trolox Equivalent) was used. The results are expressed in mmol Trolox Equiv./L.

Statistical Analysis

SPSS 21 package program was used for data analysis. Descriptive statistics such as statistics, rate, mean and standard deviation of football players were made. Nonparametric tests were used to compare the groups of quantitative data due to a lack of normality assumption. Mann-Whitney U tests were used to compare two groups.

Results

The data in this study were obtained from professional football players at Giresunspor Football Club. Information gathered as a result of the survey of players. Serum 25(OH)D level was compared with reference values (≥30 ng/mL). In addition, serum total antioxidant capacity; the total antioxidant

capacity in the serum of 30 healthy, non-football players, male subjects was compared.

Table.1. Average of the players participating in the study

Variables	Mean± SD	
Age (year)	22,96±5,26	
BMI (kg/m^2)	21,40±0,33	
Fat Percent (%)	9,06±2,59	
Serum 25-Hydroxy Vitamin D Levels (ng/mL)	31,68±12,69	
Variables	**(%)**	**N**
Smoking	5,4	3
Alcohol Consumption	8,9	5
Nutritional Supplementation	42,9	24
Whey Protein	21,4	12
BCAA (Branched Chain Amino Acids)	23,2	13
L-Carnitine	3,6	2
CLA(Conjugated Linoleic Acids)	3,6	2
Creatine	5,4	3
Vitamin B	0	0
Vitamin D	5,4	3
Multivitamin Usage	25	14
Non-Routine Training	48,2	27
Fitness	33,9	19
Abdominal Training	19,6	11
Weight Training	1,8	1
Strength Training	3,6	2
Endurance Training	5,4	3

It was determined that approximately 54% of the players in the academy teams (90 minutes of training) and 46% of them in the first team (120 minutes of training) (Figure.1).
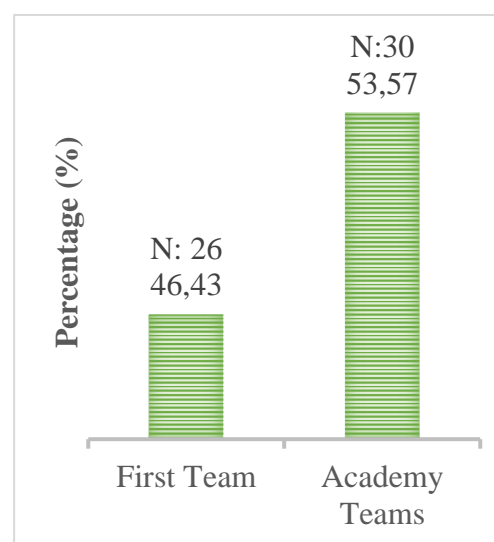
Figure.1. Distribution of players participating in the study according to the type of team

Approximately 52% of serum 25(OH)D levels of the players were within the reference range (≥30 ng/mL). Serum 25(OH)D levels were found to be below the reference range in 48.21% (Figure 2).
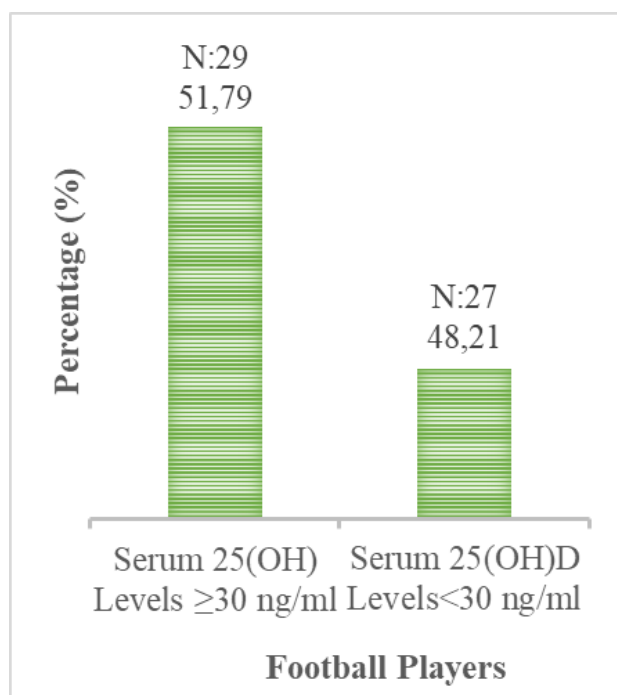
Figure.2. Distribution of participating players according to serum 25(OH)D levels.

According to the results, it was observed that there was a difference in serum 25(OH)D levels measured according to the type of team in which the players were assigned (p = 0.042). While the median value of serum 25(OH)D was 29.4 ng/mL in academy teams; serum 25(OH)D median value of the players in the first team was 33.56 ng / mL. Accordingly, players in the first team had statistically significantly higher serum 25(OH)D values (Table 2).

Table.2. Comparison of serum 25 (OH) D levels according to the type of team in which the players participated in the study

Team Type	N	Mean (min-max)	U	p
Academy Teams	30	29,40 (9-90)	266,50	0,042
First Team	26	33,56 (18,26-60,01)		

*Mann-Whitney U test was used.

Table.3. Comparison of serum total antioxidant capacity according to the type of team in which the players participated in the study

Team Type	N	Mean (min-max)	U	p
Academy Teams	30	2,01 (1,75-2,56)	266	0,041
First Team	26	1,90 (1,70-2,21)		

*Mann-Whitney U test was used.

According to the results, it was found that there was a statistically significant difference in the total antioxidant capacity of the players measured according to the type of team they were assigned (p = 0.041). The median value of the total antioxidant capacity of the players in the academy teams was 2.01 mmol Trolox Equiv/L; serum total antioxidant capacity of the players in the first team median value of 1.90 mmol Trolox Equiv/L was determined. Players in the first team had statistically significantly lower serum total antioxidant capacity values (Table 3).

According to the results, it was found that there was a difference between the nutritional status of the players and the serum 25(OH)D levels measured (p = 0.001). The median value of serum 25(OH)D was 35.82 ng/mL in nutritional supplements; the median value of serum 25(OH)D was 26.14 ng/mL in football players without nutritional supplementation. Players using nutritional supplements had statistically significantly higher serum 25(OH)D levels (Table 4).

According to the results, there was no difference between the nutritional status of the players and the total antioxidant capacity (p = 0,101) (Table 5).

The total antioxidant capacity of the players in the study was 1.97 mmol Trolox Equiv/L and 1.94 mmol Trolox Equiv/L in the control group. According to the results, there was no difference in serum total antioxidant capacity between football players and control group (p = 0.657) (Table 6).**.**

Table.4. Relationship between nutritional supplementation and serum 25(OH)D levels of the participating players

Nutritional Supplementation	N	Mean (min-max)	U	P
Yes	24	35,82 (23,45-60,01)	187	0,001
No	32	26,135 (9-90)		

*Mann-Whitney U test was used.

Table.5. Relationship between nutritional supplementation and serum total antioxidant capacity

Nutritional Supplementation	N	Mean (min-max)	U	P
Yes	24	1,945 (1,70-2,21)	286	0,101
No	32	2,025 (1,74-2,56)		

*Mann-Whitney U test was used.

Table.6. Relationship between serum total antioxidant capacity of the football players and control group

Football Player	N	Mean (min-max)	U	P
Yes	56	1,97 (1,70-2,56)	791	0,657
No	30	1,94 (1,62-2,31)		

*Mann-Whitney U test was used.

Discussion

In this study, serum total antioxidant capacity and serum 25(OH)D levels in professional athletes who play in Giresunspor Football Club were determined. Approximately 54% of the players participating in the study were from the academy teams (90 minutes training) and 46% were from the first team (120 minutes training). According to the data obtained from the survey; the average age of the players participating in the study is 22.9. In addition, mean BMI (body mass index) and fat percentage respectively; 21.40 kg/m2 and 9.06%.

The rate of using the nutritional support of the players participating in the study is 42.9%. The most preferred nutritional supplement is multivitamin with 25%. Nutritional supplements are products that athletes use to improve exercise performance. The use of such nutritional supplements, which are not considered doping, is quite common to improve exercise performance as well as ranking competition efficiency. The majority of the players participating in the study prefer to use vitamins in the form of multivitamins rather than using vitamins separately to accelerate recovery after training. Due to free radicals released as a result of excessive exercise, they meet the need for antioxidant vitamins and vitamin B that play a role in energy metabolism. It is also known that such vitamins increase endurance in athletes.

In this study, serum 25(OH)D levels were found to be higher in first team compared to the academy teams. This result can be explained by the fact that the training time is longer and that they benefit more from the sun's rays. Maroon et al. in their study, the average value of serum 25(OH)D levels in football players in the United States National League was found to be 27.4 ng/mL. The same study showed that serum 25(OH)D levels were lower in black football players than in white football players (12). Krzywanski et al. in their study, the average value of vitamin D levels of the indoor athletes in the Polish athletes found to be 27 ng/mL (13). A similar result was found by Bauer et al. also shown in their study on athletes playing handball in Germany (14). Accordingly, lower serum 25(OH)D levels are observed in indoor athletes.

The relationship between nutritional supplementation and serum 25(OH)D levels of the participating players was examined. 25(OH)D levels were found to be higher in football players with nutritional supplements. This result was associated with the content of nutritional support used by football players. In addition, it was determined that the use of nutritional supplements was more common in the first team and this result positively affected serum vitamin D levels. The increase in vitamin D levels has positive effects on the musculoskeletal system. Adequate levels of vitamin D have a positive effect on protein synthesis, muscle strength, jumping height/speed, exercise capacity and physical performance in athletes. At the same time, stress fracture rates decreased in athletes with sufficient serum 25(OH)D levels (15,16,17,18).

Sufficient serum 25(OH)D levels; reduces injury, falls, muscle relaxation, muscle pain, and weakness. Vitamin D is effective to maintain and increase optimal performance in athletes (19). Although studies investigating the effects of vitamin D on performance are limited, vitamin D is great importance for preventing muscle injuries and preventing stress fractures.

Serum total antioxidant capacity were found to be higher in academy teams compared to the first team. In general, during training, the amount of erythrocytes circulating, circulation rate, arteriovenous oxygen difference in relation to the severity of muscle activity; that is, an increase in the amount of oxygen released in the active muscle and metabolic rate (20). This leads to a faster release of free radicals. Based on this information, the free radical formation is higher since the first team is training longer (120 minutes training); therefore, the total antioxidant capacity of serum is lower than that of the academy teams players (90 minutes training).

The relationship between nutritional supplementation and serum total antioxidant capacity of the players in the study was examined. There was no relationship between nutritional supplementation and serum total antioxidant capacity.

The serum total antioxidant capacity was not different between the players and the control group. In contrast to this study, Brites et al. in a study on football players, serum total antioxidant capacity of football players was found to be 25% more than the control group (21).

Limitations

Limitations of the study can be listed as: serum vitamin D levels of professional football players (first team and academy teams) playing in Giresunspor football club were compared with reference value. Serum vitamin D measurement and survey were not applied to the control group.

Conclusions

This study is the first study conducted on football players determination of the serum total antioxidant capacity and serum vitamin D levels in Turkey.

Acknowledgment

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RESEARCH ARTICLE

The Effect of COVID-19 Pandemic on The Anxiety Levels of Radiology Experts and Clinical Functioning

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Abstract
Objective: The severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is a novel human corona virus rapidly spread all over the world and caused Corona Virus Disease-2019 (COVID-19) pandemic. Radiology clinics were reorganised according to the changes in health system in order to combat with this epidemic. We aimed to detect the changes in the functioning of radiology clinics and to state anxiety levels and relevant factors that induced anxiety in radiologists.
Methods: The research is a descriptive study, population constitudes, radiology residents, specialists and scholars actively working in Turkey during COVID-19 pandemic. The data of the study were collected digitally, through the clinical activity scale and Back anxiety scale questionnaires created over the internet. The data collection period started on 18.04.2020 and ended on 8.6.2020.
Results: Eightysix radiologists completed the survey. It was understood that the radiologists working during the pandemic had a high level of personal anxiety and worked under stress (3,74). A weak linear relationship was found between the changes in the functioning of radiology clinics and the personal concerns of radiology physicians at the p=0.05 error level (0.224). They stated that unnecessary thorax computed tomography (CT) demands increased (4,51) and they made the most thorax CT evaluation in the daily routine (4,42).
Conclusion: In our study, it was shown that there were significant changes in the functioning of radiology clinics especially related with increased thorax CT scans at the beginning of the COVID-19 pandemic and that the anxiety levels of radiologists increased due to the pandemic.
Key words: COVID-19, Radiologist, Anxiety

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Introduction

The severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is a new member of corona virus family, that emerged in Wuhan, China and led to an outbreak of viral pneumonia in December 2019 (1,2). This novel human corona virus rapidly spread all over the world and caused Corona Virus Disease-2019 (COVID-19) pandemic. The World Health Organization declared COVID-19 as a global health emergency on March 11, 2020 (3). On the same day, the first COVID-19 case is officially reported in Turkey. Although the public authorities took urgent actions such as curfews over 65 and under 18 years, travel restrictions, closure of schools, COVID-19 has spread rapidly in Turkey (4). COVID-19 mainly

transmitted through air droplets, aerosols and direct contact. The asymptomatic carriers have been reported as the main cause of rapid spread (5-7). By October 2020, 12,194,778 tests were performed, a total of 343,955 cases were detected and the number of deaths has been recorded so far is 9,153 in Turkey (8).

The health system in Turkey was restructured to combat the epidemic due to the rapid spread of the COVID-19 epidemic all over the world and the increase in the number of serious patients and mortality rates. Like other departments, radiology clinics were immediately reorganised according to new conjuncture. Radiologists have been assigned in services and polyclinics in the care of corona patients. Although chest CT scan is not recommended for the diagnosis of COVID-19 during the pandemic period, it has yielded important findings for detecting the disease at the first application and used in the diagnosis of patients in conjunction with RT-PCR (Reverse Transcriptase Polymerase Chain Reaction) (9). As a consequence, the increase in thoracic imaging has also significantly increased the radiologist's workload.

Health carrier workers -especially the front-line staff- were psychologically affected due to the high-risk viral contamination for themselves and also for their families. Recent studies have shown that emotional distress such as anxiety, depression and insomnia have increased during COVID-19 pandemic in health carrier workers (10,11). The impact of the COVID-19 pandemic on healthcare organizations and healthcare workers has significantly affected the working order. In another study from Turkey, regarding clinical functioning and anxiety levels in neurosurgery clinics, it is shown that anxiety levels in neurosurgeons have increased and workflow of clinics have changed distinctly (12).

In our study, we aimed to detect the change in the functioning of radiology clinics and radiologist's way of working during COVID-19 pandemic. Also, we aimed to state anxiety levels and relevant factors that induced anxiety in radiologists.

Methods

This study was approved by the medical ethics committee of our institution (Approval Number: 2020/65) and the Republic of Turkey Ministry of Health, COVID-19 Scientific Research Committee. Our study is a survey study based on volunteerism.

Research Universe and Sample

The research is a descriptive study, and the data were collected by quantitative method. The research population constitutes, radiology residents, specialists and scholars actively working in Turkey during COVID-19 pandemic. Due to the restraints, the data of the study were collected digitally, through the clinical activity scale and back anxiety scale questionnaires created over the internet. Announcements were made on social media networks and personal communications were established for participation in the survey. Sampling management was used in data collection for easy data collection since researchers do not have the opportunity to identify the participants in the digital environment.

The data collection period started on 18.04.2020 and ended on 8.6.2020. During this time, 86 valid questionnaires were reached. This number was found sufficient to reflect the views of radiologists under pandemic conditions.

Data Collection Tools

The data of the study consists of three parts: the questionnaire form demographic information, "COVID-19 Pandemic Radiology Clinic Activity Scale" and "Back Anxiety Scale".

Demographic Information

It consists of two open-ended questions, together with the personal characteristics of physicians, the types of hospitals they work in, their exposure to the COVID-19 outbreak and their service provision.

COVID-19 Pandemic Radiology Clinic Activity Scale

The scale was prepared by obtaining information about the pandemic, literature review, preliminary interviews with the radiology clinic chiefs and taking the opinions of the relevant academicians about the scope and structuring of the questions. SPSS program was used in the validity and reliability analysis of the scale. Factor analysis was conducted to understand the construct validity of the items of the scale. Validity is the degree to which a test or scale measures what is intended to be measured (Coşkun et al 2017). In the scale prepared as a total of 29 questions, five statements were removed because factor loads were low or inconsistent during factor analysis. The scale was validated as 24 expressions. Kaiser-Meyer-Olkin (KMO) test was performed for the sample number and it was found to be 0.724. In addition, to find out whether the correlation between items were significant, Barlett's sphericity test results were examined and it was found to be significant at

the 0.001 level (Approx.Chi-Square: 961,675 / df: 253 / sig: 0.000). In order to size the items, the "principal components" method and the "Verimax" rotation process were applied. The scale items were found to have factor loads between 0.528 and 0.867. The scale was collected under 3 factors. These factors are The functioning of the radiology clinic (8 statements), Personal Anxiety (5 statements), Clinical Approach and Combat (11 statements) factors. The explanation level of the variance of the factors that make up the scale was calculated as 52.9%.

The Back Anxiety Scale

It was validated with factor analysis under a single factor. The reliability analysis of the scales was calculated with the Cronbach's Alpha coefficient. The Cronbach's Alpha coefficient of the scales was calculated as 0.824 and 0.917, respectively. The data were analyzed with frequency, significance and correlation tests with SPSS package program. In evaluating the average of frequency values; 1-2.33 low 2.34-3.66 medium and 3.67-5 high levels.

Statistical analysis

The data were analyzed using SPSS 25.0 package software. Continuous variables are expressed as mean, standard deviation, and median (minimum–maximum) values, and categorical variables are expressed as numbers and percentages. The normal distribution of the data was examined using Shapiro–Wilk and Kolmogorov–Smirnov tests. When parametric test assumptions were met, independent t-test and one-way analysis of variance were used for the comparison of the differences between independent groups. When the parametric test assumptions were not met, Mann–Whitney U test was used in comparison of independent group differences. Logistic Regression analysis was used to determine the risk factors affecting the dependent variable. In all analyzes, $p<0.05$ was considered statistically significant.

Ethics of the Study

The study was approved by the Ordu University, Non-Interventional Ethics Committee (18-KAEK-053) and the institutions where the study was conducted. The purpose of the study was explained to the participants, and the participants were assured that their responses would be anonymous and would be used only in scientific research; they were also informed that they could withdraw at any point during the interview. Verbal and written consents were obtained from the participants. The study was performed as per the "Informed Consent, Confidentiality and Protection of Privacy and Respect for Autonomy" principles and the Helsinki Declaration. The required permissions were obtained from those who confirmed the validity and reliability of the Turkish version of the scale. The data were collected within 30 minutes via face-to-face interviews. The parents were interviewed in different environments to prevent influence from each other.

Results

Eightysix radiologists completed the survey. Of the radiologists participating in the study, 55.8% are male, 48.8% are 39 years old and younger, 33.7% have worked 6-10 years in the profession, 47.7% work in a university hospital, 53.5% work as a radiologist. Although 60.5% of them are not pandemic hospitals, they work in hospitals where covid patients are treated. The research findings of this study and descriptive variables of participants are given in Table 1.

80.2% of radiology physicians encountered patients infected with COVID-19 and provided services to these patients. 25 radiologists had the COVID-19 test and 3 physicians tested positive. Two of them recovered, one physician was in quarantine.

The data of the scale, which was developed to understand the effect of the pandemic on the functioning of radiology clinics during the ongoing pandemic, are given in Table 2. In order to understand the details of the data, the frequency distributions of the participants' participation levels in the expressions of the scale were also written in the table. When the table is examined, it is understood that there is a moderate differentiation in the functioning of the radiology clinic (3,37) during the pandemic process. Radiology physicians stated that radiology clinics could not continue routine patient admissions (3.47), they postponed routine ultrasound (3.61) and interventional radiology procedures (3.55), and continued the procedures of emergency and cancer cases (4.03). They also stated that the diagnostic processes of outpatients were interrupted (3.85) and they tried to help patients with telemedicine methods (3.86) at medium and high levels.

It was understood that the radiologists working during the pandemic had a high level of personal anxiety and worked under stress (3,74). Radiologists: Risk of developing COVID-19 disease (3.83), high expectations of colleagues about the diagnosis of COVID-19 with thoracic CT (3.56), ultrasonography (USG) applications (4.09), rapid deterioration in the thorax CT of COVID-19 patients (3, 69) and being assigned to COVID-19 patient processes (3.49), they

stated that they experienced moderate-to-high levels of anxiety and stress.

During the ongoing pandemic process, there has been a moderate change in the clinical approaches of radiologists (3,67) to combat the pandemic at the clinical level. Radiology experts stated that in-house informing about the pandemic was done effectively (3,43); have sufficient personal equipment (3,20); stated that they used personal protective equipment correctly (3,43) and found the health system successful (3.09) at a moderate level.

Radiology physicians stated that they had sufficient information to diagnose COVID-19 cases (3,63); keep up-to-date scientific information on the pandemic (3,61); that they could not hold routine scientific meetings and seminars (4,01); that they are in positive solidarity with their colleagues (3.87); they obtained a separate informed consent about COVID-19 from patients (3,16); they stated that unnecessary thorax CT demands increased (4,51) and they made the most thorax CT evaluation in the pandemic (4,42).

According to the answers they gave to the open-ended question of radiology physicians, "Write down the countries you find successful or unsuccessful in combating the pandemic"; successful countries; Germany (53), South Korea (51), China (35) and Turkey (29); failed countries; They expressed it as Italy (58), Spain (54), England (22) and USA (21).

Anxiety was not detected in 44.6% of the radiology physicians during the pandemic process. Mild anxiety was detected in 31.3% of the radiologists, moderate in 16.9% and severe anxiety in 7.2%. The data about the measurement of anxiety levels of radiologists during the pandemic process are shown in Table 3.

A weak linear relationship was found between the changes in the functioning of radiology clinics and the personal concerns of radiology physicians at the p=0.05 error level (0.224). A weak linear relationship was found between the personal anxiety factor of the radiology physicians, the clinical approach and the factor of combating the pandemic at the $P = 0.01$ error level (0.336). It was found that there is a moderate linear relationship (0.515) between the personal anxiety and anxiety level of radiologists. According to the correlation analysis results, the disruption in the functioning of radiology clinics due to the pandemic increases the personal concerns of radiology physicians, the increase in the personal anxiety of radiology physicians, increases the anxiety levels of the physicians, at the same time changes the clinical approach and increases the fight against the pandemic. The data of the relationship between the factors of the scale of the functioning of radiology clinics during the pandemic process and the anxiety scale of radiology physicians are given in Table 4.

Table 1. Frequency table of the participants descriptive variables

Variables	N	%	Variables	N	%
1.Gender			**6. Is your hospital a pandemic hospital?**		
Female	38	44,2	Yes	30	34,9
Male	48	55,8	No	4	4,7
2.Age			Not pandemic hospital, but Covid 19 patients are being cared for.	52	60,5
39 and below	42	48,8	**6. Have you ever encountered COVID-19 patients?**		
40-49	28	32,6	Yes	69	80,2
50-59	16	18,6	No	17	19,8
3. Work experience (yr)			**7 Did you serve COVID-19 patients?**		
1-5 years	13	15,1	Yes	69	80,2
6-10 years	29	33,7	No	17	19,8
11-15 years	18	20,9	**8. Have you had the COVID 19 test?**		
16-20 years	12	14,0	Yes	25	29,1
21 and over	14	16,3	No	61	70,9
4. Work place			**9. If so, what is the result of the COVID 19 test?**		
Public Hospital	36	41,9	Positive	3	11
University Hospital	41	47,7	Negative	23	89
Private Hospital	9	10,5	**10. If you have the disease, your condition?**		
5.Professional Status			In quarantine without symptoms.	1	50
Junior (Resident fellow)	10	11,6	Inpatient treatment in the service.	-	
Non-academic radiologist	46	53,5	Healed.	2	50
Asist. Dr	11	12,8			
Assoc. & Prof. Dr	19	22,1			

Table 2: Frequency distribution of the scale of the clinical activities of radiology in COVID-19 pandemic

Statements	Investigation of the Effects of the COVID-19 Pandemic on the Activities of the Radiology Clinic											
	I never agree		I do not agree		I partially agree		I Agree		I totally agree		x̄	SS
	n	%	n	%	n	%	n	%	n	%		
1. Clinical Functioning											**3,37**	**0,76**
We cannot continue routine patient admissions.	14	16,3	13	15,1	9	10,5	18	20,9	32	37,2	3,47	1,51
We postpone interventional radiology procedures.	5	5,8	12	14,0	20	23,3	27	31,4	21	24,4	3,55	1,20
We postpone routine ultrasound applications.	6	7,0	11	12,8	16	18,6	30	34,9	23	26,7	3,61	1,20
We only accept emergency cases and oncology patients.	11	12,8	6	7,0	4	4,7	13	15,1	52	60,5	4,03	1,45
We postpone all radiological procedures, except for coronavirus cases.	33	38,4	10	11,6	14	16,3	24	27,9	5	5,8	2,51	1,39
Since the routine radiological procedures of outpatients are delayed, the diagnosis processes of the patients are delayed.	3	3,5	6	7,0	14	16,3	39	45,3	23	26,7	3,85	1,01
We help our patients with tele-medicine techniques	8	9,3	7	8,1	9	10,5	27	31,4	35	40,7	3,86	1,29
I am assigned to the processes of coronavirus patients outside of radiology expertise.	57	66,3	2	2,3	7	8,1	11	12,8	9	10,5	1,98	1,49
Factor 2: Personal anxiety											3,74	0,97
I am highly anxious about getting the disease.	5	5,8	8	9,3	11	12,8	33	38,4	28	32,6	3,83	1,16
Requesting USG for patients with COVID-19 with different indications increases my stress.	3	3,5	4	4,7	11	12,8	30	34,9	36	41,9	4,09	1,03
High expectations of clinicians in diagnosing coronavirus patients with CT causes stress.	7	8,1	11	12,8	13	15,1	35	40,7	19	22,1	3,56	1,20
The rapid deterioration of the follow-up CT of coronavirus patients causes serious anxiety in me.	8	9,3	5	5,8	13	15,1	39	45,3	21	24,4	3,69	1,17
It worries me that I am assigned to the processes of coronavirus patients.	16	18,6	5	5,8	7	8,1	29	33,7	24	27,9	3,49	1,47
Factor 3: Clinical Approach and Combat											**3,67**	**0,7**
In-house information processes regarding coronavirus are carried out effectively.	6	7,0	6	7,0	35	40,7	23	26,7	16	18,6	3,43	1,09
We obtain separate consent for coronavirus from patients with interventional procedures.	13	15,1	9	10,5	29	33,7	15	17,4	17	19,8	3,16	1,31
Unnecessary CT demands are increasing in order not to bypass the diagnosis.	3	3,5	0	0	3	3,5	23	26,7	56	65,1	4,51	0,86
We mostly evaluate thorax CT, in daily routine.	2	2,3	1	1,2	3	3,5	31	36,0	47	54,7	4,42	0,82
We have enough personal protective equipment	7	8,1	17	19,8	25	29,1	25	29,1	12	14,0	3,20	1,15
We use personal protective equipment correctly.	3	3,5	9	10,5	33	38,4	30	34,9	11	12,8	3,43	0,96
We are in a positive solidarity with our colleagues	3	3,5	4	4,7	21	24,4	31	36,0	27	31,4	3,87	1,02
We cannot conduct our scientific meeting-seminar programs	12	14,0	4	4,7	4	4,7	17	19,8	49	57,0	4,01	1,44
I have enough knowledge and equipment to diagnose coronavirus	4	4,7	11	12,8	16	18,6	36	41,9	19	22,1	3,63	1,10
We can follow current scientific data on coronavirus	9	10,5	7	8,1	13	15,1	36	41,9	21	24,4	3,61	1,23
The health system is successful	6	7,0	26	30,2	16	18,6	28	32,6	9	10,5	3,09	1,16

Table 3. Evaluation of radiology physicians' back anxiety scales

Back Anxiety Scale	N	%
None	37	44,6
Mild	26	31,3
Moderate	14	16,9
Severe	6	7,2

Table 4: Relationship between factors of radiology clinical activity scale and back anxiety scale

Factors	Clinical Functioning	Personal Anxiety	Clinical Approach and Combat	Anxiety
Clinical Functioning	1			
Personal Anxiety	,224(*)	1		
Clinical Approach and Combat	,049	,336(**)	1	
Anxiety	,107	,515(**)	,176	1

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

Discussion

Throughout history, pandemics have been observed to have significant effects on societies, leading to many psychological, social and economic consequences. Similarly, the COVID-19 outbreak has become a serious global public health issue, the effects of which will be felt in the future. Probably the most affected part of the community is frontline healthcare professionals. In this study, changes in the functioning of the radiology clinics in Turkey through pandemic period was shown and the level of anxiety caused by these existing changes among radiologists was determined. A significant relationship was observed between the change in clinical functioning and the level of anxiety.

During this acute and unexpected COVID-19 pandemic, priorities of Turkish health system and organization of hospitals were revised. Regardless of their specialty, all physicians were re-assigned to outpatient clinics, services and intensive care units in order to take care of COVID-19 patients. As a result, radiology physicians, like all other healthcare professionals, were exposed to an aggravating risk of contamination. In a study conducted by Lai et al., It was shown that healthcare workers working in pandemic clinics of Wuhan city reported serious psychological symptoms (11). In a survey among Turkish neurosurgeons during the Covid 19 pandemic process, Yılmaz et al. reported that, an increase in anxiety level was found (12). Another study conducted in France found that symptoms of depression, anxiety, and insomnia were common in more than a third of radiologists in France during the pandemic (13).

In our study parallel with the literature, it was observed that radiologists expressed moderate to high levels of anxiety and stress from being caught with COVID-19 disease, from USG applications performed to COVID-19 positive patients for non-covid reasons and from being assigned to COVID-19 patient care units. Despite the increased anxiety rates, the rate of severe anxiety according to Back Anxiety Scale was found to be 7%. In a study involving all healthcare professionals (doctor, nurse, technician) during the Covid 19 pandemic, a higher level of personal anxiety and anxiety was found (14). This situation can be expressed as the radiology specialists mostly working in the reporting part, and the employees who come into close contact with the patient are technicians and nurses (15).

During the Covid 19 pandemic, exposure or fear of exposure to the virus in terms of psychologic symptoms such as anxiety and insomnia has been identified as an important risk factor (11). In our study, 80.2% of the radiologists who participated in the questionnaire stated that they encountered patients with COVID-19 and 12% tested positive. Studies have found that factors such as working in COVID-19 outpatient clinics and services increase psychological symptoms (11). In addition, it has been reported that the lack of protective equipment is of concern and more than 70% of actively working radiologists worldwide lack access to protective equipment (16-18). In our study, different from the data in the literature, radiologists stated that they had enough personal protective equipment (3,20) and used personal protective equipment correctly (3,43).

Some measures have been taken in both public hospitals and private hospitals to prevent the spread

of the Corona virus. In this context, non-emergency patient examinations were suspended. Regulations have also been made in the functioning of radiology clinics. In our study, the participants stated that routine USG and interventional radiology procedures were not performed in their clinics, and that emergency and cancer patients continued their procedures. On the other hand, due to studies showing that thorax CT can help in the diagnosis of COVID 19, the number of thorax CT scans has increased significantly (9,19,20). Although it was not recommended by radiology authorities, the widespread use of thorax CT as an auxiliary diagnostic method in the triage of COVID 19 has increased the workload (21,22). In our study, 90% of the participants stated that they mainly evaluated thorax CT examinations in their daily radiology practice, and 91% of the participants stated that unnecessary thorax CT requests were made in order not to miss the diagnosis of COVID-19. They also stated that they were concerned that their colleagues had high expectations for the diagnosis of COVID-19. Studies with CT in the diagnosis of COVID-19 and treatment follow-up have shown rapid radiological deterioration (23). In our study, participants stated that the rapid deterioration of CT in COVID-19 patients increased their anxiety.

Studies have reported important abrupt changes in the health system and the function of clinics that make up the health system during the pandemic period (12,24,25). In our study, radiologists listed the changes related to clinical functioning apart from increased thorax CT numbers as follows; They follow up-to-date scientific data on COVID 19, are unable to hold routine face-to-face scientific meetings and seminars, they are more in solidarity with their colleagues and receive informed consent about COVID-19 separately from patients.

Our study has limitations. First, this study is a questionnaire filled out by a limited number of radiologists and may not represent other radiology professionals and all radiology departments. Finally, this was a cross-sectional study and no follow-up was done. Personal concerns and anxieties may progress differently in different time periods of the pandemic. For this reason, there is a need for repeated studies with the same and larger participant groups at different times.

In our study it was shown that there were significant changes in the functioning of radiology clinics especially related with increased thorax CT scans at the beginning of the COVID-19 pandemic and that the anxiety levels of radiologists increased due to the pandemic.

In conclusion, it is important to adapt to changes in clinical functions and to take necessary precautions for the transmission of infection, which causes anxiety in radiology specialists. Also, it is an important issue to take necessary forward measures regarding the diagnosis and interventional procedures of outpatients.

Conclusion

- It was understood that the radiologists working during the pandemic had a high level of personal anxiety and worked under stress in Turkey.
- The risk of developing COVID-19 disease, high expectations of colleagues about the diagnosis of COVID-19 with thorax CT, rapid deterioration in the CT of COVID-19 patients and being assigned to COVID-19 patient care units were stated as conditions that lead to increased anxiety and stress levels.
- They stated that unnecessary thorax CT demands increased, and they made the most thorax CT evaluation in the daily routine.

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RESEARCH ARTICLE

Variations in Apelin Expression Levels during Achilles Tendon Healing

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Abstract
Objective: Research in recent years focused on the role of the apelin-APJ axis in pathologic fibrosis. The axis includes the parenchyma and mesenchymal cells of most organs. Reduction in parenchymal cells and activation of fibroblasts generally results in fibrosis of the organ. In this study, the aim was to reveal differences in apelin in tendons with primary repair.
Methods: The study used 15 male Wistar Albino rats. The tendons of the right and left legs of the rats were used. Rats were divided into 3 groups containing 5 rats each. Group 1 was the sham group; Group 2 had tendon repair performed and were sacrificed 3 weeks later; and Group 3 had tendon repair and were sacrificed 6 weeks later. Under anesthesia, bilateral tendonectomy was performed and surgically repaired. Tendons were removed in the 3rd and 6th weeks. Samples were immunohistochemically stained for apelin and stain degree was assessed from 0 to 4 with a light microscope. The scores were compared with the Friedman test.
Results: The results of statistical evaluation identified that the sham group had statistically significantly higher levels compared to the scores in the other two groups. There was no significant difference identified between the groups sacrificed in the 3rd and 6th weeks.
Conclusion: This study concluded that apelin may be beneficial for tendon healing and that apelin levels may increase with fibrosis.
Key words: Apelin, repair, fibrosis

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Introduction

In the USA nearly 300 thousand tendon and ligament repair operations are performed each year (1). In spite of surgical intervention, the healing process of tendons is slow as tendons and ligaments are hypocellular and hypovascular (2). Even 1 year later, the structure and function of injured tendons is lower than uninjured tendons. The amelioration response is divided into 3 intersecting stages of inflammation, proliferation/repair and remodeling (3). After surgical repair of the tendon, generally a

short inflammatory phase lasting up to a week begins. This is followed by a proliferative phase lasting several weeks. Then, the remodeling phase lasting several months occurs (4). During the inflammatory phase, vascular permeability increases and the entry of inflammatory cells into the healing area occurs. These cells produce a range of growth factors and cytokines involved in duties and proliferation of fibroblasts and macrophages. During the proliferation and remodeling phases of amelioration, fibroblasts multiply and begin production, storage and crosslinking of collagen (4).

Evidence in recent times proposed that inflammation modulation in the early stages following tendon repair may cause healing (5). Regulated inflammation is generally beneficial for tissue repair; however, excessive and permanent inflammation is known to cause damage. In fact, inflammatory cytokines attract fibroblasts to the repair area, with excessive inflammation causing poor clinical outcomes (6,7).

Apelin is a peptide hormone. It is an endogenous ligand for the G-protein linked receptor called APJ. Apelin and APJ are commonly expressed in the heart, lungs, hypothalamus, adipose tissue, kidneys, muscles and other organs in humans (8). Apelin is initially synthesized as 77 amino acid precursors. Later it converts to several mature forms like apelin 13, apelin 17 and apelin 36 (9). Apelin 13 is the main form circulating in plasma and is considered to be mainly effective on physiology (9). Studies in recent years focused on the role of the apelin-APJ axis in pathologic fibrosis. Many organs contain parenchymal and mesenchymal cells. The reduction in parenchymal cells and activation of fibroblasts generally results in the development of fibrosis in the organ. The leading characteristics of organ fibrosis are production of inflammatory factors, secretion in the extracellular matrix and activation and proliferation of fibroblasts (10). Organ fibrosis forms in the kidneys, heart, lungs and liver. Fibrosis reduces the functions of the organ and causes organ failure. Recent studies show that the apelin-APJ axis is associated with renal fibrosis, myocardial fibrosis, liver fibrosis and pulmonary fibrosis. Additionally, the function of apelin-APJ in development of fibrosis is controversial. Many factors like transforming growth factor (TGF-B1) beta, angiotensin 2 (Ang2) and extracellular matrix (ECM) participate in the organ fibrosis process. These factors support cell proliferation and differentiation, wound healing and extracellular matrix production contributing to the development of fibrosis (11,12). Some articles proposed that apelin-APJ inhibits renal and myocardial fibrosis via the TGF-β route. Contrarily, the apelin-APJ axis increases liver fibrosis. There is no information about the presence or efficacy of apelin during the tendon healing process. This study aimed to research whether apelin contributes to healing after primary repair of tendons.

Methods

Animals

The minimum number of animals required in order to obtain statistically significant results were used in our study. Our study used fifteen Wistar albino rats weighing 250-300 g initially and aged from 4-8 weeks. During the experiment, rats were kept in 10/14-hour light/darkness cycles, with 3 subjects per cage at normal room temperature and humidity fed with standard pellet feed (Nükleon, Ankara, Turkey) and tap water. Temperature was measured with a thermometer and humidity with a hygrometer. Ventilation was provided by a room aspirator.

Formation of the groups and experimental design

Before beginning the experiment, animals were weighed and divided into 3 equal groups with similar animal weights in the group distributions (groups are explained below). A total of 15 male rats were used.

Sham group (5 rats): This group was sacrificed on the same day. The regions of the right and left Achilles tendons had skin and subdermal tissue entered with a 3 cm incision and full layer incision was made 0.5 cm proximal of the Achilles tendon adhesion point. The Achilles tendons were removed on the same day.

Group 1 (sf-3) (5 rats): This group was sacrificed after 21 days. The regions of the right and left Achilles tendons had skin and subdermal tissue entered with a 3 cm incision and full layer incision was made 0.5 cm proximal of the Achilles tendon adhesion point. Incisions were primarily repaired with the modified Kessler method using 4.0 polypropylene sutures (Propilen, Doğsan, Trabzon, Turkey). Later subdermal layers and skin were closed in retrograde manner. The Achilles tendons were removed 21 days later.

Group 2 (sf-6) (5 rats): This group was sacrificed after 42 days. The regions of the right and left Achilles tendons had skin and subdermal tissue entered with a 3 cm incision and full layer incision

was made 0.5 cm proximal of the Achilles tendon adhesion point. Incisions were primarily repaired with the modified Kessler method using 4.0 polypropylene sutures (Propilen, Doğsan, Trabzon, Turkey). Later subdermal layers and skin were closed in retrograde manner. The Achilles tendons were removed 42 days later.

All procedures in the study were completed in accordance with ethical guidelines. Before surgery, rats were anesthetized with 3 mg/kg xylazine hydrochloride (Rompun©, Bayer, Turkey) and 90 mg/kg ketamine hydrochloride (Ketalar©, Eczacıbası, Turkey) administered intraperitoneally. After appropriate anesthesia was achieved, animals were shaved with a razor taking care not to harm the skin and skin was cleaned with polyvinyl pyrrolidone-iodine (Batticon©, Adeka, Samsun, Turkey). The animal was covered with sterile compresses leaving the surgical field open. After the surgical procedure all animals had regular daily wound dressing performed.

Samples were taken from the tissues and then sections with a thickness of 5 μm were prepared on poly-laminated slides. Slides were prepared for immunohistochemical study. A Leica Bond-Max IHK stain device (Vision Biosystems, Melbourne, Australia) was used for immunohistochemical study.

Sections were left at 60 degrees for 30 minutes. Then they were left at 72 degrees in Bond Devax solutions for deparaffinization. After washing with alcohol 3 times, they were washed 3 times with Bond Wash washing solution. They were left for 10 minutes at 100 degrees in the pre-processing solution previously defined for the antibody. Then, they were washed 3 times more in Bond Wash washing solution. Ten minutes of peroxide blockage was performed. Again, they were washed 3 times with Bond Wash washing solution. They were incubated with apelin (genetex GTX37465 (Polyclonal (1:300)). Then, they were washed 3 times with Bond Wash washing solution. They were treated with post-primer for 7 minutes. Then, after washing 3 times with Bond Wash washing solution, they were treated with the polymer for 7 minutes. Then, they were washed 2 times with Bond Wash washing solution and then with distilled water. They were incubated for 7 minutes with DAB and washed with distilled water 3 times. At the end of these processes, they were assessed with the degree procedure of Berta et al. (15).

The proportion of cells with cytoplasmic positivity was taken into account. Accordingly, 0 staining, 1 + staining, 2 + staining, or 3 + staining categories were defined on the basis of no staining, 1% to 10% staining, 11% to 50% staining, and greater than 50% staining, respectively (Figure 1-3).

Figure 1. Sham group staining example (x400 magnification)
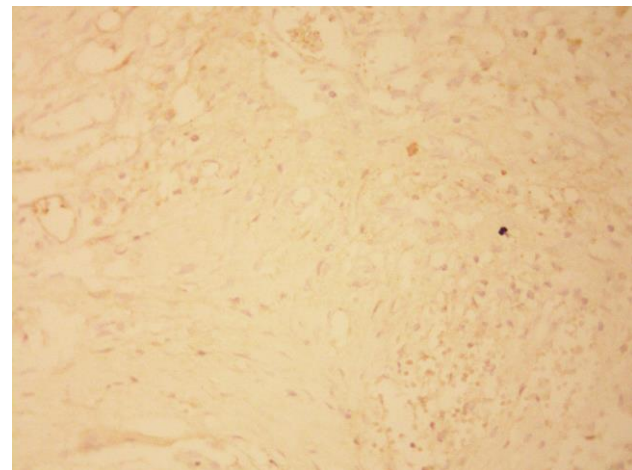
Figure 2. Sf-3 group staining example (x400 magnification)
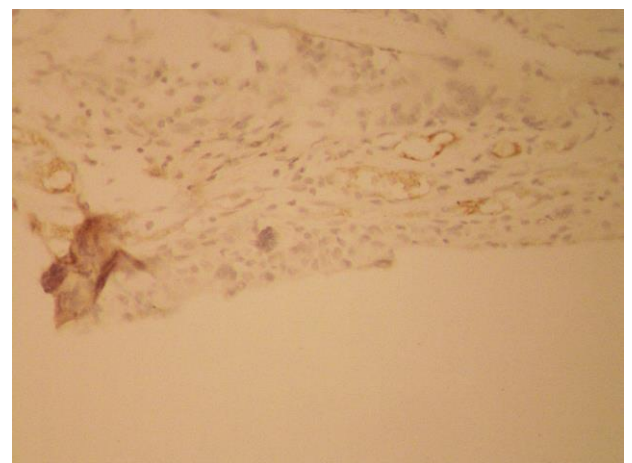
Figure 3. Sf-6 group staining example (x400 magnification)

Statistical analysis

The SPSS v20 (IBM Inc., Chicago, IL, USA) computer program was used for statistical analysis. As each group included 5 subjects, comparisons were performed with the non-parametric Friedman test and the chi-square test for stain differences between the three groups and temporal changes in the sf-3 and sf-6 groups. Statistical significance was taken as $p \leq 0.05$.

Ethics of the Study

Our study was approved by the Experimental Animals Ethical Committee of the Faculty of Medicine (Date: 30.01.2018, Issue:03).

Results

The Friedman test results for comparison of the three groups found statistically significant differences between the degree of staining in the three groups with $x2= 16.75$ and $p<0.001$. The group with most staining was Group sf-6 (mean rank: 2.70). Staining examples for the sham, sf-3 and sf-6 groups are seen in Figures 1, 2 and 3 (x400 magnification) (Graphic 1).

Additionally, as time passed between the sf-3 and sf-6 groups, the chi-square test results for staining did not have a statistically significant difference with $x2= 1.01$ and $p=0.31$.
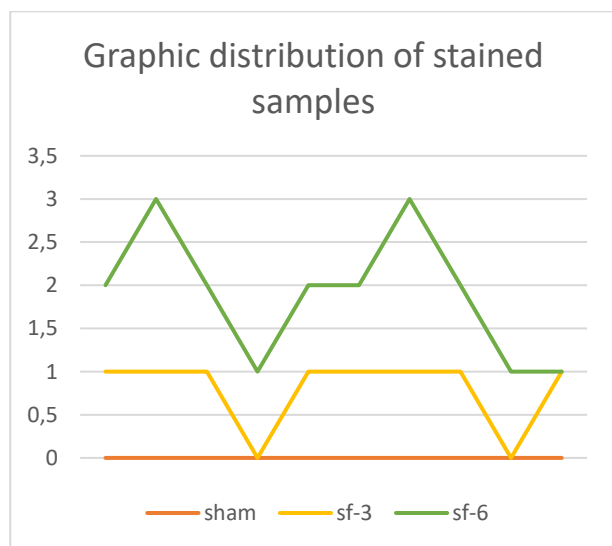
Graphic 1. Distribution of stained samples

Discussion

In our study, the apelin level was identified to increase with Achilles' tendon injury in rats. The Achilles tendon is the strongest and most used tendon in the body [13]. Many bioactive molecules play a role in regulating the cellular response during tendon repair [14]. A variety of growth factors are active in many stages of the healing process and are clearly upregulated after tendon injury, including insulin-like growth factor-I (IGF-I), TGF-β, bFGF, platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), BMP, and connective tissue growth factor (CTGF) [15-17].

Tenoblasts and tenocytes are tendon-specific cell types forming the majority of cellular content in tendons [18]. Tenocytes are accepted as being fibroblast-like cells producing necessary components like type I collagen and other ECM molecules during growth and healing of collagen fibers.

The resistance of the tendon is linked to the ability of the collagen molecules to organize and form a cross-linked structure [19]. Type I collagen is dominant in ECM in tendons, while type III collagen is the second-most common and critical collagen type in pathologic tendons and tendon healing processes [20]. The organization of type I collagen is accepted as being very important for the mechanical characteristics of tendons. Finally, research aimed to understand the role of growth factors, transcription factors and type I collagen-fibril distribution in regulation-linked mechanical forces. For example, TGFβ and FGF were shown to regulate collagen-architectural formation within tendons during development [21,22]. Additionally, the transcription factors scleraxis, Mohawk homeobox protein, and zinc-finger protein early growth response protein 1 (EGR1) regulate type I collagen formation within tendons via modulation of COL1A1 and COL1A2 gene expression [23,24]. Extrinsic cells including neutrophils and macrophages playing a key role in cleaning debris release second generation cytokines passing into the next stage of the healing process [25].

The proliferative phase characterized by scattered accumulation of granulation tissue and a peak in type III collagen and DNA concentrations continues with the transition from type III to type I collagen in later stages [6].

The majority of organs contain parenchymal and mesenchymal cells. Reductions in parenchymal cells and activation of fibroblasts generally results in the development of organ fibrosis. Structural injury from continuing fibrosis reduces organ functions and finally causes organ failure. Many factors like TGF beta, angiotensin II (Ang-II) and extracellular matrix (ECM) participate in the organ fibrosis process [10,26-28]. Research studies show the apelin-APJ axis is associated with renal, myocardial, liver and pulmonary fibrosis [26]. However, this association may not be the same in all organs. Some articles proposed that apelin-APJ inhibits renal and myocardial fibrosis via the TGF beta pathway [10,26-

28). In vitro apelin-induced TGF beta in human proximal tubular epithelium cells inhibits the epithelial-mesenchymal transition. In the unilateral ureteral obstruction model, apelin treatment significantly reduced TGF beta 1 and its receptor simultaneous to expression of interstitial matrix components. Apelin may improve renal interstitial fibrosis by suppressing the tubular epithelial-mesenchymal transition with the Smad protein-dependent mechanism pathway (27). Canakci et al. reported apelin has a protective role in experimental renal IR injury (28). These findings lead to the consideration that apelin-APJ has potential renoprotective effects and may be an effective agent in delaying progression of CRF. Additionally, recent studies lead to consideration that the apelin/APJ system may be used for treatment of insulin resistance and type 2 diabetes (29).

Similarly, the apelin-APJ axis is thought to reduce myocardial fibrosis. After MI in mice, apelin 13 treatment ensured a reduction in the degree of cardiac hypertrophy and cardiac fibrosis compared to the sham group (30,31). This effect of apelin was due to stimulation of bone marrow cells (BMC). Apelin stimulated bone marrow cells (BMC) and excessive expression of apelin by BMC increases the speed of cardiac repair and lessens cardiac fibrosis in post-MI mice (32). Strohbach et al. showed that plasma apelin-17 levels significantly fell in patients with acute myocardial infarctus (AMI) compared to the control group. They reported the platelet apelinergic system may be a new target for diagnostic and treatment purposes (33). While the apelin/APJ system has positive inotropic effect on the heart, it was also shown to ensure water excretion. Using this, it was proposed as a treatment choice for congestive heart failure accompanied by hyponatremia (34). Additionally, apelin was identified in breastmilk. It is thought to play a role in the foundation of the infant immune system. At the same time, activation of the apelin/APJ system was reported to improve muscle weakness linked to aging (35).

Angiogensin II (AII) and endothelin-1 (ET-1) increase the apelin expression in hepatic stellate cells (HSC). Increased apelin increases synthesis of collagen I and platelet-derived growth factor receptor β (PDGFRβ) closely associated with liver fibrosis (36). This data shows that apelin-APJ may be an important mediator of liver fibrogenesis. Additionally, apelin and APJ levels clearly increase in cirrhotic liver (37). Apelin causes collagen I stimulation leading to fibrosis in LC (36). However, there are studies proposing the opposite to this. Studies by Owen et al. (38) reported that plasma apelin levels significantly reduced in both the early stage of liver fibrosis and the late stage of liver cirrhosis.

Our study is the first to reveal increased apelin levels in Achilles tendon injury. This study observed the apelin expression in the 3- and 6-week groups was greater compared to the sham group. This difference in apelin may be important in the healing process after primary repair, angiogenesis, anti-inflammatory cytokines and in the remodeling process. In the literature, it was observed that apelin ensures collagen I increase. For tendon repair, provision of collagen I instead of collagen III is necessary for healthy repair to occur. In our study, increased levels of apelin in the Achilles tendon after tendon repair may target healthy repair.

Conclusions

This study observed the apelin expression in the 3- and 6-week groups was higher compared to a control group. In the healing process after primary repair, this difference in apelin may be important for angiogenesis, anti-inflammatory cytokines and in the remodeling process. This difference in apelin during tendon healing, especially, appears to be a candidate as a valuable topic for further research.

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Clinical Correlation of Change in Sagittal Parameters after Anterior Cervical Microdiscectomy

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Abstract

Objective: Cervical radiculopathy is the syndrome of pain and / or sensorimotor deficit caused by compression of the cervical nerve root. Symptoms of cervical radiculopathy in the upper limb are described as pain, numbness, or weakness. Conservative treatment is recommended initially for degenerative cervical radiculopathy. Surgical treatment is recommended in cases where progressive loss of muscle strength does not respond to conservative therapy. Many radiographic parameters are used to define the sagittal alignment of the cervical spine. This variation contrasts with the assessment of caudal spine segments where there are more established guides for measuring deformity angles. The aim of this study is to evaluate the effect of anterior cervical discectomy and fusion, which are widely used in spinal surgery practice, on cervical sagittal alignment.

Methods: We retrospectively evaluated 33 patients who were operated with anterior cervical discectomy and fusion technique with the diagnosis of single level degenerative cervical disc hernia after an average of 3 months of follow-up period. For radiological evaluation, we analyzed the C2-C7 lordosis angles, the anterior and posterior disc heights at the operating level on lateral scoliosis radiographs, preoperatively and at 3rd month postoperatively. Japanese Orthopedic Association scores and visual analog scale scores were examined to evaluate clinical results.

Results: A statistically significant difference was found between the preoperative radiological sagittal parameters and the postoperative 3rd month ($p = 0.001$). When the clinical correlation of the findings was examined, a statistically significant difference was found in the Japanese Orthopedic Association scores and visual analog scale scores of the patients measured preoperatively versus 3 months postoperatively ($p < 0.001$).

Conclusion: Radiological and clinical parameters improve significantly in patients after single level anterior cervical discectomy surgery.

Key words: Cervical disc hernia, microdiscectomy, sagittal lordosis.

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Introduction

Degenerative changes in the cervical spine can impair quality of life and decrease functionality (1). These degenerative changes can often result in pain, radiculopathy, and myelopathy, and they sometimes require surgery. Both anterior and posterior methods are used in surgical treatment. Anterior cervical discectomy and fusion (ACDF) technique is most commonly used in the surgical treatment of cervical degenerative disc diseas (2). Many studies show that cervical kyphosis is the common cause of increased neck pain before and after cervical surgery. In addition to decompression of neural structures, achieving cervical lordosis is an important surgical goal in ACDF (3). The basic physiopathology of disc degeneration is the dehydration of the disc after changes develop in the collagen tissue in the structure of the disc, which consequently decreases the disc height in the spinal segment (4). Loss of height at the level of the cervical spine in the degenerative process often results in loss of lordosis, causing chronic neck pain. In the degenerative process leading to the loss of disc height, the amount of load carried by the cervical anterior column is transferred to the posterior elements of the spine at an increasing rate. With the disc cages used in anterior surgery, the height between discs can often be restored (5). Thus, the height of the foramen also increases (1). The aims of this study were to evaluate the effect of ACDF on cervical sagittal alignment and to correlate the surgical effect with clinical results.

Methods

In this study, 33 patients who underwent ACDF for a single-level cervical disc hernia at the Ordu University Faculty of Medicine and the KTO Karatay University Faculty of Medicine, Medicana Konya Hospital, Neurosurgery Department, between January 2019 and December 2019 were evaluated (Table 1). Patients younger than age 18 years and patients who had previously undergone anterior and/or posterior cervical surgery were not included in the study. Surgical procedures were performed by a single surgeon who had worked in both academic institutions. In the preoperative and postoperative follow-up of the patients, the visual analog scale (VAS) scores and Japanese Orthopedic Association (JOA) scores were evaluated for neck pain and clinical improvement. The C2-C7 lordosis angle (Figure 1A-B) and the anterior/posterior disc heights (Figure 2A-B) were measured preoperatively and at 3 months postoperatively to assess cervical sagittal parameters.

Operative Technique

The patients underwent operation under general anesthesia using the standard Smith-Robinson method with microscopy (6). After the decompression procedure, a locked polyetheretherketone cage was placed according to the patient's preoperative cervical lordosis or kyphosis (a lower cage was placed in patients with preoperative lordosis, and a higher cage was placed in patients with preoperative kyphosis). The height of the cage used was 6-7 mm

Statistical analysis

The descriptive statistics of the continuous data were reported as the mean ± standard deviation (SD) and the median range values. Categorical variables were summarized by frequency and percentage. Normality assumptions of continuous variables were evaluated using visual (histogram and Q-Q plots) and statistical (Shapiro-Wilk test) methods. Before-and-after comparisons were performed using the paired samples t-test for normally distributed variables and the Wilcoxon signed-rank test for non-normally distributed variables. All data were analyzed using SPSS 23 software (IBM, Inc., Chicago, IL, USA), and a p value less than 0.05 was considered statistically significant.

Ethics of the Study

This study was conducted with the approval of Ordu University Clinical Research Ethics Committee number (2021/29)

Results

Thirty-three patients were included in the study; 20 (60.6%) of the patients were women, and 13 (39.4%) were men. The mean age of the patients was 44.06 ± 10.33 years (range, 29-74 years), and the median age was 42 years. One patient (3.0%) had C4-C5 disc herniation, two patients (6.1%), C3-C4; 12 patients (36.4%), C5-C6; and 18 patients (54.5%), C6-C7. The sociodemographic and medical characteristics of the patients included in the study are summarized in Table 1.

As shown in Table 2, the Wilcoxon signed-rank test indicated that the postoperative C2-C7 lordosis angle (median = 7.30°) was significantly higher than the preoperative angle (median = 3°; p = 0.001). The postoperative anterior disc height (median = 0.64 cm) was significantly higher than the preoperative height (median = 0.37 cm; p < 0.001). The postoperative JOA score (median = 18) was significantly higher than the preoperative score (median = 16; p < 0.001). The postoperative VAS score (median = 2) was

significantly lower than the preoperative score (median = 9; p < 0.001).

The paired samples t-test indicated that the postoperative posterior disc height (mean ± SD, 0.54 ± 0.13 cm) was significantly higher than the preoperative height (mean ± SD = 0.37 ± 0.07 cm; p < 0.001). A comparison of the pre- and postoperative variables is shown in Figure 3.

Table 1. Patients characteristics

Patient Number	Age	Gender	Spinal Level
1	29	M	C6-7
2	74	F	C3-4
3	38	F	C5-6
4	59	M	C6-7
5	46	F	C5-6
5	31	F	C5-6
7	44	M	C5-6
8	44	M	C6-7
9	38	F	C6-7
10	45	M	C5-6
11	54	F	C6-7
12	48	F	C6-7
13	41	F	C6-7
14	33	F	C6-7
15	40	F	C4-5
16	57	F	C5-6
17	30	F	C5-6
18	42	F	C5-6
19	65	F	C3-4
20	34	M	C6-7
21	44	M	C6-7
22	58	F	C6-7
23	46	M	C6-7
24	41	M	C6-7
25	39	M	C6-7
26	56	F	C6-7
27	41	M	C6-7
28	43	F	C5-6
29	39	F	C5-6
30	37	M	C5-6
31	48	M	C6-7
32	33	F	C6-7
33	37	F	C5-6

M:Male; F:Female.
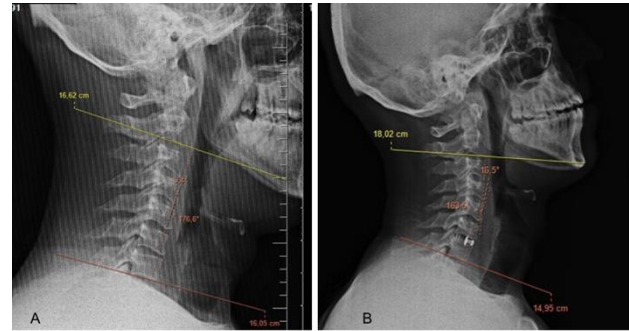
Figure 1. A. Preoperative C2-7 lordosis angle, B. Postoperative C2-7 lordosis angle
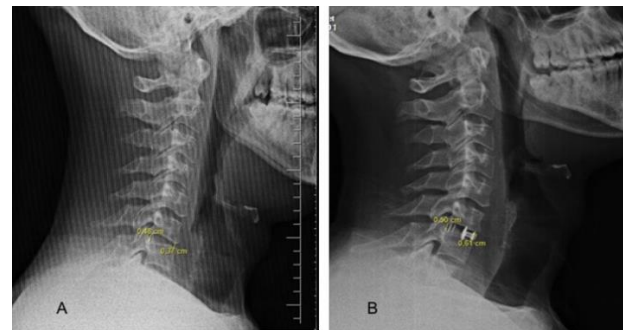
Figure 2. A-B: A.Preoperative disc height, B. Postoperative disc height
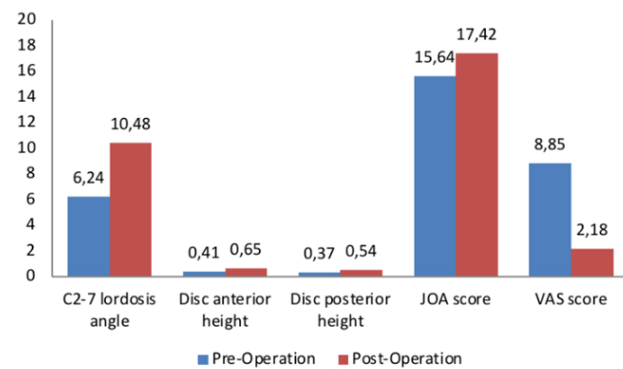
Figure 3. Comparison of the study variable values in preoperative and postoperative period.

Discussion

Cervical disc hernias are one of the most common degenerative diseases of the cervical spine (4, 7). Pain radiating to the neck and arms is typical. Flattening of cervical lordosis is observed in radiological images taken in many patients. In contrast to the lumbar and cervical spine, which should almost always be lordotic for standing with two legs, the thoracic spine must be kyphotic to balance the caudal lumbar spine (8). Continuation of the kyphosis towards the cervical levels disrupts the sagittal alignment and may cause pain. In addition, it is known that the lordosis of the cervical spine is important to maintain a horizontal gaze (9). In the degenerative process leading to the

loss of disc height, the amount of load carried by the cervical anterior column is transferred to the posterior elements of the spine at an increasing rate. Although some studies found flattened cervical spine alignment in asymptomatic participants, most patients with chronic neck pain show lordosis flattening. (10, 11, 12).

Clinical studies have shown that one of the most important causes of neck pain before and after cervical surgery is associated with kyphosis (13). Achieving cervical lordosis is an important surgical goal in ACDF as well as decompression of neural structures. ACDF is currently the most common surgical approach in cervical degenerative disc disease. ACDF effectively restores the sagittal sequence, especially at C2-C7 angle (14). Another study showed that improvement in focal lordosis correlated with improvement in overall cervical lordosis (C2-C7) (15). Another clinical study investigated clinical outcomes and sagittal alignment in patients who underwent ACDF and fusion, and minor changes were detected in preoperative and postoperative kyphosis angles. There was no significant relationship between the change in kyphotic angle and postoperative functional status. In addition, no significant change was found in the mean C2-C7 Cobb angles (16). However, in our study, a statistically significant relationship was observed between postoperative functional status and achieving lordosis. The postoperative C2-C7 lordosis angle (median = 7.30°) was significantly higher than the preoperative angle (median = 3°; p = 0.001). In our results, cervical lordosis improved during the postoperative period compared with the preoperative period, and the resulting difference was statistically significant.

In a study, in which 48 patients who were operated with anterior or posterior technique with the diagnosis of spondylotic myelopathy were examined, it was shown that C2-7 lordosis of patients who underwent anterior approach improved more than patients who were operated with the posterior method (17). In our study, anterior surgery was performed with the diagnosis of cervical disc herniation and similar results to the literature were obtained. The difference between the preoperative cervical lordosis angle (between C2 and C7) and the angle measured 3 months postoperatively was statistically significant. In addition, the change in favor of lordosis correlated with a statistically significant improvement in postoperative VAS scores and JOA scores. In our study, the postoperative JOA score was significantly higher than the preoperative score (p < 0.001) and the postoperative VAS score was significantly lower than

the preoperative score (p < 0.001). Removing all disc material anteriorly from the uncinate process to adjacent uncinate process following placement of bone grafts or cages maintains the cervical disc height and prevent kyphosis resulting in indirect foraminal decompression (18). In our study, the postoperative anterior and posterior disc heights were significantly higher than the preoperative heights. Likely as a result of decompression and increased disc distance, the postoperative VAS scores decreased significantly. Regaining the disc height also increases the carrying capacity of the anterior column and decreases the load on the posterior column. In this way, there is a significant reduction in the pain levels felt in the back of the neck. This work shows that, in patients with abnormal cervical sagittal alignment, single-level ACDF in the cervical region provides significant clinical improvement, as documented by radiological improvements early in the postoperative period.

Conclusions

ACDF is a method that can be used to provide cervical sagittal restoration for patients with cervical degeneration. ACDF in cervical disc hernias has a positive effect on correcting cervical lordosis. In our study, a statistically significant difference was found in the results of the radiological and clinical evaluations before and after surgery. Maintaining the normal disc and foramen height of the cervical spine has a significant effect on clinical pain parameters and lordosis. In terms of clinical evaluation, a significant improvement was observed in VAS and JOA values after ACDF. However, the study is limited by its small number of patients and relatively short patient follow-up periods. More patients and longer follow-up times are required to draw more detailed conclusions about the effectiveness and impact of ACDF on cervical sagittal alignment.

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The Effect of Incidental Parathyroidectomy on Hypocalcemia in Patients with Benign and Malignant Thyroid Diseases

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Abstract

Objective: Hypocalcemia is characterized by clinical findings resulting from a decrease in serum calcium (Ca2+) and many etiological factors may cause this condition. The most common cause of postoperative hypocalcemia is hypoparathyroidism and the most frequent complication that occurs after thyroid surgery is hypocalcemia. We aimed to investigate the effect of incidental parathyroidectomy on postoperative early hypocalcemia in patients after thyroid surgery.

Methods: Retrospectively analyzed the data of patients who underwent thyroidectomy in General Surgery Department of Abant Izzet Baysal University between January 2009 and December 2018. Age, gender, serum Ca2+ and parathormone (PTH) levels were obtained. The histopathological results of thyroidectomy materials were grouped as benign (Group 1) and malignant (Group 2).

Results: The study population was consisted of 3841 patients. 3154 patients were in group 1 and 687 patients were in group 2. The postoperative average serum Ca2+ levels of group 1 and 2 were 8.50 mg/dl (6.80-9.80) and 8,50 mg/dl (6.80-9.80), respectively (p=0.996). Postoperative PTH levels of group 1 and 2 were 44.5 ng/l (0-65) and 44.5 ng/l (0-65), respectively (p=0.979). Overall postoperative hypocalcemia (8.4 mg/dL) was observed in 1742 (45.4%) patients. There was no difference in Ca2+ and PTH levels between group 1 and group 2. Incidental parathyroidectomy (%5.4) was performed in 209 of total study population who underwent thyroidectomy. 155 (4.9%) and 54 (7.9%) of the patients in groups 1 and 2, respectively and the incidental parathyroidectomy rates of the groups were statistically different (p=0.02).

Conclusion: We think that incidental parathyroidectomy does not stimulate the development of postoperative hypocalcemia.

Key words: Thyroidectomy, Incidental Parathyroidectomy, Hypocalcemia, Hypoparathyroidism

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Introduction

The regulation of plasma calcium levels is important for cell function, neuronal transmission, membrane stability, bone structure, blood coagulation, and intracellular signaling (1). Hypocalcemia is defined as an ionized serum Ca2+ concentration that falls below the lower limit of the normal range (8.4-10.2 mg/dL). In normal health, approximately 50% of the total serum Ca2+ is in the ionized form in the circulation. The other part of calcium is bound to albumin or complexed with anions such as phosphate (2). Hypocalcemia is characterized by clinical findings resulting from a decrease in serum Ca2+ below a certain level (8.0 mg / dL). Many etiological factors may cause this condition in patients. Parathyroid hormone (PTH) is the main regulator of serum Ca2+ and phosphate homeostasis (1). PTH deficiency, which also occurs in hypoparathyroidism, causes low calcitrol levels. This prevents the absorption of Ca2+ from the intestines (2). The most common cause of postoperative hypocalcemia is hypoparathyroidism. Early hypocalcemia refers to low calcium levels that occur in the first 24 hours postoperatively. This condition is frequently observed after surgical procedures of thyroid and parathyroid glands. The close relationship of the parathyroid glands and the thyroid gland reveals postoperative hypocalcemia in patients with surgical trauma in this region. The most frequent complication that occurs after thyroid surgery is hypocalcemia (3, 4). The rate of temporary hypocalcemia after total thyroidectomy is around 15-30% (5). Six months after surgery, persistent hypocalcemia supports the diagnosis of hypoparathyroidism in the presence of inappropriate or low PTH levels. Hypoparathyroidism is seen in 0.5%-6% after total thyroidectomy (6). This situation occurs when the parathyroid glands are accidentally removed or damaged, or the blood flow of the parathyroid glands is impaired (7). Although hypocalcemia is an expected outcome of parathyroid surgery, it is an undesired consequence of thyroid surgery. In study, we aimed to investigate the effect of incidental parathyroidectomy on postoperative early hypocalcemia in patients after thyroid surgery.

Methods

We retrospectively analyzed the data of patients who underwent thyroidectomy in General Surgery Department of Abant Izzet Baysal University Hospital between January 2009 and December 2018. This study was approved by Haseki Training and Research Hospital ethics committee with permission number 348, dated 02/03/2016. One hundred and twenty patients, who underwent lobectomy and thyroid surgery with parathyroidectomy for hyperparathyroidism, were excluded from the study. We included the patients only who underwent the total thyroidectomy in our study. Patients' laboratory results and pathology reports was obtained from hospital automation system. Since our study was retrospective, consent could not be obtained from the patients.

Age, gender, serum Ca and parathormone (PTH) levels were obtained. Blood samples were taken 24 hours after thyroidectomy for serum calcium and parathyroid hormone levels. All serum Ca2+ and PTH values were measured in the biochemistry laboratory of Abant Izzet Baysal Training and Research Hospital. The normal range of serum Ca level was considered 8.4-10.2 mg/dl, therefore, we grouped patients with a calcium lower than 8.4 mg/dL levels as hypocalcemic. Normal range of PTH was 15-68.3 ng/l and we grouped subjects with a PTH lower than 15 ng/l as hypoparathyroidy. Pathology materials were examined in Abant Izzet Baysal University pathology department. The histopathological results of thyroidectomy materials were grouped as benign (Group 1) and malignant (Group 2). Incidental parathyroidectomies on thyroidectomy materials are determined. The presence or absence of incidental parathyroidectomy in benign and malignant groups and its relationship with hypocalcemia and hypoparathyroidism were investigated.

Statistical analysis

Statistics were carried out by Statistical Package for the Social Sciences (SPSS) software (SPSS 15.0 for Windows, IBM Inc, Chicago, IL, USA). Comparison of the non-homogenously distributed quantitative variables in study groups were done by Mann-Whitney U Test and expressed as median (IQR) and qualitative variables were conducted by Chi-Square test and expressed as n (%). A p value less than 0.05 was considered as statistically significant.

Results

The study population was consisted of 3841 patients. Three thousand one hundred fifty four patients were in group 1 and 687 patients were in group 2. The average ages of both group 1 and 2 were similar 47 years old (p=0.97). Two thousand five hundred thirty eight patients of group 1 were female and 616 patients were male; 551 patients of group 2 were female and 136 patients were male. Gender difference between the groups was not significant (p=0.874). The postoperative average serum Ca

levels of group 1 and 2 were 8.50 mg/dl (6.80-9.80) and 8,50 mg/dl (6.80-9.80), respectively (p=0.996). Postoperative hypocalcemia was observed in 1742 (45.4%) patients and 1430 (45.3%) of them were in group 1; 312(45.4%) of them were in group 2 (p=0.97). The postoperative hypocalcemia patients serum Ca2+ levels of group 1 and 2 were 7.80 mg/dL (6.80-8.30) and 7.80 mg/dL (6.80-7.30), respectively (p=0.929). Postoperative hypoparathyroidism was observed in 660 (20.9%) of group 1 and 143 (20.8%) of group 2 (p=0.94). Postoperative PTH levels of group 1 and 2 were 44.5 ng/l (0-65) and 44.5 ng/l (0-65), respectively (p=0.979).

Incidental parathyroidectomy was performed in 209 (5.4%) of total study population who underwent thyroidectomy. Incidental parathyroidectomy was performed in 155 (4.9%) and 54 (7.9%) of the patients in groups 1 and 2, respectively. The incidental parathyroidectomy rates of the groups were statistically different (p=0.02).

The rate of postoperative hypocalcemia in patients undergoing parathyroidectomy was 45.8% in group 1 and 46.3% in group 2. The difference between the groups was not significantly different (p=0.95) (Table 1).

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Table 1. Demographical and clinical data of study population

		Group 1	Group 2	p
Gender	Female (n,%)	2538(80.5)	551(80.2)	0.874
	Male (n,%)	616(19.5)	136(19.8)	
Average age (years)		47	47	0.968
Postoperative hypocalcemia (n,%)		1430(45.3)	312(45.4)	0.996
Postoperative hypoparathyroidism (n, %)		660(20.9)	143(20.8)	0.979
Incidental parathyroidectomy	Present (n,%)	155(4.9)	54(7.9)	0.02
	Absent (n,%)	2999(95.1)	633(92.1)	

Discussion

The most striking result of present study is that incidental parathyroidectomy does not associate with postoperative hypocalcemia during thyroidectomy procedures. Nowadays, more systematic approach to thyroid gland diseases has developed. The prevalence of the thyroid diseases is still higher in women compared to men. In our study, we found female to male ratio as 4/1. Bilateral total thyroidectomy is currently the most common procedure in thyroid surgery (8). In our study we included only the patients who underwent total thyroidectomy. In our study, we included patients who underwent only total thyroidectomy, in benign patients because malignant patients underwent total thyroidectomy as a surgical method in our clinic. Thus, we formed homogen groups in which the same surgical method was applied. In order to compare the groups in terms of postoperative hypocalcemia, patients who underwent the same surgical method were selected.

It is a fact that every invasive surgery procedure has a certain complication rate. In thyroid surgery, especially surgery for malignancy, complication rates may increase when total thyroidectomy at a level without remnant thyroid tissue is desired. Among the early complications of thyroid surgery, nerve damage, hypocalcemia and bleeding are the most common (9). It is because of the close anatomical location of thyroid and parathyroid glands. In most people there are four parathyroid glands. Incidental removal or deterioration of blood supply of these glands during surgery, are the most common causes of hypocalcemia. However, postoperative hypocalcemia has still multifactorial etiology. The rate of incidental parathyroidectomy in thyroid surgery varies between 5-31% (10, 11). We reported this rate as 5.4%. In a prospective clinical study conducted by Erbil et al. it has been reported that hypoparathyroidism rate was 9% in patients who underwent near-total thyroidectomy and was higher in patients undergoing total thyroidectomy with a rate of 26% (12). In our study the rate of early hypoparathyroidism in patients undergoing total thyroidectomy was 20.9%. Our incidental parathyroidecemia rates in thyroid surgery are similar within the literature. Our early hypoparathyroidism rates after total thyroidectomy are slightly lower than the literature.

One of the important factors in incidental parathyroidectomy is aggressive surgery and central neck dissection in malignant thyroid conditions. In our study, 17.9% of patients undergoing thyroidectomy had malignant disease. It was reported that incidental parathyroidectomy rates and hypocalcemia increased in thyroidectomy operations performed according to the principles of oncological

surgery with the diagnosis of cancer (13-15). In present study, incidental parathyroidectomy in malignant group (7.9%) was more common than benign group (4.9%). In our study, after thyroid surgery which performed for malignancy were founded parathyroidectomy rates high and this condition was compatible with literature. However, in our study unlike the literature, there was not difference between the rates of early hypocalcemia on patients who underwent to thyroid surgery for benign group (45.3%) or malign group (45.4%).

In many studies, postoperative hypocalcemia has been reported in 0.3% to 68% of patients undergoing thyroidectomy (16) and the rate of hypocalcemia in early postoperative period is varies between 5.5% and 6.8% (17). Incidental parathyroidectomy on its own, has limited effect on hypocalcemia and hypoparathyroidism. Sasson et al. (18) reported that parathyroidectomy was not associated with hypocalcemia. Accordingly, we found that incidental parathyroidectomy rate was 5.4% in present study, while early hypoparathyroidism rate was 20.9% and early hypocalcemia rate was 45.9%. Our study had similar results therefore, incidental parathyroidectomy on its own does not appear to be associated postoperative hypocalcemia. Postoperative hypocalsemia can occur when the parathyroid glands are damaged or the parathyroid glands the blood flow of was impaired, therefore the necessary sensitivity should be shown during surgery.

The fact that our study is retrospective is the most important limiting factor. This study emphasizes that hypocalcemia that develops after thyroidectomy cannot be attributed to incidental parathyroidectomy alone.

Conclusion

Incidental parathyroidectomy is seen to a certain extent in thyroidectomy surgeries. This condition is seen more in malignant ones than benign ones. But its effect on early hypocalcemia is not relevant. Therefore, we suggest that incidental parathyroidectomy does not stimulate the development of postoperative hypocalcemia.

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Transfer Learning-Based Classification of Breast Cancer using Ultrasound Images

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Abstract

Objective: One of the most significant cancers impacting the health of women is breast cancer. This study aimed to provide breast cancer classification (benign and malignant) using the transfer learning method on the ultrasound images.

Methods: In the present study, a public imaging dataset was used for the breast cancer classification. Transfer learning technique was implemented for the detection and classification of breast cancer (benign or malignant) based on the ultrasound images. The current research includes data of 150 cases of malignant and 100 normal cases obtained from the Mendeley data. The relevant dataset was partitioned into training (85% of the images) and validation (15% of the images) sets. The present study implemented Teachable Machine (teachablemachine.withgoogle.com) for predicting the benign or malignant of breast cancer tumor based on the ultrasound images.

Results: According to the experimental results, accuracy, sensitivity and specificity with 95% confidence intervals were 0.974 (0.923-1.0), 0.957 (0.781-0.999) and 1 (0.782-1.0), respectively.

Conclusion: The model proposed in this study gave predictions that could be useful to clinicians in classifying breast cancer based on ultrasound images. Thus, this system can be developed in mobile, web, or alternative environments and offered as a computer-aided system for the use of radiologists, pathologists or other healthcare professionals in hospitals.

Key words: Breast Cancer, Classification, Ultrasound Images, Transfer Learning.

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Introduction

One of the most significant cancers impacting the health of women is breast cancer. According to global cancer incidence statistics released by the International Agency for Research on Cancer (GLOBOCAN 2018) of the World Health Organization, there are approximately 2.89 million new cases of breast cancer in women worldwide every year, accounting for 24.2 percent of the total cases of female cancer, ranking first (1).

For patients, early detection, diagnosis, and care also generate several benefits. The conventional breast detection approaches to date include breast self-examination, physician palpation, and medical imaging examination. Mammography, ultrasonography, and magnetic resonance imaging are part of the imaging test. Mammography and ultrasonography are among those widely used for the detection of breast tumors. However, mammography sensitivity and precision are still relatively low. In addition, the diagnostic capacity of mammography is inadequate for dense breast and multicenter lesions in patients, in which reduced accuracy contributes to incorrect or missing diagnoses. Ultrasonography has become an essential component of clinical medical exams since it has the advantages of real-time dynamics. Identifying clinically suspicious breast tumors offers vital imaging information and can be used as a screening tool for early, hidden, and noncalcified breast cancer (2). However, the diagnosis of breast cancer ultrasound images is largely dependent on the diagnostic experience of the doctor. Consequently, misdiagnosis and missed diagnosis are easily caused by the lack of qualified ultrasound physicians, immense workload, and exhaustion. In breast cancer diagnosis, computer-aided diagnostic systems show great promise (1).

In artificial intelligence, machine learning and computer-aided detection applications, deep convolutional neural networks (CNN) have been of great and widespread use. By monitoring their depth and width, the CNN capabilities can be handled where the precision of assumptions is high for nature-based datasets. But, its utility for classification, segmentation, and identification has been witnessed when it comes to medical imaging. However, certain drawbacks are encountered due to the lack of medical training data from large numbers of images and the absence of deep learning models pre-trained on medical data. In order to help solve those drawbacks, transfer learning is used in two ways. First, it is possible to improve the learning of other layers and change the output size of the end layer by using the pre-trained architecture as a feature extractor that minimizes the dimensionality of the dataset by using it as an input to a narrow classifier, and secondly, by fine-tuning by which layers can be defined to freeze. (3).

This study aimed to provide breast cancer classification (benign and malignant) using the transfer learning method on the ultrasound images.

Methods

Public dataset

The current research includes breast cancer ultrasound images of 150 cases of malignant and 100 normal cases obtained from the Mendeley website (4). There is no ground truth for tumor segmentation in this dataset. Thus, manually segmenting tumors in conventional images has been used as a training set for our segmentation model (4).

Transfer learning

A promising machine learning methodology for solving the above problem is transfer learning, which focuses on transferring knowledge across domains. Initially, the concept of transfer learning may originate from educational psychology. As proposed by psychologist C, according to the generalization theory of transfer. H. Judd, the outcome of the generalization of experience is learning to transfer. A person can realize his transition from one personal situation to another if he generalizes his experiences. According to this theory, communication must be accompanied with connections between learning activities. In practice, since both the violin and the piano are musical instruments, and share some common knowledge, a person who knows how to play the violin will be able to play the piano at an easier speed than others (5). These benefits for transfer learning were emphasized in the "Learning to Learn: Knowledge Consolidation and Transfer in Inductive Systems," post-conference workshop at the NeurIPS conference in December 2012. In that workshop, the implications of transfer learning were discussed in detail. More people have been studying transfer learning techniques since that time. A variety of learning, including the learning of lifetime, inductive transfer, multitask learning, and meta-learning have been proposed and applied. Until recently, there was no clear definition of transfer learning (6). There are four types of learning which includes instance based, feature based, parameter based, and relation based (shown in Table 1). Combining different machine learning methods can give better results (6).

Table 1. Four transfer learning method categories (6)

Technique	Explanation
Instance-based	Reweighting or selecting highly similar samples (e.g., molecules) from the source data that match the target data for training support.
Feature-based	Identifying the exact features (e.g., molecular fingerprints) between two different types of molecules. Various techniques can be used to determine target information.
Parameter-based	Transfer of parameters (weights) or prior knowledge learned from source data to target data (e.g., common chemical knowledge).
Relation-based	Building a map between source and target data for relational knowledge.

Inspired by the ability of the human being to transfer knowledge across domains, Transfer Learning aims to leverage knowledge from a domain (known as a source domain) to enhance learning performance or minimize the number of examples of labeling required in a target domain. Not all concepts are always readily transferred or applied successfully. If there is little in common between fields of expertise, there will be no success in the transfer of ideas (5).

Construction of the models

In the present study, transfer learning approach was used for the classification and detection of breast cancer (benign or malignant) based on the ultrasound images. The relevant dataset was partitioned into training (85% of the images) and validation (15% of the images) sets. In order to better understand the model's results, the model was trained and tested using the training data and the test data of the datasets individually. The present study implemented Teachable Machine (teachablemachine.withgoogle.com) for predicting the benign or malignant breast cancer tumor based on the ultrasound images.

Teachable Machine is a web application that allows any user to train their own machine learning models without technical expertise. Since it uses ANN, a simple model is easy to classify the images. Users can add new information to a model and the model can then be trained on top of a previously trained model. The feature extractor was trained to recognize 1000 classes for the portion of the image of Teachable Machine (like a dog, phone, bed, trombone, etc.). This model can be used for identifying new classes created by the user. The data is hidden from the end-users who benefit from simple models with minimal data and training time (7). Teachable Machine offers a training panel for those who prefer more control over model training process. The learning mode advanced could be extended to

include an epoch, batch size, and learning rate. For training image classification models, the default parameters to all-new image classification projects - although most users will never need to tweak them for satisfactory results (7). In the current study, all possible combinations of three hyper-parameters: epoch (1 to 100), batch size (16, 32, 64 and 128), and learning rate (0.01 and 0.00) were tested for best The graphical representation for the various performance metrics of the proposed model is plotted in Figure 1.

performance metrics. Epoch, batch size, and learning rate, were selected to be 50, 16, and 0.001, respectively.

Evaluation metrics

The current research assessed the proposed model regarding many performance metrics calculated from the confusion matrix. Our DTROC software calculates accuracy, sensitivity, specificity, positive/negative predictive values, F1 score, Youden's index, Mathew's correlation coefficient (MCC), and so on (8). We reported all appropriate classification metrics using DTROC software (8) in this study.

Results

From the construction of the proposed approach, the classification matrix of the test samples for the transfer learning model used to classify breast cancer is shown in Table 2.

Table 2. Classification matrix of the test samples for transfer learning model

True \ Prediction	Positive	Negative	Total
Positive	22	0	23
Negative	1	15	15
Total	23	15	38

Accuracy, F1-Score, MCC, prevalence, true prevalence, sensitivity, specificity, diagnostic accuracy, Youden's index, positive predictive value, and negative predictive value for transfer learning model are summarized together with 95% confidence intervals for test samples in Table 3. According to the experimental results, accuracy, sensitivity and specificity with 95% confidence intervals were 0.974 (0.923-1.0), 0.957 (0.781-0.999) and 1 (0.782-1.0), respectively.

The graphical representation for the various performance metrics of the proposed model is plotted in Figure1

Table 3. Performance Metrics of the proposed model on test samples

Metrics	Estimated Value	95% Confidence interval for lower limit	95% Confidence interval for upper limit
Accuracy	0.974	0.923	1.0
F1-Score	0.978	0.931	1.0
MCC	0.947	0.876	1.0
Prevalence	0.579	0.408	0.737
True Prevalence	0.605	0.434	0.76
Sensitivity	0.957	0.781	0.999
Specificity	1.0	0.782	1.0
Diagnostic Accuracy	0.974	0.862	0.999
Youden's index	0.957	0.562	0.999
Positive Predictive Value	1.0	0.846	1.0
Negative Predictive Value	0.938	0.698	0.998
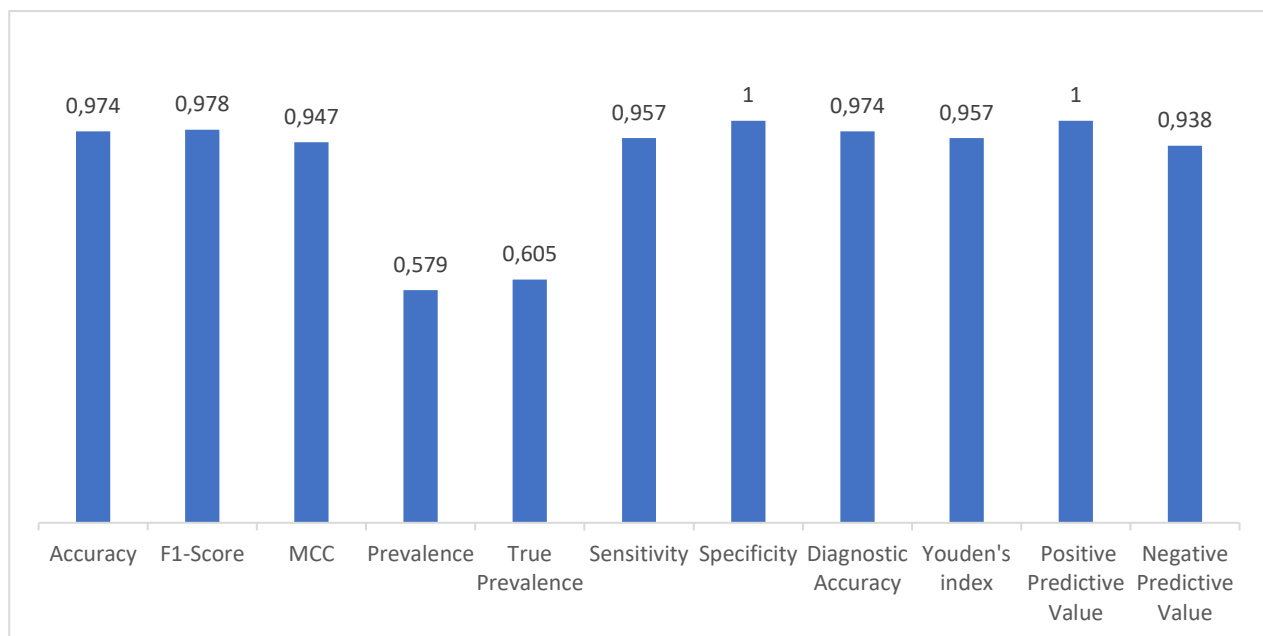
Figure 1. Graphical representation for the various performance metrics of the proposed model

Discussion

Cancer is a disease in which cells multiply, crowding out other cells. One of the most common types of cancer disease is breast cancer. Breast cancer is the most common type of cancer in women. Due to late diagnosis and ignorance of the disease, many women die from breast cancer. Breast cancer detection systems based on female imagery have gained popularity in recent years. In recent years, Deep Learning has attracted a lot of researchers, and a great variety of computer vision applications have appeared in a wide variety of environments. The use of computer programs to help diagnose breast cancer has significantly eased the burden on doctors (9). To construct a computer-aided system for the diagnosis of breast cancer, this study was carried out to construct a model for the classification of breast cancer from ultrasound images using the transfer learning approach.

Transfer learning is defined as transferring to another domain for classification, and feature extraction purposes of knowledge learned earlier in one domain. Transfer learning is performed in the deep learning perspective by using a deep convolutional neural network (CNN) previously trained on a large dataset. The CNN pre-trained model is further trained (fine-tuned) on a new dataset with a smaller number of training images comparable to the previously trained datasets. Transfer learning has recently become popular among deep learning applications because it is faster and easier than training a pre-trained CNN model. We recognize basic special characteristics, like edges, corners, curves, and blobs. Only the last three layers are a major requirement in the practical applications and the remaining stages are applied for classification (10). There has been a large amount of studies in recent years on the widespread use of transfer learning techniques to predict and classify different cancer diseases in medicine and other health fields (11-14). A recent paper suggests a machine learning-based approach to automate breast cancer classification from histopathological images using the deep neural network ResNet-18. The experimental findings on the publicly available BreaKHis dataset show that the approach is promising and efficient, outperforming recent state-of-the-art magnification dependent and magnification independent counterparts by a fair margin (15). Another up-to-date work focuses primarily on the process of transfer learning for detecting breast cancer on datasets of 2D and 3D mammogram images through transfer learning models. Experimental results demonstrated that a 94.3% accuracy is provided by the proposed hybrid transfer learning model (a fusion of Modified VGG and ImageNet), and a precision of 89.8 percent is only provided by the proposed MVGG architecture (16). In a recently published paper, to overcome the existing limitations regarding medical image detection, the model uses real-time data processing augmentation and transfer learning. The results showed that the Xception model trained using transfer learning provided the best results (with 90.86 percent accuracy on the classification task), exceeding the results previously obtained on the BreakHis dataset by the state-of-the-art system. (17). The proposed model in the present study classified benign and malignant breast cancer with very high predictive values on the ultrasound images. A new algorithm developed by a study makes use of deep learning algorithms to detect and classify pathological characteristics of breast cancer. Transferred learning attempts to transfer knowledge from one problem to another problem. Feature Extraction uses pre-trained feature extraction models, namely VGGnet and ResNet, which include features for fully connected layers which classified images into benign or malignant cells. This proposed system has shown to be quite effective, and accuracy rate of the proposed system is very high (18). In another study, a convolutional neural network approach to extract the best features from the Breast Imaging dataset to diagnose breast cancer. The experiments in this study were measured by a magnification factor of 4. (40X, 100X, 200X and 400X). Each image is a picture. The network model was trained and validated on 80% of the work images and 20% of the test images. The system has achieved accuracy, sensitivity, specificity, and AUC values of 95, 97, 90, and 99.36 respectively. Although the number of images in the target data set (BreaKHis) is not large, AlexNet achieved superior results with the four magnification factors (19). The accuracy rate from this study was higher than other studies on the same topic previously described. This result reveals that the proposed architecture in this study is very useful for predicting benign or malignant breast cancer and can be used by clinicians as a computer-aided diagnosis system. However, in order to test the external validity of the predictions of the proposed classification model, more ultrasound images of breast cancer are necessary for achieving robust results.

There was a class imbalance problem for the breast cancer ultrasound images used in this study. Yet, performance metrics of the proposed transfer learning model for classifying breast cancer may not have been affected by the class imbalance problem, and quite high estimation results (e.g., F1-

Score=0.978; MCC=0.947) were obtained from this study. In order to solve the class imbalance issue not implemented in this study, various techniques have been proposed for image processing and classification processes (20-22). If the desired level of classification results is not obtained and there is a class imbalance, it may be very useful to apply hyperparameter optimization and similar approaches to solve the class imbalance in such cases.

Conclusions

In summary, the model proposed in this study gave predictions that could be useful to clinicians in classifying breast cancer based on ultrasound images. Thus, this system can be developed in mobile, web, or alternative environments and offered as a computer-aided system for the use of radiologists, pathologists, or other healthcare professionals in hospitals

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RESEARCH ARTICLE

Effect of Anesthesia Methods During Elective Cesareans on Neonates: Ordu Province Example

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Abstract

Objective: To research the short-term effects on neonates of different anesthesia methods administered for elective cesareans.

Methods: Data obtained from files and electronic medical records of 157 singleton cesarean cases and neonates from January 2018 to December 2019 were retrospectively analyzed and 6 cases were excluded from the study. A total of 151 cases were divided into general anesthesia-propofol (n=30), spinal (n=100) and general anesthesia-pentothal (n=21) groups.

Results: A total of 151 cesarean cases that meet the inclusion criteria in the date interval of the study were assessed. Of cases, 100 (66%) were in the spinal anesthesia group, 30 (20%) were in the general anesthesia-propofol group and 21 (14%) were in the general anesthesia-pentothal group. There was no significant difference between the study groups in terms of demographic data. The umbilical cord pCO_2 value was significantly low in the spinal anesthesia group (43.60±5.52) compared to the general-pentothal group (47.38±5.71). The umbilical cord HCO_3 value was lower in the spinal anesthesia group (22.69±1.62) compared to the general-pentothal (23.48±1.53) and general-propofol groups (23.49±1.83). There was a significant variation in postnatal treatment types according to anesthesia method (p=0.012). The rate not requiring treatment was lowest in the general-propofol group (46.7%), while the rate of balloon-valve mask use (46.7%) was highest compared to the other groups. In terms of 5th minute Apgar scores, there was a significant difference between the groups (p=0.024). Patients in the general-propofol group had significantly lower 5th minute Apgar scores compared to patients in the spinal group.

Conclusion: The balloon-valve mask rate was highest for those with propofol general anesthesia. Additionally, it was identified that neonates in both general anesthesia groups had higher neonatal intensive care unit requirements compared to the spinal anesthesia group.

Key words: Cesarean section, neonatal outcome, pentothal, propofol, spinal anesthesia

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Introduction

For cesareans, the use of regional anesthesia (RA: spinal, epidural and combined spinal-epidural) methods as alternatives to general anesthesia (GA) methods has increased in recent years (1). Both anesthesia methods have advantages and disadvantages, with factors like the urgency of the cesarean, degree, presence of comorbid health problems, patient choice, anesthesiologist or surgeon choice and experience affecting the determination of anesthetic technique to be used. Advantages of GA are rapid induction, less hypotension, preserved cardiovascular balance, and better respiratory tract and ventilation control, while disadvantages are aspiration of stomach contents, intubation difficulty and respiratory depression of the neonate. Significant advantages of regional anesthesia are the mother being awake, seeing the neonate at birth, being able to breastfeed in the early period and lack of respiratory depression in the neonate (2). Disadvantages include headache in the mother linked to cerebrospinal fluid (CSF) leak after lumbar puncture, possibility of nausea-vomiting and limited duration of effect (3). Additionally, the sympathetic blockage induced by RA reduces uteroplacental perfusion and intervillous blood flow causing fetal acidemia via hypotension (4). Differences in choice of anesthetic method have caused an increase in research investigating the effects of these methods on fetus and neonate in recent years (5,6).

Apgar scoring is commonly used to rapidly assess the clinical status of neonates. Umbilical cord blood gas values are accepted as a more reliable marker of fetal oxygenation and neonatal clinical status (7).

The aim of the study is to assess the Apgar scores and umbilical cord blood gas, hemogram, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) values, with neonate urine and meconium excretion times for cases undergoing cesarean administered GA with propofol or thiopental sodium or spinal anesthesia (SA).

Methods

The study began after receiving permission from Ordu University Clinical Research Ethics Committee. Cases giving birth with elective cesarean indications from January 2018 to December 2019 in the Ministry of Health Ordu University Education and Research Hospital Obstetrics and Gynecology Clinic, aged from 18-45 years, with pregnancy week ≥37, singleton pregnancy and no chronic disease or medication use history were assessed. All cesarean interventions were performed by experienced obstetricians. In terms of neonates, infants born electively, singleton, at term, with birth weight above 2500 g, and no fetal anomalies, growth retardation, meconium or amniotic fluid aspiration were included in the study. Patient files and automation records were retrospectively assessed. From a total of 157 cases, 6 had missing data and were excluded. The remaining 151 cases were analyzed. Cases were divided into three groups according to anesthetic method as general anesthesia-propofol (G-propofol, n=30), general anesthesia-pentothal (G-pentothal, n=21), and spinal anesthesia (SA, n=100).

Patients undergoing elective cesareans in our hospital are primarily recommended central regional blocks (spinal and epidural anesthesia), patients who do not choose these are administered GA. All patients undergoing elective cesarean surgery have preoperative anesthesia assessment performed before entering the operating room. Oral intake is stopped 6-8 hours preoperatively. Before entering the operating room, patients are administered 15 ml/kg intravenous (iv) balanced crystalloid solution. After preoperative checks, patients are prepared according to the anesthesia type chosen. Those choosing regional anesthesia mainly choose spinal anesthesia. In our spinal anesthesia practice, after routine monitoring, patients are given oxygen support (mask/nasal cannula) and then a 25 gauge (G) quincke spinal needle is used to administer 10-13.5 mg hyperbaric bupivacaine in the lumbar 2-3 and 3-4 interval. Patients administered spinal anesthesia are given 5-10 mg ephedrine (iv) if systolic arterial pressure is <100 mmHg in spite of iv fluid treatment to prevent maternal hypotension. After routine monitoring and 3 minutes of preoxygenation, when the surgery team is ready for the operation, general anesthesia is administered with iv 2-2.5 mg/kg propofol or 4-5 mg/kg thiopental sodium. After administering 0.6-1 mg/kg rocuronium bromide muscle relaxant, and then endotracheal intubation, maintenance is provided by inhalation of 50% O2 + 48-49% N2O and 1-2% sevoflurane.

Demographic data (maternal age, pregnancy week, birth weight), preoperative hemoglobin values, skin incision-birth duration, 1st and 5th minute Apgar scores of the neonate (assessed by pediatric health and diseases specialist), blood gases, AST and ALT in samples taken from the umbilical cord, full blood counts, neonatal balloon-valve-mask (BVM), intubation and neonatal intensive care unit (NICU) requirements in the first 24 hours (those with low Apgar score, those with respiratory distress, those with low blood glucose) and urination and meconium excretion times were retrospectively recorded from patient files and the hospital data system.

Findings obtained in the study had statistical analysis performed using SPSS ("Statistical Package for Social Sciences") v26 (IBM, Armonk, NY, USA). Comparison of groups used one-way ANOVA for continuous variables and Kruskal-Wallis test for score variables. Analysis of categoric variables used the chi-square test. If expected frequencies on the chi-square test were ≥5, the Pearson value was calculated; if <5, the likelihood ratio value was calculated. Statistical significance level was taken as 5%.

Statistical analysis

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Results

A total of 151 cesarean cases that meet the inclusion criteria were assessed in the date interval for the study. Of cases, 100 were in the SA group (66%), 30 in the G-propofol group (20%) and 21 in the G-pentothal group (14%). There were no significant differences between the study groups in terms of demographic data (p>0.05) (Table 1).

The umbilical cord blood gas, ALT and AST values are given in Table 2. Umbilical cord pCO_2 values were statistically lower in the SA group (43.60±5.52) compared to the G-pentothal group (47.38±5.71) (p<0.05). Umbilical HCO_3 values in the SA group (22.69±1.62) were statistically lower compared to both the G-pentothal (23.48±1.53) and G-propofol (23.49±1.83) groups (p<0.05). However, there was no statistical differences between the groups in terms of umbilical cord pH values (p>0.05) and as pH values were in the normal interval they

were not accepted as clinically significant (Table 2). There were no statistically significant differences between the groups in terms of AST and ALT (p>0.05).

The distribution of postnatal treatment, urine and meconium times for neonates according to group are given in Table 3. There was a significant change in postnatal treatment types according to anesthesia method (p=0.012). The rate not requiring treatment in the G-propofol group (46.7%) was lower compared to the SA and G-pentothal groups (79% and 81%, respectively); while the BVM rate (46.7%) was higher compared to the other groups (18% and 9.5%, respectively). The NICU requirements in the G-pentothal and G-propofol groups (9.5% and 3.3%, respectively) were higher compared to the spinal group (2%). One neonate in each of the G-propofol and SA groups required endotracheal intubation (ETI) and mechanical ventilation (MV).

There was no difference between the groups in terms of urine and meconium excretion times (p>0.05). In all groups, nearly three quarters of neonates excreted urine and meconium within the first 12 hours postnatal.

Descriptive statistical values for the 1st and 5th minute Apgar scores in the groups are given in Table 4. There were no significant differences between the groups in terms of 1st minute Apgar scores (p>0.05). In terms of 5th minute Apgar scores, there was a significant difference between the groups (p<0.05). Patients in the G-propofol group had significantly lower 5th minute Apgar scores compared to patients in the SA group (p=0.024). The 5th minute Apgar scores for patients in the G-pentothal groups were not statistically different to patients in both the G-propofol and SA groups (p>0.05).

Table 1. Demographic data in groups

	G-Propofol (n=30)		SA (n=100)		G-Pentotal (n=21)		p
	Mean	SD	Mean	SD	Mean	SD	
Maternal age at delivery (years)	29.20	5.77	30.69	5.00	29.81	5.28	0.355
Preoperative hemoglobin (g/100 ml)	11.62	1.41	12.04	1.21	11.60	1.07	0.144
Gestational age at delivery (weeks)	38.37	0.76	38.69	0.85	38.62	0.67	0.163
Birth weight (gram)	3512.67	499.02	3427.60	441.23	3492.86	545.21	0.628
Surgical time (seconds)	226.33	63.71	264.30	322.42	227.19	55.32	0.714

One-way ANOVA

Table 2. Descriptive statistics for cord blood parameters of neonates

	G-Propofol (n=30)		SA (n=100)		G-Pentotal (n=21)		p
	Mean	SD	Mean	SD	Mean	SD	
Umbilical cord							
pH	7.32	0.03	7.33	0.04	7.32	0.04	0.210
pCO2	45.86 [ab]	4.91	43.60 [b]	5.52	47.38 [a]	5.71	0.006**
HCO3	23.49 [a]	1.83	22.69 [b]	1.62	23.48 [a]	1.53	0.023*
AST (IU/l)	26.10	8.11	29.29	13.48	28.67	10.34	0.456
ALT (IU/l)	9.70	3.43	10.72	5.40	11.38	4.13	0.452

One-way ANOVA
*:<0.05,**:<0.01
AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

Table 3. Distribution according to group for treatment, urine and excretion times among neonates after birth

		Anesthesia type				p
		G-Propofol	SA	G-Pentotal	Total	
Postpartum treatment	No	14(46.7%)	79(79.0%)	17(81.0%)	110(72.8%)	0.012*
	BVM	14(46.7%)	18(18.0%)	2(9.5%)	34(22.5%)	
	ETI	1(3.3%)	1(1.0%)	0(0.0%)	2(1.3%)	
	NICU	1(3.3%)	2(2.0%)	2(9.5%)	5(3.3%)	
Time to urinate (hours)	0-12	30(100.0%)	96(96.0%)	19(90.5%)	145(96.0%)	0.160
	13-24	0(0.0%)	4(4.0%)	2(9.5%)	6(4.0%)	
Meconium extraction time (hours)	0-12	25(83.3%)	78(78.0%)	16(76.2%)	119(78.8%)	0.913
	13-24	5(16.7%)	20(20.0%)	5(23.8%)	30(19.9%)	
	25-36	0(0.0%)	1(1.0%)	0(0.0%)	1(0.7%)	
	37-48	0(0.0%)	1(1.0%)	0(0.0%)	1(0.7%)	

Chi-square test (Likelihood Ratio)
*:<0.05
BVM: Balloon-valve mask ETI: Endotracheal intubation NICU: Neonatal intensive care unit

Table 4. 1st and 5th minute Apgar scores in the groups

	G-Propofol (n=30)				SA (n=100)				G-Pentotal (n=21)				p
	Mean	Median	IQR	Mean Rank	Mean	Median	IQR	MeanRank	Mean	Median	IQR	MeanRank	
1-min Apgar	7.90	8.00	0.0	64.48	8.26	8.00	1.0	80.79	8.05	8.00	0.5	69.64	0.081
5-min Apgar	8.87	9.00	1.0	58.60[b]	9.24	9.00	1.0	80.80[a]	9.19	9.00	1.0	78.00[ab]	0.024*

Kruskal-Wallis test, *:<0.05

Discussion

Spinal anesthesia generally is more practical and more reliable for the mother compared to other techniques and as a result is used widely. Similarly, for cesareans SA is assumed to be better than GA for neonates. The basis of this assumption is that GA lowers the Apgar score, maternal hypotension that may occur with SA can be controlled by suitable vasopressors and the low medication dose required for SA induction does not cause systemic effects in neonates (8). Patients with contraindications for RA are administered GA for cesareans; at this point, the greatest concern is the effect of anesthetic agents on the neonates (9).

The Apgar score, developed by Virginia Apgar in 1952, ensures rapid and practical assessment of the clinical status of neonates. This scoring, performed in the 1st and 5th minutes and rarely 10th minute after birth, examines the neonate's cardiac rhythm, respiration, muscle tone, reflex response and skin color (10). A study by Mueller et al. investigating the effects of regional (spinal and epidural) and GA on neonates found the 5th minute Apgar scores were higher in the RA groups (both spinal and epidural groups) compared to the GA group (11). Sener et al. in studies investigating the effects of general and epidural anesthesia on fetal well-being reported the 1st minute Apgar scores were high in the epidural anesthesia group, while 5th minute Apgar scores were similar in both groups (12). Studies by Dyer et al. and Hodgson et al. researched the effect of spinal anesthesia and GA on Apgar scores and in conclusion, found the 1st minute Apgar scores were lower in the GA groups and 5th minute Apgar scores were similar in both groups (13,14). A study by Kavak et al. found the 1st and 5th minute Apgar scores were similar in spinal and general anesthesia groups (15). This may be due to the use of perioperative fluid and ephedrine in regional anesthesia to prevent maternal hypotension. Cochrane database analyses showed the 5th minute Apgar scores performed to determine resuscitation response and asphyxia were similar in anesthesia groups. Thus, when determination of asphyxia is required, it was concluded that one anesthetic method was not superior to others (16).

In our study, there was no difference between the groups in terms of 1st minute Apgar scores. In the G-pentothal group, the 5th minute Apgar score was not statistically different compared to the G-propofol and spinal groups. The general-propofol group had 5th minute Apgar score that was statistically significantly low compared to the SA group (p<0.024). However, all groups had mean Apgar score above 8 so this was not clinically significant.

Studies in the past have stated there is a hypotension risk caused by sympathetic blockage in RA and the use of RA techniques should be avoided due to the dangers of the vasopressor agents or large volumes of fluids required to correct this (11). Due to this concern, a study by Roberts et al. in 1995 found that RA was associated with fetal academia (17). Studies about this topic increased due to the diversity of anesthetic methods administered and anesthetic agents chosen. Umbilical cord blood pH and acid-base balance are the most accurate markers of neonatal well-being. If there is no metabolic acidosis in umbilical cord blood, asphyxia is not possible and if cord blood gas pH is lower than 7.20 it is assessed as pathologic acidosis (18). In studies where the primary focus point is adjustment of the fetus and maternal variables (like anesthesia studies), no large difference was observed between pH values of the umbilical artery (UA) and umbilical vein (UV) and both are accepted as directly related to the acid-base balance (8).

A study by Gunusen et al. in the last 10 years did not identify a difference between mean pH values of the UA and UV between the groups (19). A study by Petropolus et al. found the UA pH was higher in the GA group compared to the combined spinal-epidural group; however, fetal acidemia was not identified in any group (1). A 2014 study by Kirecci et al. found umbilical cord pH value was low in the GA group; however, they stated this was not clinically significant as pH values were in normal intervals in the general and spinal anesthesia groups (6). The probable reason for this situation is effect of the

general anesthetic on the infant. In our study, the umbilical cord pCO2 values were lower in the spinal group compared to the G-pentothal group and the HCO3 values were lower in the spinal group compared to both the G-pentothal and G-propofol groups (p<0.05). However, this was not assessed as clinically significant due to pCO2 and HCO3 values being within the normal range and the lack of significant difference between the three groups in terms of umbilical cord mean pH values.

To exclude perinatal stress, apart from Apgar and cord blood gas, there are studies assessing some enzymes and hormones. Of these, Kavak et al. studied ALT, AST, total cortisol and creatine kinase enzymes in cord blood and did not find statistically significant differences in enzyme values in the general and spinal anesthesia groups (15). Another similar study found ALT and total cortisol values were statistically significantly high in the GA group (20). A 2014 study by Karadogan et al. found the 4th hour ALT value in neonates was significantly high in cases with epidural anesthesia compared to other groups (21). In our study, there were no statistically significant differences found between groups in terms of cord blood AST and ALT values. Although there was a statistically significant difference in biochemical test results in some studies, the results were found to be within normal limits. Therefore, we believe there is a need to perform more studies to interpret whether or not there are differences between groups in terms of enzyme values.

A study assessing the postnatal BVM, ETI or NICU requirements of neonates found that no neonate in the general and spinal anesthesia groups required BVM or ETI (6). A study of 230 cases by Petropolus et al. similarly stated there was no difference between general, epidural and spinal-epidural anesthesia groups in terms of mask ventilation and NICU admissions (1). Another study found a significantly high number of neonates required BVM in the GA group; however, there was no difference in terms of ETI and NICU requirements (19). In our study, BVM use was highest in the G-propofol group. Additionally, both GA groups (propofol and pentothal) had higher NICU admission rates compared to the spinal anesthesia group.

The sympathetic nervous system has physiological effects like reducing the motility and secretions in the gastrointestinal system, relaxing the bladder detrusor muscle and causing contractions of the internal sphincter (22). Hypotension related to sympathetic blockage caused by regional anesthesia may affect short-term outcomes in neonates by disrupting uteroplacental perfusion (23). In our

literature screening, we did not encounter a study investigating the effects of the anesthesia method administered to cesarean cases on neonatal urine and meconium excretion times. In our study, there was no difference between the groups in terms of neonatal urine and meconium excretion times (p>0.05). Nearly three-quarters of neonates in all groups had urine and meconium excretion within 12 hours of birth.

Conclusions

All three anesthesia methods for elective cesareans do not have much superiority to each other in terms of short-term effects on the neonate. However, due to the higher rate of BVM and NICU requirements in GA groups, we think it is more appropriate to choose SA for pregnant cases in terms of neonatal health

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Characteristics of Child and Adolescent Psychiatry Consultations at a University Hospital and Accuracy Rates of Recognition of Childhood Psychiatric Diseases by Nonpsychiatry Specialists

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Abstract
Objective: Physical and mental health are closely related. Psychiatric problems increase in the presence of a physical illness. Consultation liaison psychiatry provides a combination of medical treatment, psychiatric treatment, and psychosocial care to patients when necessary. In this study, we aimed to examine the consultation-liaison services provided by the child and adolescent psychiatry department of a university hospital within two years and to examine the accuracy rates of recognition of childhood psychiatric diseases nonpsychiatry specialists.
Methods: Consultations for pediatric patients from other clinics were screened retrospectively at Gaziantep University Hospital between January 1st, 2018, and December 31st, 2019. Data relating to the departments requesting a consultation, reasons for consultation, diagnoses made by children and adolescent psychiatrists, and psychiatric treatments were evaluated.
Results: A child and adolescent psychiatry consultations were requested for 290 children over a two-year period. The average age of the cases for whom consultation was requested was 12.1, and 61% of the cases were female. The most common reason for consultation was suicide attempts (26.6%). The most common mental disorder was depression (19%), while the most common intervention was psychoeducation (48.9%). The disorders with the highest diagnostic accuracy were delirium (100%), autism (100%), substance use disorders (80%), and mental disability (70%), while the disorders with the lowest diagnostic accuracy were psychotic disorder (0%), depression (%18,2) and anxiety disorder (22.2%).
Conclusion: Mental disorders are common in children with physical illnesses, but the rate of correct recognition of childhood mental disorders by other physicians is low. The high rates of psychiatric disorders highlight the importance of educating physicians that work with children about childhood mental problems and cooperation between child psychiatrists and other physicians.
Key words: Psychiatry, Child, Consultation

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Introduction

Until recently, the general medical approach focused on the biomedical model in which physical health was prioritized, whereas the currently accepted approach gives weight to the biopsychosocial model that treats the person as a whole in terms of physical, spiritual and social aspects (1). As a holistic approach, the biopsychosocial model emphasizes that all biological, psychological, environmental and sociocultural factors should be taken into account while treating the patient. Along the same lines, World Health Organization (WHO) defines the state of being healthy as "a state of complete physical, mental and social well-being", which is a definition compatible with the biopsychosocial model (2).

Consultation-liaison psychiatry (CLP) is a branch of psychiatry that is based on the biopsychosocial model, which concerns with the emotional and behavioral assessment and treatment of patients referred by non-psychiatric physicians, providing psychiatric treatment and psychosocial care simultaneously with the medical treatment to patients (3). Previously conducted studies established that the hospitalization rates were higher in cases with both mental health disorders and physical illnesses compared to the cases with either physical illness or mental illness (4). Similarly, many studies have reported that the prognosis was worsened, the duration of hospital stay was prolonged, and the cost of the disease to the healthcare system was higher in cases with a psychiatric disorder as comorbidity (5-8). Additionally, psychiatric consultation has been shown to improve outcomes in inpatients (9, 10).

Childhood mental health problems are increasing gradually. A national survey study recently conducted in U.S. revealed that approximately 17% of children have a mental health problem (11), whereas a study conducted nationwide in Turkey reported that 37.6% of children have mental health problems and that 17% of children have a psychopathology impairing their functionality (12). It is a known fact that the incidence of psychopathology is higher in children and adolescents with medical diseases (13). Despite the high prevalence of psychiatric diseases in childhood, the high rates of psychiatric comorbidities in physical diseases, and the fact that psychiatric diseases increase mortality and morbidity, psychiatric diseases are still not recognized and treated sufficiently (14).

Many studies have been conducted in Turkey investigating the psychiatric consultations, yet the number of studies investigating the rates of accurate prediagnoses made for the psychiatric diseases by non-psychiatric physicians is quite limited (15-19). A thorough review of the literature revealed only a few studies conducted on the rates of accurate recognition of adult psychiatric diseases (20-22). Still, it did not reveal even one study conducted on the rates of accurate recognition of child and adolescent psychiatric diseases.

In view of the foregoing, in this study, it was aimed to investigate the psychiatric consultation services provided by Gaziantep University Faculty of Medicine Department of Child and Adolescent Psychiatry in the last two years and the rates of accurate recognition of child psychiatric diseases by non-psychiatric physicians.

Methods

This study was carried out in accordance with the principles of the Declaration of Helsinki and was approved by the Gaziantep University Clinical Research Ethics Committee in advance (Date: 22.06.2020, decision number: 202).

Selection and Characterization of Cases

The patient files regarding the psychiatric consultations requested from Gaziantep University Faculty of Medicine Department of Child and Adolescent Psychiatry between January 1st, 2018 and December 31st, 2019, were reviewed retrospectively. Those with missing information in the file records were excluded from the study. All consultations requested for children aged 0-18 were included in the study. Diagnostic assessments were made based on the evaluation of the interviews conducted with children and adolescents for whom psychiatric consultations were requested, family members of these children and adolescents, and the healthcare professionals working in the department that requested the psychiatric consultations, in accordance with the diagnostic criteria set forth in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

Statistical analysis

The data obtained were evaluated statistically. Descriptive statistics of the obtained data were made. SPSS 22.0 package program was used for analysis (IBM Corporation; Armonk, NY, USA), and $P<0.05$ was considered significant. The sociodemographic characteristics of the children and adolescents, the departments which requested the psychiatric consultations, the reasons for requesting the psychiatric consultations, the psychiatric diagnoses made as a result of the consultations, and the interventions performed by the child psychiatrist were analyzed by descriptive statistics (median, standart deviation, frequency distribution).

Diagnostic accuracy in psychiatric consultations was calculated by percantages of the diagnoses confirmed by the psychiatrist to all consultations requested for that diagnosis.

Results

It was determined that a child psychiatry consultation was requested from various departments for a total of 290 children and adolescents between January 1st, 2018 and December 31st, 2019. During this period, the number of children aged 0-18 who applied to the clinic subject to this study was 134,030 in total, and child psychiatry consultations were requested for 0.002% of these patients. The number of patients that received inpatient treatment was 10,491 and child psychiatry consultations were requested for 0.01% of these patients, whereas child psychiatry consultations were requested for 0.001% of the patients that have been receiving outpatient treatment. The mean age of the children for whom psychiatric consultations were requested was calculated as 12.1 ± 3.8 (2 to 18). One hundred seventy-seven of these cases were female (61.03%), and 113 (38.97%) of them were male. 73.8% (n = 214) of the children and adolescents who were provided psychiatric consultation services were found to have previously applied to a child psychiatry outpatient clinic, whereas the remaining 26.2% (n = 76) of the children and adolescents were determined to have received psychiatric consultation services for the first time.

The clinic which requested the highest rate (43.7%) of psychiatric consultations was the pediatric inpatient service, followed by the emergency service, pediatric outpatient clinic, and intensive care anesthesia service in descending order (Table-1).

The most common reason (n = 77) for requesting psychiatric consultations was suicide attempt, followed by agitation, depressive symptoms, non-compliance to treatment, anxiety symptoms, somatic complaints, psychotic symptoms, sleep and eating problems, in descending order (Table-2).

The most common diagnoses made following the assessment of the CLP team was depression (21.9%), followed by adjustment disorder (15.8%), mental disability (14.3%), anxiety disorders (11.2%) and attention deficit hyperactivity disorder (7.7%), in descending order (Table-3).

There was no prediagnosis in the consultation notes of 70% of the patients. The most common prediagnoses indicated in the consultation notes that include prediagnoses were depression (7.6%), anxiety disorder (5.9%), psychosis (4.5%), and mental disability (3.4%), respectively. Comparison of the prediagnoses with the final diagnoses made based on the psychiatric assessment revealed that autism, delirium, substance use disorders and mental disability were the disorders with the highest rates of accurate prediagnoses as compared to the final diagnoses, whereas that psychosis, depression, and anxiety were the disorders with the highest rates of misdiagnoses made during the prediagnosis stage as compared to the final diagnoses (Table-4).

In terms of psychiatric interventions, following up of the patients by providing them psychoeducation was determined to be the most common (48.9%) form of intervention. Other commonly used treatment options included the use of selective serotonin reuptake inhibitors (SSRI), antipsychotics, benzodiazepines, and stimulants, in descending order. No intervention was deemed necessary in 13.4% of the patients (Table-5).

Table-1: Clinics That requested psychiatric consultations

Clinic	Number*	%
Pediatric Inpatient Service	127	43,7
Emergency Service	116	40,0
Pediatric Outpatient Clinic	39	13,4
Intensive Care Anesthesia Service	8	2,7

* Number of patients for whom a non-psychiatric physician requested psychiatric consultations

Table-2: Reasons indicated for psychiatric consultation requests

Reasons	Number*	%
Suicide Attempt	77	26,6
Agitation	35	12,1
Depressive Symptoms	22	7,9
Non-compliance to Treatment	19	6,6
Anxiety Symptoms	18	5,9
Somatic Complaints	17	5,9
Psychotic Symptoms (Hallucinations / Delusions)	15	5,2
Sleeping and Eating Problems	10	3,4
Mental Retardation Symptoms	10	3,4
Conversive Symptoms	8	2,8
Side Effects Caused by Psychiatric Medications	7	2,4
Presence of a History of Psychiatric Disorders	5	1,7
Alcohol/Substance Use	5	1,7
Attention Deficit Hyperactivity Disorder Symptoms	5	1,7
Other Reasons	37	12,8

* Number of patients for whom a non-psychiatric physician requested psychiatric consultations

Table-3: Final diagnoses made on the basis of the requested consultations

Type of Diagnoses	Number*	%
Depression	43	21,9
Adjustment Disorder	31	15,8
Attention Deficit Hyperactivity Disorder	15	7,7
Mental Disability	28	14,3
Anxiety Disorder	22	11,2
Conversion	14	7,1
Delirium	10	5,1
Autism Spectrum Disorder	7	3,6
Substance Use Disorder	6	3,1
Psychosis	3	1,5
Bipolar Disorder	7	3,6
Obsessive Compulsive Disorder	5	2,6
Dystonia	2	1,0
Eating Disorder	3	1,5

* Number of patients for whom a non-psychiatric physician requested psychiatric consultations

Table-4: Rates of accuracies of the prediagnoses indicated by the non-psychiatric physicians in the consultation notes

	Prediagnoses Made by the Non-Psychiatric Physicians	Prediagnoses Made by the Child Psychiatrists	Rates of the Prediagnoses Confirmed
	n*	n**	%
Depression	22	4	18,2
Anxiety Disorder	18	4	22,2
Psychotic Disorder	13	0	0
Mental Disability	10	7	70
Conversion	8	4	50
Substance Use Disorder	5	4	80
ADHD	5	2	40
Delirium	2	2	100
Autism	2	2	100

ADHD: Attention Deficit Hyperactivity Disorder
*Number of patients for whom non-psychiatric physicians made prediagnoses
**Number of patients, whose prediagnoses were confirmed by the child psychiatrists

Table-5. Interventions performed by the child and adolescent psychiatrists

Types of Interventions/Medications	Number*	%
Patients for whom no intervention was deemed necessary	38	13,4
Psychoeducation and follow-up	139	48,9
SSRIs	48	16,9
Antipsychotics	44	15,5
Benzodiazepines	9	3,2
Methylphenidate	6	2,1

SSRI: Selective Serotonin Reuptake İnhibitors
* Number of patients for whom psychiatric consultations were requested by a non-psychiatric physician

Discussion

Despite the fact that the evidence indicating the importance of CLP is growing, it is noteworthy that the rates of patients for whom child psychiatry consultations were requested have been quite low in Turkey, as it can be seen from the low rates of patients that have been receiving inpatient treatment and for whom child psychiatry consultations were requested, which were reported to be between 1.2% and 2.3% (16-18, 23). In comparison, in this study, it was found that child and adolescent psychiatry consultations were requested only for 0.01% of the children that have been receiving inpatient treatment and 0.001% of the children that have been receiving outpatient treatment. These rates were lower than the respective rates reported in the above-mentioned studies conducted in Turkey, and substantially lower than the rates of patients that have been receiving inpatient treatment abroad and for whom child psychiatry consultations were requested, which were reported to be between 27% and 66% (24, 25). It has been suggested that the low rate of child psychiatry consultations in Turkey may be due to several factors such as physicians' difficulties in recognizing mental symptoms, the fact that the physicians do not have enough knowledge about the effect of psychiatric comorbidities on medical pathology, the fact that the physicians do not think that psychiatric consultations will be beneficial, non-existence of effective pediatric CLP teams in hospitals and absence of effective communication and collaborative approach between the CLP teams and other physicians (15, 16).

Organization of awareness-raising trainings by CLP teams for non-psychiatric physicians and holding meetings where complex cases are discussed with a multidisciplinary perspective by psychiatrists and non-psychiatric physicians in psychiatry clinics can raise awareness about the issue and contribute to the more effective use of CLP services. As a matter of fact, the results of relevant studies available in the literature indicate that cooperation among physicians and consultations have increased as a result of the development and implementation of new models that provide effective use of CLP (26, 27).

In this study, only patients for whom the child and adolescent psychiatric consultations were requested in writing could be evaluated. It is also known that there are cases frequently encountered in outpatient clinics where a psychiatric consultation is not officially requested yet the patients are verbally recommended to apply to the psychiatry/child psychiatry clinic, especially in cases when the complaints of the patients cannot be explained by a medical condition. Taking into consideration the prejudice against the psychiatric specializations in the Turkish society, it would not be inaccurate to make a prediction that some of the patients would leave the health centers without applying to psychiatry clinics after such recommendations communicated verbally, which might be one of the reasons for the low rate of psychiatric consultation requests found in this study as well as in other studies conducted in Turkey. For this reason, it is essential to seek official consultations rather than making verbal recommendations to that effect, in order to ensure that the patients are assessed psychiatrically and receive the treatments they need.

In this study, the mean age of the children and adolescents for whom a psychiatric consultation was requested was calculated as 12. The rate of psychiatric consultations requested for girls (61.03%) was significantly higher than the rate of psychiatric consultations requested for boys, which is a compatible finding with the results reported in the literature, considering that the reported rates of psychiatric consultations requested for girls' range between 54% and 70% (18, 23, 28-32). It is known that psychiatric referrals are more common in boys in the pre-adolescence period, however that the prevalence of psychopathologies increases in girls as opposed to boys beginning with early adolescence

(33). It has been suggested that the strengthening in response to stress with the effect of cortisol and estrogen the levels of which increase with puberty, makes adolescent girls more sensitive to psychological stress and internalizing disorders (34). Thus, the fact that psychiatric consultations are requested more for adolescent girls compared to the adolescent boys may be attributed to the increase in the psychopathology observed in girls during the adolescence period.

In this study, the most common reason for requesting psychiatric consultations was found to be suicide attempt, followed by agitation and depressive symptoms. Similarly, a review of the national literature revealed that the most common reasons submitted for requesting psychiatric consultations were suicidal attempts (16, 31, 35) and depressive symptoms (15, 16, 18). On the other hand, it was reported in several studies that the most common reasons submitted for requesting psychiatric consultations internationally were behavioral problems and hyperactivity (25, 36). In a survey study including 64 independent pediatric CLP services, Shaw et al. (37) reported that the most common reasons for requesting psychiatric consultations were suicide risk assessment, presence of medically unexplained symptoms, compliance problems with medical illness, assessment in terms of psychopharmacological treatment, delirium and non-compliance to treatment.

In sum, suicide attempts constitute one of the main reasons for requesting a child psychiatry consultation in both domestic and international studies. Adolescents often attempt to commit suicide compulsively rather than as a result of a planned attempt (17, 31). Adolescence is a period where biological, spiritual and social growth accelerate. The biological, psychological and social changes that occur can be emotionally challenging for adolescents, and it can be difficult for them to cope with these emotional difficulties since their experience and maturation are not sufficient just yet. Consequently, adolescents may compulsively resort to suicide in such moments which they have difficulty coping. For this reason, it is very important to perform a psychiatric assessment of every young person presenting with acute intoxication in terms of a possible suicide attempt.

Comparison of the prediagnoses with the final diagnoses made based on the psychiatric assessment revealed that the most common prediagnoses made by t non-psychiatric physicians were depression and anxiety disorder. However, it was found that most of these prediagnoses were not confirmed by the child

psychiatrists. The psychiatric disorders which were misdiagnosed the most by non-psychiatric physicians as compared to the final diagnoses made by based on the psychiatric assessment were found to be the psychotic disorders; whereas prediagnoses made in respect of autism, delirium, substance use disorders and mental disability were determined to be the disorders which were accurately diagnosed the most as compared to the final diagnoses made by based on the psychiatric assessment. Nevertheless, the relatively low number of prediagnoses of delirium and autism, each of which were diagnosed in 2 children and adolescents, compared to the total number of final diagnoses of delirium and autism, that is, 10 children and adolescents with delirium and 7 children and adolescents with autism, which also includes the number of children and adolescents diagnosed with delirium and autism however not referred by a non-psychiatric physician for consultation, has been interpreted such that most of these disorders were not known to the physicians that have requested psychiatric consultations.

Several studies conducted in the adult population have demonstrated that the non-psychiatric physicians predominantly recognize cognitive disorders, delirium and substance use disorders, but recognize depression, anxiety and psychotic disorders only occasionally (20, 38, 39). In a study conducted in an adult population in Turkey, it was stated that the prediagnoses in respect of the respective mental disorder were not made in more than half of the patients for whom a psychiatric consultation was requested due to symptoms such as agitation, depressive findings and symptoms, anxiety and conversion symptoms, despite the fact that it would be expected that the diagnoses in question were accurately made given that the stated symptoms and findings clearly indicated the respective mental disorder (40). The respective results obtained in this study in respect of the pediatric age group were found to be comparable to the above-mentioned results reported in respect of the adult population.

In terms of psychiatric interventions, the most common form of intervention performed by the CLP team subject to this study was found to be patient follow-ups through psychoeducation. Psychoeducation includes educational interventions intended to teach the patients with mental or physical illnesses about their illnesses and their emotional responses to the disease, to improve their ability to cope with difficult situations, to increase their adaptation skills, and to ensure their compliance with the treatment (41-42). The aim of these interventions is to teach the patients how to cope with their

problems, to help them understand the situation they are in, and to increase their general well-being and quality of life, through furnishing them with the necessary knowledge and ensuring them to adopt the appropriate behavioral changes. The effectiveness of psychoeducation when used alone as an intervention method has been shown based on evidence, yet it can also be used in combination with other treatment methods (42).

Second to the psychoeducation, the next most common form of intervention performed by the CLP team subject to this study was found to be pharmacotherapy, and the most commonly pharmacological agents used in this regard were SSRIs, antipsychotics, benzodiazepines and methylphenidate, respectively. A review of the literature in this respect revealed that pharmacotherapy was used as a method of intervention by the CLP teams in 28% to 85% of the patients, for whom a psychiatric consultation was requested (15-18, 28). In this study, it was determined that pharmacotherapy was used as a method of intervention by the CLP team in 37.7% of the patients, for whom a psychiatric consultation was requested, and psychoeducation practices were found to be ahead of medical treatment. Psychopharmacological approaches are preferred by physicians over psychotherapeutic approaches, which are difficult to apply due to reasons such as time limitation and the need for specially trained personnel in children and adolescents with physical diseases (43). The fact that the clinic subject to this study is a child-adolescent psychiatry clinic that focuses on psychotherapy training and practices might have led the respective CLP team to attach priority to psychosocial interventions.

Conclusions

In conclusion, the findings of this study indicate that most of the children with physical illnesses and for whom psychiatric consultation was requested had a mental disorder. However, the rate of requesting child and adolescent psychiatric consultations is very low. Child mental health diseases are not recognized correctly by non-psychiatric physicians. Autism, delirium, substance use disorders and mental disability were found to be the disorders with the highest rates of accurate prediagnoses as compared to the final diagnoses, whereas psychosis, depression, and anxiety were found to be the disorders with the highest rates of misdiagnoses made during the prediagnosis stage as compared to the final diagnoses. Nevertheless, the relatively low number of prediagnoses of delirium and autism, compared to the total number of final diagnoses of delirium and autism, which also includes the number of children and adolescents diagnosed with delirium and autism however not referred by a non-psychiatric physician for consultation, has been interpreted such that most of these disorders were not known to the physicians that have requested psychiatric consultations, suggesting that it is highly likely that most of the children with delirium and autism have been overlooked.

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Predictive Role of Large Unstained Cells (LUC) and Hematological Data in the Differential Diagnosis of Orchitis and Testicular Torsion

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Abstract

Objective: The main aim of this retrospective evaluation of patients presenting with the complaint of acute scrotal pain was to investigate whether large unstained cells (LUC) in the hematological data, percentage of LUC, and the other haematological parameters would be of benefit in differential diagnosis. The secondary aim was to investigate the utility of LUC and LUC% as a new biochemical marker in the differential diagnosis of TT and EO.

Methods: In this study, a retrospective evaluation was made of patients who presented with the complaint of acute scrotal pain at the emergency polyclinic. The patients were evaluated in three groups; testicular torsion, orchitis, and the control group. Primarily the large unstained cell and other hematological data of the patients were evaluated.

Results: Statistical differences were evaluated in LUC, LUC%, platelet, neutrophil, leucocyte, mean platelet volume, neutrophil / lymphocyte, platelet / lymphocyte values among the groups (p values respectively 0.001, <0.001, 0.491, <0.001, <0.001, 0.031, <0.001, 0.001). The cutoff values for the differentiation of epididimo-orchitis (EO) were determined in the differential diagnosis of EO and TT. The highest area under curve values were found for LUC, LUC% and neutrophils, respectively, 0.752 (0.660-0.843), 0.698 (0.605-0.790), 0.383 (0.284-0.482).

Conclusion: The results of this study showed that the LUC and LUC% values obtained from complete blood count (CBC) can be reliably used in the differential diagnosis of EO and TT

Key words: Orchitis, large unstained cell (LUC), testis torsion, predictive value, nlr

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Introduction

Testis torsion (TT) is one of the most important and frequently seen emergency conditions in urology practice. In males aged 1-25 years, it is seen at an annual frequency of 4.5/100,000 (1). Testis torsion occurs as a result of the spermatic cord wrapping around the longitudinal axis, causing first a venous block then an arterial block. If intervention is made for TT within the first 6 hours, there is a 90%-100% chance of recovery without injury to the testis tissue, if treatment is applied in 6-12 hours this rate is 20%-50%, and if at 12-24 hours, 0%-10% (2). When TT is not treated as an emergency and appropriately, infertility and testis loss can result because of germinal cell damage. In the differential diagnosis, the disease with which TT is most confused is epididymo- orchitis (EO).

An important differentiating examination finding of EO is a decrease in pain with elevation of the scrotum (Prehn sign) (3). However, the same clinical findings have been shown in patients diagnosed with torsion (4). Power Doppler ultrasonography (DUS) is used most often in the differential diagnosis and this test has high reported rates of sensitivity (86-100%) and specificity (95-100%) (5). However, not all centres have the facilities for DUS of patients at the time of presentation at an emergency polyclinic. This is a great disadvantage for TT cases requiring emergency treatment and leads to the risk of unnecessary surgical treatment. Therefore, clinicians have been motivated to search for more easily accessible methods to facilitate the differential diagnosis. Parameters have been previously researched on this subject, such as several hematological parameters, leukocyte count, neutrophil/leukocyte ratio (NLR), and mean platelet volume (MPV) (6, 7).

The main aim of this retrospective evaluation of patients presenting with the complaint of acute scrotal pain was to investigate whether large unstained cells (LUC) in the hematological data, and the percentage of LUC, and the systemic anti-inflammatory response data (NLR, MPV) would be of benefit in differential diagnosis. The secondary aim was to investigate the utility of LUC and LUC% as a new biochemical marker in the differential diagnosis of TT and EO.

Methods

Study population

In this study, a retrospective evaluation was made of patients who presented with the complaint of acute scrotal pain at the Emergency and Urology Polyclinic of Ankara City Hospital between March 2019 and August 2020. The group evaluated ranged in age between 3 and 37 years. The protocol was approved by local Ethics Committee at Ankara City Hospital (Protocol No: E1-20-1126). The patients included in the study were those who were applied a scrotal Doppler ultrasonography, were then diagnosed with TT or EO and treated. Patients included in the TT diagnosis group had presented at the emergency polyclinic within 12 hours of the onset of pain and were treated with surgery (detorsion and orchiectomy). The EO patient group were also accepted as those with scrotal pain for a maximum of 12 hours, and an upper age limit of 37 years was determined. All of the orchitis patients participating in this study were unilateral.A control group was formed of healthy individuals with no similar complaints. Patients were excluded from the study if they had any liver, kidney or hematological disease, were receiving any treatment (chemotherapy, steroids) that could affect secondary hematological results, or had a history of scrotal surgery or scrotal trauma.

Laboratory and radiologic analyses

All the patients were examined by the emergency specialist and an urology specialist. Scrotal DUS was applied to all the patients and recorded. Venous blood samples were withdrawn into tubes containing ethylene-diamine-tetra-acetic acid (EDTA) for the measurement of hematological parameters of the patients and the control group. The blood samples were sent to the hospital's central laboratory, and as routine, were analyzed with the flow cytometry method on a Siemens Advia 2120i ® device within 20 minutes of reaching the laboratory. All the hematological parameters were stated as $10^3/\mu L$. Using these parameters, the NLR and platelet/lymphocyte ratio (PLR) were calculated. The MPV value was denominated in femtoliter.

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS for Windows vn 22.0 software (SPSS ®, Chicago, IL, USA). Group parameters were stated as mean ± standard deviation (SD) values. Conformity of the data to normal distribution was assessed with the Kolmogorov-Smirnov test. In the comparison of groups not showing normal distribution, the non-parametric Kruskal-Wallis test was used and the Tamhane posthoc analysis was completed. A value of p<0.05 was accepted as statistically significant. Receiver Operating Characteristic (ROC) curve analysis was performed to determine the cutoff, sensitivity,

specificity, positive predictive value (PPV) and negative predictive value (NPV) of the hematological data.

Results

A retrospective evaluation was made of the medical records of 129 male patients. The patients were separated into 3 groups, as the TT group (n:39) treated with orchiectomy or surgical detorsion and testicular fixation, the EO group (n:49), and a control group (n:41) of healthy males. The mean age was 17.9±6.7 years in the TT group, 19.4±6.9 years in the EO group, and 19.0±7.8 years in the control group. No difference was determined between the groups in respect of mean age.

No statistically significant difference was determined between the TT and EO groups in respect

of platelet count and MPV. A statistically significant difference was determined between the groups in respect of LUC, LUC%, neutrophil count, lymphocyte count, leukocytes, NLR and PLR (Table 1). LUC distribution according to groups is shown in Figure 1 and LUC% in Figure 2.

The cutoff values for the differentiation of EO were determined in the differential diagnosis of EO and TT. As the predictive values for leukocytes, MPV, and thrombocytes had no statistical significance, and were not calculated. The sensitivity and specificity values, NPV and PPV were determined for LUC, LUC%, neutrophils, NLR and PLR (Table 2). A ROC curve was drawn for each parameter (Figure 3).

Table 1   Comparison of parameters according to groups

	GROUPS			
	Torsion n=39	Orchitis n=49	Control n=41	p
Age	17.87±6.66 a	19.04±6.85 a	18.93±6.85 a	0.023
LUC	0.124±0.057 b	0.177±0.66 a	0.124±0.033 b	<0.001
LUC %	1.17±0.58 b	2.00±0.81a	1.75±0.57 a	<0.001
Platelet	285.97±71.76 a	257.47±79.90 a	251.27±52.80 a	0.491
Neutrophil	8.49±2.74 b	5.22±3.03 a	4.09±1.06 a	<0.001
Leucosytes	11.17±2.98 b	8.42±3.14 a	7.04±1.38 c	<0.001
MPV	7.91±1.06 b	7.90±0.83 b	8.29±0.87 b	0.031
Neutrophil/Lymphpcyte	5.37±2.77 b	2.75±3.25 a	1.97±0.68 a	<0.001
Platelet/Lymphocyte	179.65±92.44 b	125.15±66.38 a	120.63±35.26 a	0.001

Arithmetic mean ± standard deviation; a, b, c: no difference between groups with the same letter.LUC: Large Unstained cell, NLR:Neutrophil/Lymphocyt, PLR: Platelet/Lymphocyte

Table 2   Receiver operating characteristic analysis for the epididymitis group

	AUC	Cut-off	p	Sensivity	Specificity	PPV	NPV
LUC	0.752 (0.660-0.843)	0.135	0.000	71.4	66.3	56.5	79.1
LUC %	0.698 (0.605-0.790	1.55	0.000	71.4	78.8	67.3	81.8
Neutrophıl	0.383(0.284-0.482	4.75	0.026	44.9	43.8	32.8	56.5
NLR	0.357(0.259-0.455)	2.22	0.007	42.9	40	30.4	53.3
PLR	0.386(0.285-0.488)	114.6	0.031	48.9	42.5	34.3	57.6

As plAs pleateatelet MPV and lLeucosyte, were not significant, the cut-off values were not determined.AUC: Area under curve, p: p value. PPV: Positive Predictive Value, NPV: Negative Predictive Value, NLR:Neutrophil/Lymphocyt, PLR: Platelet/Lymphocyte
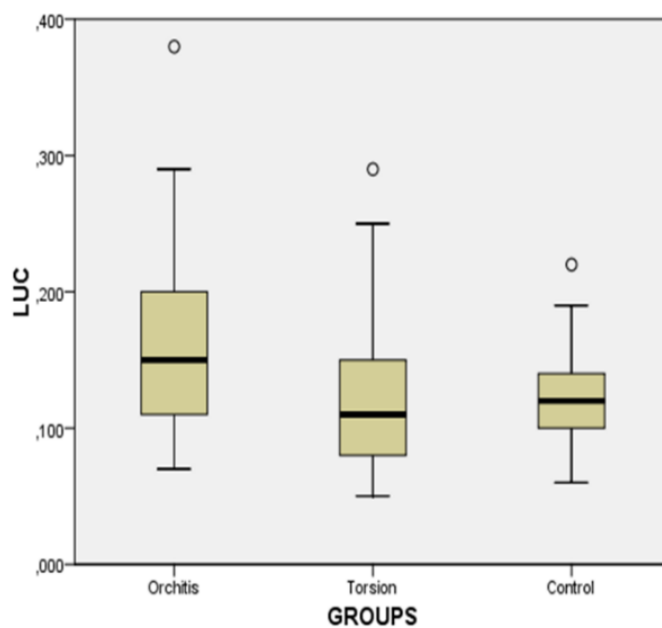
Figure 1. Box graph of large unstained cell (LUC) according to groups
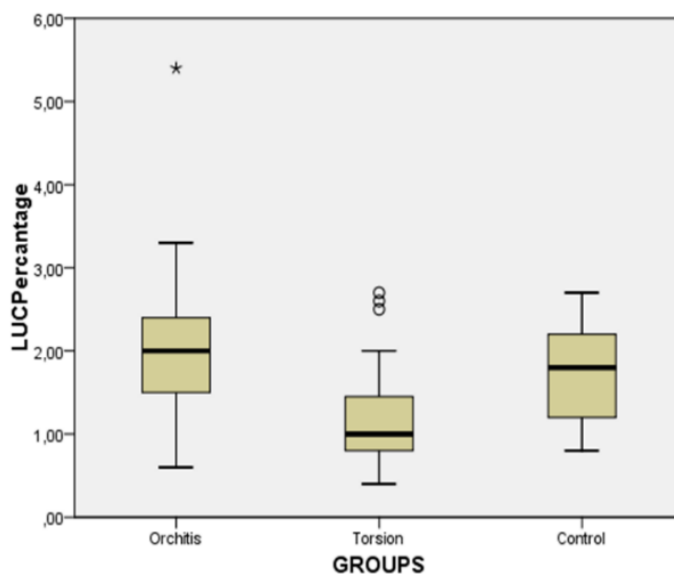
Figure 2. Box graph of large unstained cell (LUC) Percentage (%) according to groups
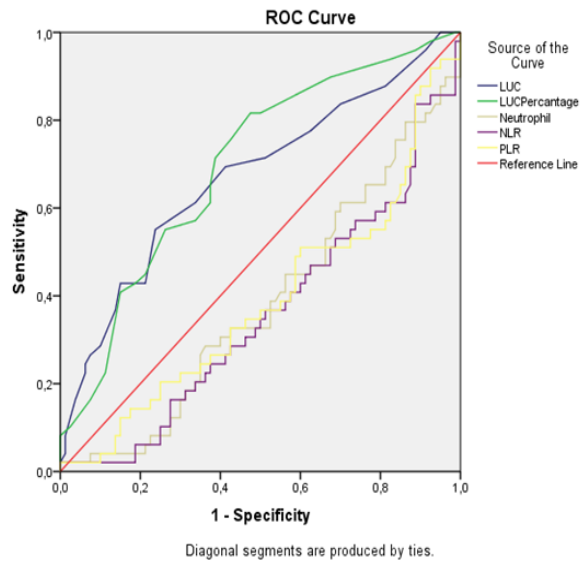
Figure 3. Receiver operating characteristic curve of large unstained cell (LUC), large unstained cell (LUC) %, Neutrophil, Neutrophil/Lymphocyte (NLR) and Platelet/Lymphocyte(PLR) count

Discussion

The two most common causes of acute scrotum are TT and EO. TT is a urological emergency requiring emergency diagnosis and treatment as it can cause loss of the testis. The pathophysiology of these two diagnoses is different from each other. While the basic pathology is acute ischemia in torsion, it is an infective process in EO.

To date, many studies have been conducted with the idea that different hematological parameters could be used as biomarkers in the differential diagnosis of the two diseases. In a study of a paediatric age group, full blood count parameters such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and neutrophils were evaluated in the differential diagnosis of inflammatory and non-inflammatory diseases in the etiology of acute scrotum. A significant difference was found between the two groups especially in the neutrophil and CRP levels (8). In a study of procalcitonin to be used in the differential diagnosis of TT and EO, Yamis et al (9) determined elevated levels in EO. Conflicting results have been obtained in studies that have evaluated the utility of thrombocyte and MPV values in the differential diagnosis of EO and TT. Cicek et al found no difference between the two groups in the thrombocyte values, while Bitkin et al reported a significant difference between the thrombocyte counts of the two groups. The MPV values were found to be significant in both studies (6, 7). In the current study, these two biomarkers were not found to be statistically significant, which was thought to be for two reasons. The first was that the EDTA in the tubes used for the blood samples could have impaired the thrombocyte structure, and the second was that in literature, different results of both parameters have been shown to have been obtained in measurements made using different technologies (10).

It is also noticeable that there are different results in the literature related to the predictive values of leukocyte and neutrophil counts in the differential diagnosis of EO and TT. In a study the patient groups showed a significant elevation compared to the control group, but the predictive values were not found to be significantly high (10). In another study, the evaluation between groups was similar, but while the predictive value of leukocyte count was found to be statistically significant, the predictive value of the neutrophil count was not significant. Similar to the findings in the literature, when the role of the leukocyte count in differential diagnosis was evaluated in the current study, a significant difference was found between groups, but the predictive value was not determined to be significant.

Previous studies have examined the predictive value of NLR and PLR in the differential diagnosis of EO and TT. In all the studies on this subject in the literature, in both parameters, the difference between groups has been shown to be, significant and statistically significant predictive values have been determined. Similar results were obtained in the current study. However, the sensitivity and specificity values obtained as a result of the predictive evaluation were seen to be lower than those reported in the literature (Table 2).

Large unstained cells (LUC) are large peroxidase negative cells, which do not conform to other leukocyte subtypes, and these generally include

virally activated lymphocytes, plasma cells, hairy cells, pediatric lymphocytes, and peroxidase negative lymphoblasts (11). The focus in the literature has been towards the possible use of LUC values as a marker for treatment response or prognosis particularly in hematological malignancies (12, 13). Moreover, it has been reported that they could be a marker in the differential diagnosis or prognosis of many infectious diseases (14-16). Therefore, this is the first study to have shown that LUC and LUC% values can be used in the differential diagnosis of EO and TT. Both values were found to be significantly higher in the EO group than in the TT group (Table 1, Figure 1 and Figure 2). In addition, there was observed to be higher significance in all the other parameters examined in respect of predictive values (Figure 3, Table 2). This is not the first use of these values in differential diagnosis reported in literature, but this study is the first to have shown a comparison of a disease where the main pathology is ischemia and a disease where it is infection.

Limitations

Limitations of this study were that it was retrospective and conducted in a single centre. A further limitation was that parameters such as procalcitonin, CRP and Amyloid A, which are acute phase reactants, were excluded from the study as testing is expensive and they are not used routinely.

Conclusions

Complete blood count (CBC) is an inexpensive and rapidly accessible test, which can be easily accessed even in the most basic of healthcare centres. The parameters within CBC are of guidance for diseases that require comparison and a rapid decision. The differentiation of EO and TT encountered in the emergency polyclinic is a situation that requires emergency diagnosis and emergency treatment. Furthermore, scrotal Power Doppler USG, which should be used as a rule in the differential diagnosis, may not have the same reliability in every centre, as it is an experience-based examination and may not always be immediately available. The results of this study showed that the LUC and LUC% values obtained from CBC can be reliably used in the differential diagnosis of EO and TT. Nevertheless, there is a need for further prospective multi-centre studies to strengthen the reliability of the use of these values and to enable them to be used routinely in emergency polyclinics.

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Prediction of Renal Cell Carcinoma Based on Ensemble Learning Methods

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Abstract

Objective: In recent years, ensemble learning methods have gained widespread use for early diagnosis of cancer diseases. In this study, it is aimed to establish a high-performance ensemble learning model for early diagnosis and classification of renal cell carcinomas.

Methods: In the study, hemogram and laboratory data of 140 patients with renal cell carcinoma and 140 patients without renal cell carcinoma were included in the study. The data set includes 27 predictors and 1 dependent variable. The data were obtained retrospectively. In the study, classification performances of machine learning methods and ensemble learning methods were compared. In the study, classification performances of boosting, bagging, voting and stacking ensemble learning methods as well as IB1, IBk, Kstar, LWL, REPTree, Random Forest and SMO classifiers were compared.

Results: REPTree classifier provided the highest performance among machine learning methods (Accuracy = 0.867). Among the ensemble learning methods, the Stacking ensemble learning method provided the highest performance in Model 6 (Accuracy = 0.906). Stacking ensemble learning methods performed higher than boosting, voting, bagging ensemble methods and machine learning methods.

Conclusion: Stacking ensemble learning methods provide successful results in the early diagnosis of renal cell carcinomas. Stacking ensemble learning methods can be used as an alternative to existing methods for diagnosing renal cell carcinoma. In order to further increase the classification performance of the stacking ensemble learning method, it is recommended to choose a meta classifier suitable for the data set and variable types.

Key words: Ensemble Learning Methods, Meta Classifier, Renal Cell Carcinoma, Early diagnosis

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Introduction

Renal cell carcinoma is a type of malignancy tumor that originates from the renal cortex and grows starting from the inner surface of the renal tubules (1). Renal cell carcinoma accounts for approximately 2-3% of all cancer types. In recent years, there has been an increase of 2% in the incidence of renal cell carcinoma disease. Renal cell carcinomas constitute approximately 85% of kidney malignancies (1). Clear cell renal carcinomas, papillary cell renal carcinomas and chromophobe cell renal carcinomas are the most common types of renal cell carcinoma (2). Mostly, in advanced stages, renal region pain, weight loss, high fever, hematuria and defatigation are the physical findings of renal cell carcinoma (3-6). Physical examination, laboratory tests, ultrasonographic and radiological imaging techniques and renal biopsy are generally used for the diagnosis of renal cell carcinoma. Renal cell carcinomas generally progress asymptomatically even in advanced stages. In the physical examination phase, the possibility of early diagnosis of the disease is low. This situation makes it difficult to diagnose the disease early. Early diagnosis is one of the most important factors for successful treatment in cancer diseases. Important advances have been made for early diagnosis of cancer diseases with technological advances in medical imaging techniques. Another important development for early diagnosis of cancer diseases has been achieved with artificial intelligence and machine learning methods. Machine learning methods have produced solutions for many issues in the field of health in recent years. Machine learning methods are applied in early diagnosis of diseases, risk estimation, genetic sequencing, clinical decision support systems, classification of diseases, and identification of patterns for medical images. Machine learning methods can infer and classify real data by learning the patterns in the training data set and the relationship structures between data. Machine learning methods generally perform the classification of data to diagnose diseases (7-8). Although machine learning methods are generally very good classifiers, they cannot provide the desired classification performance for some data sets. Overfitting and underfitting problems are the main causes of failure in this classification (9-11). There are different reasons due to the data set not being suitable for the model or the poor quality of the data set (12). Different solution suggestions have been developed to overcome these problems. One of these solutions is ensemble learning methods. Ensemble learning methods provide a common classification result from the estimates of each classifier by classifying the data of more than one machine learning algorithm separately, rather than classifying the data set by a machine learning algorithm. Thus, common prediction results obtained from more than one machine learning method offer more accurate, more reliable and higher performance compared to the prediction results of a machine learning method (13). Ensemble learning methods are based on the principle that more than one classifier can perform classification with higher accuracy than a single classifier predicts.

A great deal of research has been carried out to predict renal cell carcinomas using machine learning methods. Liu et al. conducted a study on the data they obtained from gene expressions to predict renal cell carcinomas. They used the K-NN algorithm and genetic algorithms to classify renal cell carcinomas. Algorithms have provided successful results in the classification of renal cell carcinomas. Machine learning methods can be successful in the classification of patterns (14). Won et al. classified renal cell carcinoma and other urological diseases with C4.5 algorithm in their study. In the classification process, the data set was obtained from texture patterns. Machine learning methods have shown that they can be used for the early diagnosis of renal cell carcinomas by using patterns (15). Lee et al. used the K-NN classifier (K-NN), the Support vector Machine (SVM) classifier and the Random Forest classifier (RF) to classify renal cell carcinomas in their studies (16). Fuchs et al. stated that pathology findings could be used to predict the survival time of patients with renal cell carcinoma in their study. The researchers who used the random forest classifier to estimate the survival times determined that the findings were compatible with the findings of the pathologists (17). Lin et al. made use of CT images in their study to classify renal cell carcinomas with gradient boosting method (18). Tabibu et al. carried out the classification of panrenal cell carcinomas using convolutional neural networks. A new SVM model was also proposed in the study (19).

Although the ensemble learning method has emerged recently, many researchers have included ensemble learning methods in their studies. Tan and Gilbert can classify cancer diseases in their study by using ensemble learning methods and gene expression values (20). Luo and Cheng benefited from ensemble learning methods in the diagnosis of breast cancers in their studies. The findings of the model provided higher performance than single classifiers (21). Wang used the Stacking ensemble learning method for the diagnosis of prostate cancer. The ensemble model has produced successful results

in the diagnosis of prostate cancer (22). Onan made use of ensemble learning methods for breast cancer classification in his study. They have observed that ensemble models provide better classification performance than single classifiers. In addition to classifying diseases, ensemble learning method can also be applied to predict the success of treatment methods (23). Shayesteh et al. predicted the results of treatment methods applied to rectal cancer patients with the MRI-based ensemble learning model in their study (24).

In this study, it is aimed to create an ensemble learning model that will serve as a basis for artificial intelligence applications for early diagnosis of renal cell carcinoma. It was aimed to predict renal cell carcinoma with high accuracy performance using the ensemble learning model. In addition, it was aimed to determine suitable ensemble models and classifiers to predict the disease with the highest accuracy performance.
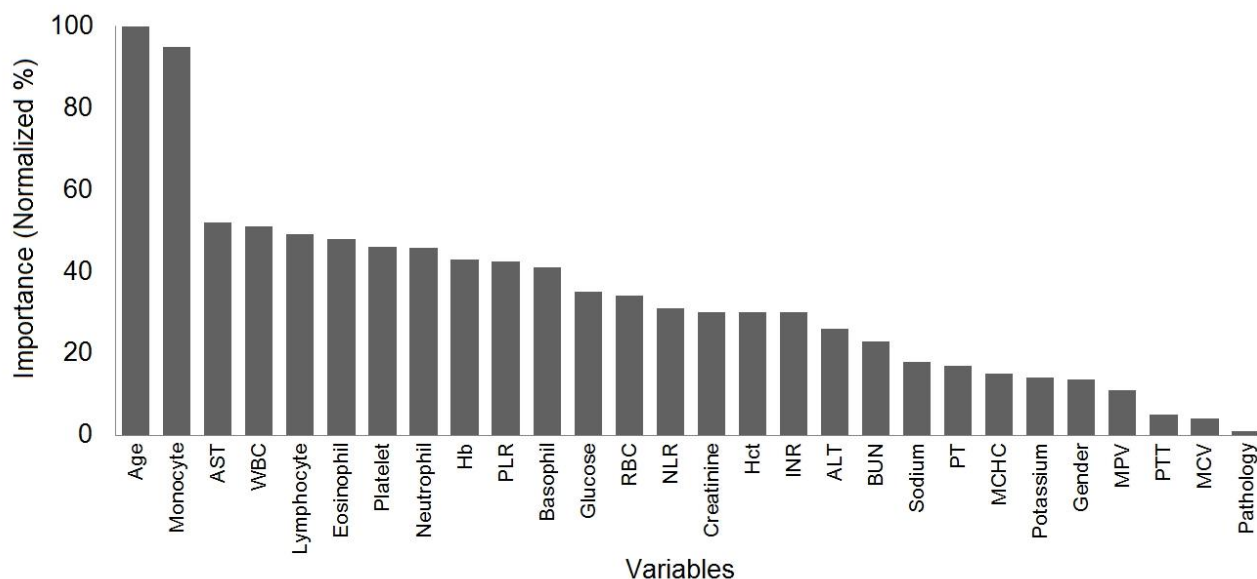
Methods

The data of the study consisted of 140 patients diagnosed with renal cell carcinoma and 140 patients diagnosed other than renal cell carcinoma, who applied to the Urology service of Kahramanmaras Sutcu Imam University Health practice and research hospital. Permission was obtained from the Clinical Research Ethics Committee of Kahramanmaras Sutcu Imam University (Ethics committee approval Protocol No: 2018 / 07-21) to conduct the study. The data were obtained retrospectively. Age, gender, hemogram and biochemical laboratory variables of the patients constitute the data set of the study. The variables and their properties in the data set are given in table 1. Power analysis was used to determine the sample size of the study. Considering the values of Mean ± SD: 12.7 ± 7.2 and Mean ± SD: 15.7 ± 7.6 in the reference studies; it was planned to include α: 0.05 first type error level, β: 0.20 type 2 error level, n: 97 for each group with a power of 0.80 test, and at least n: 194 patients in total. The high number of data in data mining, machine learning and multivariate research increases the learning ability of the model. Therefore, a total of n: 280 patient data, n:140 for each group, were included in the study. The data set of the study includes 1 dependent (target) and 27 independent (predictor) variables.

Table 1. Variables in the model

Variables	Variable Type	Definition	Role
Renal Cell Carcinoma (RCC)	Categorical	RCC Present/ RCC Absent	Dependent (Target)
Age	Numerical	Positive Real Number	Independent (Predictor)
Gender	Nominal	Male/Female	Independent (Predictor)
Pathology	Nominal	Positive/Negative	Independent (Predictor)
White Blood Cell (WBC)	Numerical	Positive Real Number	Independent (Predictor)
Hemoglobin (Hb)	Numerical	Positive Real Number	Independent (Predictor)
Hematocrit (Hct)	Numerical	Positive Real Number	Independent (Predictor)
Mean Corpuscular Volume (MCV)	Numerical	Positive Real Number	Independent (Predictor)
Neutrophil	Numerical	Positive Real Number	Independent (Predictor)
Lymphocyte	Numerical	Positive Real Number	Independent (Predictor)
Eosinophil	Numerical	Positive Real Number	Independent (Predictor)
Basophil	Numerical	Positive Real Number	Independent (Predictor)
Red Blood Cell (RBC)	Numerical	Positive Real Number	Independent (Predictor)
Platelet	Numerical	Positive Real Number	Independent (Predictor)
Platelet-Lymphocyte Ratio (PLR)	Numerical	Positive Real Number	Independent (Predictor)
Mean Platelet Volume (MPV)	Numerical	Positive Real Number	Independent (Predictor)
Blood Urea Nitrogen (BUN)	Numerical	Positive Real Number	Independent (Predictor)
Creatinine	Numerical	Positive Real Number	Independent (Predictor)
Sodium	Numerical	Positive Real Number	Independent (Predictor)
Aspartate aminotransferase (AST)	Numerical	Positive Real Number	Independent (Predictor)
Alanine aminotransferase (ALT)	Numerical	Positive Real Number	Independent (Predictor)
Protrombine Time (PT)	Numerical	Positive Real Number	Independent (Predictor)
International Normalized Ratio (INR)	Numerical	Positive Real Number	Independent (Predictor)
Partial Thromboblastin Time (PTT)	Numerical	Positive Real Number	Independent (Predictor)
Potassium	Numerical	Positive Real Number	Independent (Predictor)
Mean Corpuscular Hemoglobin Concentration (MCHC)	Numerical	Positive Real Number	Independent (Predictor)
Neutrophil to Lymphocyte Ratio (NLR)	Numerical	Positive Real Number	Independent (Predictor)
Glucose	Numerical	Positive Real Number	Independent (Predictor)

Figure 1. Importance of variables

The Local Outlier Factor (LOF) algorithm has been applied to the data in order to determine the outliers in the data set. LOF algorithm is a powerful method applied in detecting outliers (25-26). As a result of the evaluation, outliers were removed from the data set. Standardization was applied to the quantitative variables in the data set.

Feature selection was carried out to determine the contribution of predictor variables to the classification. Findings regarding feature selection are given in figure 1. According to the findings, the contribution of the "pathology" variable to the classification performance was found to be quite low. The "pathology" variable has been removed from the model.

In the study, in addition to machine learning methods, ensemble learning methods were also applied to predict renal cell carcinoma. IB1, IBk, Kstar, LWL, REPTree, Random Forest and SMO classifiers were applied to classify the data in the model. In the model, besides the individual performances of the classifiers, the performances of voting, boosting, bagging and stacking ensemble learning methods were also evaluated. In the Boosting ensemble learning method, the "Adaboost" algorithm has been applied. In the Stacking ensemble learning method, the "Logistic" classifier is used as a meta classifier. Gridsearch and Multisearch algorithms were used for hyperparameter optimization of classifiers (27-29). Stacking and voting ensemble methods include more than one classifier in the model. For this reason, 7 different models were created to evaluate the stacking and

voting ensemble methods. Classifying information for the models is given in Table 2.

Dataset and Model Evaluation

A 10-fold cross validation method was applied to evaluate the performance of classifiers and ensemble learning methods in the model. Weka 3.9 (Waikato Environmental Knowledge Analysis) and R 3.6.0 open source coded softwares were used to evaluate the data with classifiers and ensemble model (30-31). Hyperparameter optimization has been applied to increase the performance of the classifiers. The performances of classifiers and ensemble methods were evaluated with accuracy, sensitivity, specificity, AUC (Area of under curve) and precision metrics. The complexity matrix for the metrics used to evaluate the performance of classifiers and ensemble models is given in table 3.

Table 2. Models and classifiers for voting and stacking enbemble methods

Model	Classifiers
Model 1	IB1
Model 2	IB1, IBk
Model 3	IB1,IBk, Kstar
Model 4	IB1,IBk, Kstar, LWL
Model 5	IB1,IBk, Kstar, LWL, Random Forest
Model 6	IB1,IBk, Kstar, LWL, Random Forest, REPTree
Model 7	IB1,IBk, Kstar, LWL, Random Forest, REPTree, SMO

Table 3. Confusion matrix

		Disease		
		Positive	**Negative**	**Total**
Prediction	**Positive**	True Positive (TP)	False Positive (FP)	TP+FN
	Negative	False Negative (FN)	True Negative (TN)	FP+TN
	Total	TP+FN	FP+TN	TP+FP+FN+TN

$$Accuracy = \frac{TP + TN}{TP + FP + FN + TN}$$

$$Sensitivity = \frac{TP}{TP + FN}$$

$$Specificity = \frac{TN}{TN + FP}$$

$$Precision = \frac{TP}{TP + FP}$$

Ensemble Learning Methods

Machine learning methods are constantly evolving to provide higher accuracy performance in classification and prediction operations. Ensemble learning methods are also one of the methods developed so that machine learning methods can do classification with higher accuracy. Ensemble learning methods are based on the principle that more than one classifier will provide higher classification performance together rather than the classification performance of a single classifier. Common prediction of more than one classifier has higher reliability than the estimation of one classifier (32). The training of the data in the model is performed with more than one machine learning method, and predictions with higher accuracy can be made than only one machine learning method. In ensemble learning models, rather than combining classifiers, a common predictive value is obtained by combining the estimates obtained by the classifiers (33). Different merging and learning techniques can be applied in ensemble learning methods. Choosing the appropriate merging and learning method for the data set and variables provides an increase in performance.

Boosting Ensemble Learning Methods

The Bootstrap Aggregating (Bagging) ensemble learning method is based on the bootstrap sampling method. In the Bagging method developed by Breiman, many different subsets are obtained from the data set with the bootstrap sampling method Subsets obtained from the data set are trained with classifiers (32). All classifiers train different subsets at the same time. Estimates of a large number of classifiers are combined by majority vote. Estimation of the majority among the classifiers is accepted as the estimate of the bagging ensemble learning method (33).

Bagging Ensemble Learning Methods

The Boosting ensemble learning method is based on providing high performance by combining many weak classifiers instead of using only one classifier. In the Boosting ensemble method, the training of data is carried out by iterative operations (35). At every stage of iterative operations, taking into account the mistakes made in the previous stage, the same mistakes are prevented. At the end of the iterative stages, a powerful classifier providing high performance is obtained (34). Adaboost method is a powerful ensemble method suggested by Freud and Shapire (36). In the Adaboost method, weighting is applied at each iterative stage. With the weighting process, the accuracy performance is increased by reducing the error at each stage (33).

Voting Ensemble Learning Methods

Voting is essentially an aggregation technique of classifiers rather than an ensemble learning model. In

the voting technique, estimation of majority among different types of classifiers is accepted as the ensemble estimate. The classification of a single data set by different types of classifiers provides different results in estimates. Different estimates increase the accuracy performance of the results. Increasing the variety of classifiers used for training the data set contributes to the reduction of classification errors (33-35).

Stacking Ensemble Learning Methods

The stacking ensemble learning method was developed by Wolpert (37). Stacking ensemble learning method, similar to voting ensemble method, is based on training the data set by different types of classifiers. The main difference in the stacking ensemble learning method is that it has a meta classifier. Estimates obtained from different types of classifiers constitute the input data for the meta classifier. The estimate obtained by the meta classifier from the input data is accepted as the estimate of the stacking ensemble learning method (37).

Results

In the study, 140 patients with Renal Cell Carcinoma and 140 patients with different kidney diseases other than Renal Cell Carcinoma were classified using machine learning methods and ensemble learning methods. For classification, variables related to the descriptive and laboratory findings of the patients were included in the model. In the study, classification performances of boosting ensemble learning method, bagging ensemble learning method, voting ensemble method and stacking ensemble learning methods as well as classifiers applied without using ensemble method were evaluated. The performances of the methods were compared in terms of accuracy, sensitivity, specificity, precision, and AUC metrics. Renal cell carcinoma classification performances of machine learning methods and ensemble learning methods are shown in table 4.

According to the findings in the table, the Stacking ensemble learning method provided the highest value in terms of accuracy, sensitivity, specificity, precision and AUC metrics (Model 6 Accuracy = 0.906; Sensitivity = 0.906; Specificity = 0.906; Precision = 0.910 and AUC = 0.944 respectively). The Stacking ensemble learning method provided the highest performance in the classification of renal cell

carcinomas. It has been observed that Boosting and Bagging ensemble learning methods do not contribute to the performance of some classifiers. The stacking ensemble learning method provided the highest performance in Model 6. Model 6 consists of IB1, IBk, Kstar, LWL, REPTree, Random Forest classifier. The "Logistic" classifier, determined as a meta classifier for the Stacking ensemble learning method, contributed to the classification performance of the ensemble model. The performances of the ensemble methods are shown in figure 2.

Discussion

The incidence of renal cell carcinomas has increased significantly in recent years. Early diagnosis of renal cell carcinomas increases the success rate of the disease in treatment. Medical imaging techniques, laboratory tests, biopsy and physiological examination are important for diagnosing the disease. Recently, artificial intelligence technologies have been applied in addition to traditional methods for early diagnosis of cancer diseases. Machine learning methods are important artificial intelligence techniques applied for early diagnosis and classification of diseases. There have been many studies using machine learning methods for early diagnosis of cancer diseases (38-41).

Machine learning methods provide successful results for early diagnosis and classification of cancer diseases with high prevalence. Skin cancer, lung cancer, breast cancer, prostate cancer, stomach cancer, cervical cancer and colorectal cancer are some of the cancer diseases with the highest prevalence in the population (42). Although many studies have been conducted on cancer diseases with a high prevalence, machine learning methods have been applied less for cancer types with low prevalence. It is easier to reach a high number of data in cancer diseases with a high prevalence. The number of data is low in cancer diseases with low prevalence. In order for machine learning methods to be applied successfully, the number of samples in the data set should be high. In cases where the number of samples in the data set is low, the machine learning model cannot learn the pattern between data and variables well. This situation causes underfitting problem. The model shows low classification performance when the number of samples in the data set is small.

Tablo 4. Comparison Performance of Ensemble Learning Methods

		Performance Metrics				
		Accuracy	Sensitivity	Spesificity	Precision	AUC
No Ensemble Learning Methods	IB1	0.847	0.851	0.847	0.892	0.849
	IBk	0.847	0.851	0.847	0.892	0.849
	KStar	0.808	0.814	0.808	0.862	0.932
	LWL	0.682	0.684	0.684	0.671	0.726
	REPTree	0.867	0.867	0.867	0.861	0.932
	Random Forest	0.706	0.706	0.706	0.710	0.729
	SMO	0.753	0.753	0.753	0.753	0.752
Boosting Ensemble Learrning Methods	IB1	0.824	0.830	0.824	0.879	0.855
	IBk	0.847	0.851	0.847	0.891	0.849
	KStar	0.796	0.803	0.796	0.852	0.831
	LWL	0.784	0.784	0.784	0.791	0.847
	REPTree	0.863	0.864	0.863	0.845	0.938
	Random Forest	0.788	0.788	0.788	0.801	0.878
	SMO	0.741	0.741	0.741	0.737	0.782
Bagging Ensemble Learning Methods	IB1	0.843	0.847	0.843	0.884	0.894
	IBk	0.847	0.849	0.847	0.879	0.893
	KStar	0.800	0.807	0.800	0.853	0.853
	LWL	0.717	0.720	0.718	0.702	0.786
	REPTree	0.847	0.851	0.847	0.817	0.919
	Random Forest	0.757	0.762	0.757	0.732	0.832
	SMO	0.737	0.737	0.737	0.739	0.809
Voting Ensemble Learning Methods	Model 1	0.847	0.851	0.847	0.891	0.849
	Model 2	0.847	0.851	0.847	0.891	0.849
	Model 3	0.847	0.851	0.847	0.891	0.942
	Model 4	0.847	0.851	0.847	0.891	0.922
	Model 5	0.854	0.861	0.855	0.907	0.934
	Model 6	0.870	0.874	0.871	0.909	0.928
	Model 7	0.878	0.881	0.878	0.911	0.926
Stacking Ensemble Learning Methods	Model 1	0.847	0.851	0.847	0.891	0.835
	Model 2	0.847	0.851	0.847	0.891	0.835
	Model 3	0.858	0.860	0.859	0.881	0.909
	Model 4	0.863	0.864	0.863	0.883	0.905
	Model 5	0.902	0.902	0.902	0.909	**0.944**
	Model 6	**0.906**	**0.906**	**0.906**	**0.910**	**0.944**
	Model 7	0.902	0.902	0.902	0.909	0.942
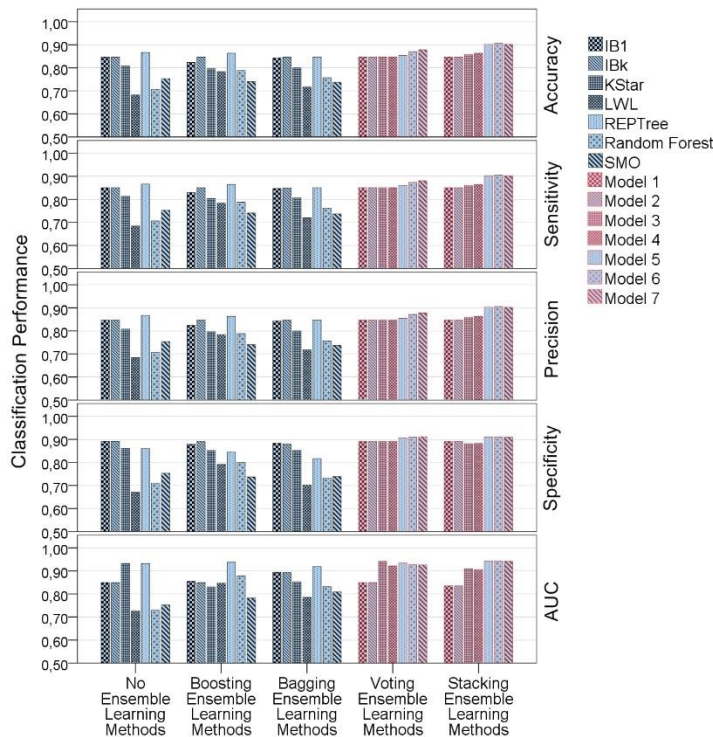
Figure 2. Comparison performance of ensemble learning methods.

In ensemble learning methods, more than one classifier functions in the model. The overall classification error of the ensemble model is reduced by combining the estimates of each classifier. Thus, higher performance and lower errors can be obtained in the ensemble learning method compared to only one classifier (13). Ensemble learning methods can provide higher performance than machine learning methods in the classification and early diagnosis of cancer diseases with low prevalence.

In this study, the classification performance of ensemble learning methods and machine learning methods were evaluated for the prediction of renal cell carcinoma. Classifiers IB1, IBk, KStar, LWL, Random Forest, REPTree and SMO were included in the model. In the model, besides the performance of each classifier, their performances in bagging, boosting, voting and stacking ensemble learning methods are also evaluated. According to the findings of the study, REPTree classifier achieved the highest performance among the classifiers which was not subjected to the ensemble method. The accuracy value of REPTree classifier was obtained as = 0.867 and AUC value = 0.932. In the study, the stacking ensemble learning method achieved the highest performance among the ensemble learning methods. The highest performance in the stacking ensemble learning method was observed in Model 6 (IB1, IBk, KStar, LWL, REPTree and Random Forest). The accuracy value of the Stacking ensemble learning method was obtained as = 0.906 and AUC value = 0.944. The classification performance of the classifiers which was not subjected to the ensemble learning method in the study was found to be compatible with the literature. Sing et al. compared the performance of Naive Bayes, SVM, K-NN algorithm and Random Forest classifiers to predict the progression of late stage papillary renal cell carcinoma. Random Forest classifier provided the highest performance. The accuracy value of the Random Forest classifier was determined as 0.885 (43). Kocak et al. used artificial neural networks to classify renal cell carcinomas in their studies. The accuracy value of the artificial neural network classifier was obtained as 0.692 (44). Jagga and Gupta used Random Forest, SVM, J48 and K-NN classifiers to classify renal cell carcinomas in their studies. Random Forest provided the highest classification performance. The accuracy value of the Random Forest classifier was obtained as 0.77 (45). Bektas et al. classified renal cell carcinomas according to tomography images in their study. They used random forest, K-NN, artificial neural networks and Naive Bayes classifiers in their studies (46). Lin et al. worked on decision tree-based classifiers to predict renal cell carcinomas with tomography images in their studies. They compared the performances of machine learning methods in the model. The highest performance value was achieved as AUC 0.87 (18). The random forest algorithm generally exhibits high performance in the classification of renal cell carcinomas. In this study, REPTree classifier achieved the highest performance among machine learning methods where ensemble learning methods were not used.

In the study, the performances of ensemble learning methods as well as machine learning methods were evaluated to predict renal cell carcinomas. The performance of the boosting, bagging, voting and stacking ensemble methods are evaluated in the model. The REPTree classifier provided the highest performance in the Boosting ensemble learning method. In the Boosting ensemble learning method, the accuracy value of the REPTree classifier was obtained as 0.863. The IBk and REPTree classifiers provided the highest performance in the bagging ensemble learning method. In the bagging ensemble learning method, the accuracy value of both classifiers was obtained as 0.847. Model 7 provided the highest performance in the Voting ensemble learning method. The accuracy value of Model 7 was obtained as 0.878. Model 6 provided the highest performance in the stacking ensemble learning method. The accuracy value of Model 6 was obtained as 0.906. According to these values, Stacking ensemble learning method provided the highest performance among machine learning and ensemble learning methods. Ensemble learning methods generally show higher classification performance than machine learning methods. Classification performances in our study are consistent with the literature. Mohebian et al. worked on the ensemble learning method for predicting breast cancer in their studies. Artificial neural networks, SVM and decision tree classifiers are included in the model. As a result of the classification of the model, the accuracy value was obtained as 0.892 (47). Hsieh et al. used ensemble learning methods to predict breast cancer in their studies. The classification performance of the model was obtained as 0.679 (48). Cai et al. used the ensemble learning method for the classification of lung cancer in their studies. Classification accuracy value of the model was obtained as 0.865 (49). Farahani, Ahmadi and Zarandi in their study, applied ensemble learning methods to detect lung nodules on tomography images. Support vector machine, K-NN and artificial neural networks are applied in the model (50).

In our study, ensemble learning methods showed a higher classification performance compared to machine learning methods in cancer types with low prevalence such as renal cell carcinoma. It has been observed that the ensemble model significantly contributes to the reduction of classification error. In order to increase the classification performance in ensemble learning method, it is very important to select the appropriate ensemble model, merging model and appropriate classifiers for the data set. Choosing the right meta classifier in the stacking ensemble method improves the classification performance. Ensemble learning methods can be successfully applied for the classification and early diagnosis of renal cell carcinomas. There are very few studies in the literature regarding the early diagnosis of renal cell carcinomas by ensemble learning methods. Our study will make a significant contribution to the literature in this field.

Conclusions

In this study, the classification performances of ensemble learning methods and machine learning methods were evaluated for the classification of renal cell carcinomas. High accuracy performance ensemble learning model has been established for early diagnosis of renal cell carcinoma. IB1, IBk, Kstar, LWL, REPTree, Random Forest and SMO classifiers were applied in the study. These classifiers are also included in ensemble learning methods. In the study, boosting, bagging, voting and stacking ensemble learning methods were applied. Stacking ensemble learning method provided the highest classification performance. Model 6 (IB1, IBk, Kstar, LWL, REPTree, Random Forest) provided the highest performance in the stacking ensemble learning method. The accuracy value of Model 6 was 0.906, the sensitivity value was 0.906, the specificity value was 0.906, the precision value was 0.910, and the AUC value was 0.944.

In our study, renal cell carcinomas were successfully classified with high performance using ensemble learning methods. The model created using the ensemble learning method can be successfully applied for early diagnosis of renal cell carcinomas. In our study, stacking ensemble learning methods provided higher classification performance than machine learning methods. Stacking ensemble learning method can diagnose renal cell carcinomas early with high accuracy performance using hemogram and laboratory findings.

Including more variables in the model in ensemble learning methods can increase the classification performance of the model. Increasing the number of samples in the dataset may contribute to the increase in classification performance. It is recommended to choose the appropriate meta classifier for the dataset in the stacking ensemble learning method. In order to increase the classification performance in ensemble learning methods, it is recommended to include different types of classifiers (decision tree-based, function-based and distance-based) into the model.

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RESEARCH ARTICLE

Assessment of Oxidative Stress with Thiol Disulfide Homeostasis and Ischemia-Modified Albumin Level in Acute Urticaria

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Abstract
Objective: There is no study in the literature investigating ischemia-modified albumin (IMA) values and thiol disulfide homeostasis (TDH) parameters in acute urticaria patients. This study aimed assessment of TDH parameters and IMA in acute urticaria patients.
Methods: The study included a total of 68 cases, with 35 acute urticaria patients and 33 healthy volunteers. Patients who presented to Ordu University Hospital and were diagnosed with acute urticaria between January 2019 and June 2019 and healthy individuals as the control group were included in the study. Serum albumin, IMA, native thiol, total thiol, and disulfide thiol levels were measured, and the results were compared between the groups.
Results: IMA values of 0.93±0.09 in the study group were significantly high compared to 0.8±0.10 in the control group (p<0.01). Native thiol (SH) level was 353.66±87.5 in the study group, 393.62±47.7 in the control group (p:0.022), and total thiol (TSH) level was 385.46±86.6 in the study group and 433.53±56.06 in the control group (p:0.008). In the patient group there was a significant negative correlation between SH levels and IMA levels (r=-0.626, p<0.001).
Conclusion: In acute urticaria, IMA increases while SH and TSH levels reduce. However, TDH does not change. The lack of change in the balance may be explained by acute urticaria being an acute event and not being a chronic inflammatory process.
Key words: acute urticaria, thiol disulfide, ischemia-modified albumin, oxidative stress

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Introduction

Urticaria is a disease occurring as itchy and edematous papules/plaques called urtica, with

angioedema (AE) linked to deep dermis or subcutis involvement or development of one or the other. Clinical tableau lasting less than six weeks is called acute urticaria (AU), while clinical tableau lasting six weeks or longer is called chronic urticaria (CU). Nearly 15-20% of people are determined to experience one AU attack during a period of their lives (1).

The most common triggers of AU attacks are infections, medications, and foods; however, in 50% of patients the situation remains idiopathic. Detailed history and physical examination are required for assessment of AU patients (2).

The balance between oxidants and antioxidants in the organism is the basis of preserving cellular and biochemical functions. Oxidants damage lipids, proteins and DNA in cells and even cause death (3,4). The most common and rapidly affected proteins are thiols containing sulfhydryl. Plasma thiols are strong antioxidants physiologically removing free radicals (ROS). Serum levels of plasma thiols are counted among markers showing antioxidant levels in the body (5). Normally there is a balance between thiols and disulfides, and these play a protective role for cellular redox homeostasis. This is called dynamic thiol/disulfide homeostasis. Defects in this balance may be associated with a variety of diseases (6). There is increasing evidence that ROSs play a role in the pathogenesis of a variety of inflammatory and allergic diseases including urticaria (7,8).

In recent times, another marker known as an oxidative stress marker is ischemia-modified albumin (IMA). Recent studies have shown ischemia-modified albumin (IMA) levels increase in free oxygen radicals formed because of ischemia, acidosis, or oxidative stress. The most common use is early myocardial injury. There are studies showing IMA levels increase in diseases causing oxidative stress like non-cardiac hypoxia, chronic renal disease, hypercholesterolemia, systemic sclerosis, and type 2 diabetes mellitus. In recent years, high levels of IMA are associated with a variety of diseases linked to oxidative stress (9).

There are very few studies about the correlation with oxidative stress in urticaria (4,10). There are a variety of studies reporting contradictory information about the oxidative stress status of chronic idiopathic urticaria patients. However, the number of studies investigating the thiol disulfide homeostasis in urticaria is very low and the majority are associated with chronic urticaria (4,10-12). There is no study in the literature investigating IMA values and TDH parameters in acute urticaria patients. In this sense, our study is the first to investigate IMA and TDH

parameters together in acute urticaria patients. With this aim, the new oxidative stress markers of thiol disulfide homeostasis and ischemia-modified albumin and the place of oxidative stress in acute urticaria pathogenesis was investigated.

Methods

The study included a total of 68 cases, with 35 being acute urticaria patients and 33 healthy volunteers. Patients who presented to Ordu University Hospital and were diagnosed with acute urticaria between January 2019 and June 2019 and healthy individuals as the control group were included in the study. Patients with physical urticaria and urticarial vasculitis were excluded from the study.

Serum albumin, ischemia-modified albumin, native thiol, total thiol and disulfide thiol levels were measured, and the results were compared between the groups. Patients' demographic data such as age and gender, vital signs, symptoms, lesion onset time, and urticaria activity score according to Turkey's urticaria diagnosis and treatment guidelines 2016 were recorded.

Biochemical analyses

Venous blood samples of cases attending with acute urticaria attack symptoms were taken in smooth gel tubes for biochemical tests (Becton Dickinson and Company, New Jersey, USA) and plasma samples for TDH tests were taken in EDTA tubes (Becton Dickinson and Company, New Jersey, USA). All samples were centrifuged at 1600xg for 10 minutes and stored at -70 °C until study. Biochemical tests were studied with an AU 2700 autoanalyzer (Beckman Coulter Inc. USA) with spectrophotometric methods.

Thiol measurements were assessed with spectrometry (Roche, cobas 501, Mannheim, Germany) using Erel et al.'s "modified Ellman method". Disulfide bonds (-S-S) were broken with sodium borohydride (NaBH4) to create free functional thiol groups (-SH). Unused sodium borohydride waste was removed with formaldehyde. In this way, reduction of any disulfide bond created by the DTNB reaction with 5,5'-dithiobis-(2-nitrobenzoic) acid (DTNB) was prevented. As a result of the DTNB reaction, total thiol groups were determined as reduced and native thiols. Disulfide parameter is a parameter calculated as half of the SH and TSH content. After SH and TSH were determined, SS, SS/SH+SS %, SH/SH+SS % and SS/SH % were calculated.

Ischemia-modified albumin was analyzed with the albumin cobalt binding (CAB) test. The serum sample had 50 mL 0.1% cobalt (II) chloride added (CoCl2, 6H2O) (Sigma-Aldrich ChemieGmbHRiedstrasse 2, Steinheim, Germany). After waiting 10 minutes, binding of albumin to cobalt was ensured and 50 mL 1.5 mg/mL dithiothreitol was added. After waiting for the 2-minute incubation period, 1.0 mL 0.9% sodium chloride solution was added. Using a spectrophotometer at 470 nm, the absorbance of samples was measured (Jenway 6315 UV/visible Scanning Spectrophotometers, United Kingdom). Results are given as mg/dL. The albumin concentration was calculated by using the bromocresol green staining method (Biolabo, LesHautesRives, 02160, Maizy, France).

Statistical analysis

All data analyses were conducted using the SPSS v25 (IBM Inc., Chicago, IL, USA) statistical software package. Prior to the statistical analyses, the data were tested for normality using the Shapiro–Wilks test and for homogeneity of variance using the Levene's test. Independent samples t-test was used to assess differences between two groups. Cross-tabulations were generated to describe the relationship between categorical variables, and the independence check was performed on the cross-tabulations using a chi-square test ($\chi 2$) and Contingency Coefficient (CC). Likelihood Ratio Chi-square values (LR $\chi 2$) were calculated for frequencies below 5. The Pearson's correlation analysis test was used to determine the relation between continuous variables. All comparisons were two-tailed and P-value less than 5% was considered statistically significant.

Power analysis

The sample size for this study was estimated by a priori power analysis using GPower 3.1 (Universität Düsseldorf, Düsseldorf) statistical software; assuming a large effect size (d=0.80), $\alpha=0.05$ and $1-\beta=0.80$, a minimum sample size of 26 in each group was required to detect the significance of the independent groups in the t-test.

Ethics of the Study

This study was approved by the local ethic committee of Ordu University Medical Faculty with the 2018/234 numbered decision. All participants were informed in detail about the objective of the study and gave written consent. The study was performed in accordance with the ethical principles of the Declaration of Helsinki.

Results

A total of 35 patients with urticaria (patient group) and 33 healthy subjects (control group) participated in this study. IMA values were significantly higher in the patient group than in the control group (p<0.01). Native thiol (SH), Total thiol values were significantly lower in the patient group than in the control group (p<0.01). No other differences regarding study variables were observed between the patient group and the control group (p>0.05) (Table 1).

Table 1. Descriptive statistics and comparison results for the study variables in the patient and control groups.

	Control (n=33)	Patient (n=35)	P-Value
Albumin	4.476±1.551 (1.5-7.2)	4.559±1.432 (1.7-7.6)	0.819[NS] (t=-0.230)
IMA	0.848±0.106 (0.6-1.1)	0.936±0.096 (0.7-1.09)	0.001** (t=-3.582)
NATIVE THIOL (SH)	393.621±47.727 (239.8-481.0)	353.669±87.506 (145.5-517.9)	0.022* (t=2.355)
TOTAL THIOL	433.536±56.067 (267.8-549.0)	385.469±86.663 (187.5-549.0)	0.008** (t=2.731)
DISULFIDE (SS)	19.958±7.772 (1.0-36.0)	16.95±3.64 (8.0-23.0)	0.051[NS] (t=1.99)
SS/SH %	5.052±1.718 (0.2-7.8)	4.916±2.519 (0.9-14.4)	0.797[NS] (t=0.259)
SS/TOTAL THIOL %	4.544±1.449 (0.2-6.8)	4.387±1.980 (0.8-11.2)	0.711[NS] (t=0.371)
SH / TOTAL THIOL %	90.910±2.896 (86.5-99.6)	91.225±3.961 (77.6-98.3)	0.711[NS] (t=-0.372)

Mean±Standard Deviation (Minimum-Maximum); t, Independent samples t-test.
[NS] Statistically not significant (p>.05); * Statistically significant (p<0.05); ** Statistically significant (p<0.01).

In the patient group, there was a significant negative correlation between the native thiol (SH) levels and the IMA levels (r=-0.626, p<0.001). In the patient group, there was a significant positive correlation between the SS/SH (%) levels and the IMA levels (r=-0.626, p<0.001). Native thiol decreased significantly as IMA increased in the patient group (r=-0.684, p<0.001; r=-0.626, p<0.001, respectively) (Table 2 and Table 3).

Table 2. Pearson correlation coefficients between the study variables of patient and control groups.

		ALBUMIN	IMA	NATIVE THIOL (SH)	TOTAL THIOL	DISULFIDE (SS)	SS/SH %	SS/TOTAL THIOL %	SH/TOTAL THIOL %
Albumın	r		*-0.232*	*0.043*	*0.044*	*0.009*	*-0.046*	*-0.032*	*0.032*
	P		*0.181*	*0.808*	*0.801*	*0.960*	*0.793*	*0.857*	*0.855*
Ima	r	-0.088		*-0.626*	*-0.620*	*0.102*	*0.410*	*0.409*	*-0.410*
	P	0.627		*0.000****	*0.000****	*0.560*	*0.014**	*0.015**	*0.014**
Natıve Thıol (Sh)	r	0.327	-0.684		*0.994*	*-0.141*	*-0.693*	*-0.686*	*0.687*
	P	0.063	0.000***		*0.000****	*0.418*	*0.000****	*0.000****	*0.000****
Total Thıol	r	0.303	-0.665	0.968		*-0.029*	*-0.618*	*-0.607*	*0.607*
	P	0.087	0.000***	0.000***		*0.871*	*0.000****	*0.000****	*0.000****
Dısulfıde (Ss)	r	0.088	-0.298	0.421	0.635		*0.716*	*0.755*	*-0.755*
	P	0.627	0.092	0.015*	0.000***		*0.000****	*0.000****	*0.000****
Ss/Sh %	r	-0.022	-0.088	0.091	0.337	0.937		*0.996*	*-0.996*
	P	0.905	0.627	0.616	0.055	0.000***		*0.000****	*0.000****
Ss/Total Thıol %	r	-0.010	-0.072	0.077	0.324	0.933	0.999		
	P	0.954	0.692	0.671	0.066	0.000***	0.000***		
Sh/Total Thıol	r	0.010	0.072	-0.077	-0.324	-0.933	-0.999	-1.000	
	P	0.956	0.690	0.670	0.066	0.000***	0.000***	0.000***	

r, Pearson correlation coefficient in the patient group; r, Pearson correlation coefficient in the control group.
*, Statistically significant (p<0.05); ***, Statistically significant (p<0.001).

Table 3. Pearson correlation coefficients between the study variables of patient and control groups.

	Control (n=33)			Patient (n=35)		
	IMA	NAT. T	TOTAL T	IMA	NAT. T	TOTAL T
NATIVE THIOL (SH)	-0.684***			-0.626***		
TOTAL THIOL	-0.665***	0.968***		-0.620***	0.994***	
DISULFIDE (SS)	-0.298	0.421*	0.635***	0.088	-0.192	-0.113
Index I	-0.088	0.091	0.337	0.410*	-0.693***	-0.618***
Index 2	-0.072	0.077	0.324	0.409*	-0.686***	-0.607***
Index 3	0.072	-0.077	-0.324	-0.410*	0.687***	0.607***

r, Pearson correlation coefficient
*, p<0.05; ***, p<0.001

Discussion

There is a balance between free radical production and the antioxidant system suppressing the increase in ROS in the body. If this balance is disrupted, oxidative stress (OS) occurs. There are studies assessing the oxidative stress in urticaria patients. Some studies have shown an increase in OS, while some studies have chosen no change in OS (13-17).

Most studies researching oxidative stress have been performed on chronic urticaria patients (4,10-12).

Oxidative stress has been studied in acute urticaria (AU) and chronic urticaria patient groups with different markers such as malondialdehyde (MDA), glutathione peroxidase (GSH-Px) and catalase (CAT). Studies by Kalkan et al. compared acute urticaria patients with healthy controls and found Cu/ZN superoxide dismutase (SOD) activities and

MDA levels were high and plasma GSH-PX activity reduced (1,10,14). In allergic diseases, especially asthma and to a lesser degree atopic dermatitis, there is increasing literature about the role of oxidative stress.

Free radicals occurring due to normal metabolism or pathologic processes disrupt the structure and functions of thiol dependent enzymes and cause changes in the thiol/disulfide ratio in the cell environment. Reduced plasma thiol concentration shows increased production of free radicals (6). In this study native thiol and total thiol levels reduced but disulfide thiol levels did not increase. But another oxidant parameter, IMA increased. Reduced native thiol levels are not definitely associated with increasing disulfide levels and similarly increased native thiol levels are not definitely associated with reduced disulfide levels. This may be associated with the immune response of thiols to inflammation. Reduced plasma thiol concentration is proof of free radical production. Reduced thiol levels are also associated with leukocyte activation. Urticaria mast cells are associated with immunologic activation and inflammation with oxidative stress (OS) activation of basophils and eosinophils and finally increased ROS (18). Stimulation of all inflammatory cells produces a significant amount of ROS. Eosinophils have higher peroxidase levels compared to other inflammatory cells and have a unique role in formation of oxidative stress (19).

In the acute urticaria patient group in our study, we identified reduced SH and TSH levels compared to the healthy control group. In the literature there are studies of dynamic thiol/disulfide homeostasis in different diseases. Eren et al. (20) showed total thiols were clearly reduced in migraine patients compared to a control group. Ates et al. (21) showed primary hypertension patients had total disulfide balance moving toward disulfide. Kundi et al. (22) identified reduced native and total thiol levels in patients with acute myocardial infarction compared to the control group and stated that thiol/disulfide homeostasis may be a new oxidative stress (OS) marker for acute myocardial infarction patients. A study by Ozyazıcı et al. (23) stated that the total disulfide balance had slid toward disulfide linked to thiol oxidation in a patient group with acute appendicitis and that this balance may be an OS marker for acute appendicitis patients. Yilmaz et al. (24) reported research on the thiol/disulfide homeostasis in asphalt workers exposed to polycyclic aromatic hydrocarbons.

In ischemic conditions, the shape of the amino terminal tip (N-terminal) of albumin changes and metal binding capacity reduces. As a result, this new form is a new ischemia marker called ischemia-modified albumin (IMA). Though IMA levels were initially considered specific to ischemia, superoxide radical damage, and exposure to free iron and copper have been shown to cause IMA formation (25). Based on these factors, in addition to ischemia-associated diseases, IMA values were shown to increase in some inflammatory diseases (26-28). In our study, a significant increase was identified in IMA levels in the acute urticaria patients compared to the control group.

Ozdemir et al. (29) reported increased IMA levels in patients with psoriasis due to an adaptive response to oxidative stress and systemic inflammation. However, Erem et al. (30) found the IMA irrelevant to oxidative stress.

Mast cells are known to play an important role in allergic diseases. As a result of antigen exposure, mast cells are sensitized and release many mediators causing allergic symptoms (31). Oxidative stress may ease degranulation of mast cells in response to allergens contributing to the development of allergic reactions. In the literature, there are some studies showing an association between oxidative stress and a variety of allergic diseases (3,13,14,19,31,32). Patella et al. (32) found that hymenoptera venom allergy levels of advanced oxidation protein products were consistently high during immunotherapy. They suggested that an oxidative stress state occurs in patients with hymenoptera allergy.

The colorimetric test performed on serum is based on decreased binding of exogenous cobalt to albumin which occurs in tissue damage caused by free radicals. (33). This issue was supported by the reports suggesting that IMA is strongly related with oxidative stress rather than being a myocardial ischemia marker (34,35).

Limitations

The lack of follow-up data, single blood sampling and small sample size are the limitations of our study. This study does not allow any conclusion about the causative correlation between acute urticaria and underlying interactions. To clarify the underlying mechanisms, it is necessary to confirm these findings in future studies with larger sample sizes.

Conclusions

Acute urticaria is a disease without definitely known cause. There are studies related to OS as a part of studies about etiopathogenesis. In our study, our objective data identified that SH and TSH levels reduce, and IMA values increase in AU. In

conclusion, based on our data and literature information, we think increased IMA levels and reduced SH and TSH levels may be markers of oxidative stress in acute urticaria.

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An Interactive Web-Based Software for Epidemiological Research Designs

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Abstract
Objective: The aim of this study is the development of Epidemiological Research Design software that enables to determine the correct epidemiological research design have web-based, free and Turkish / English language options.
Methods: From Epidemiological Research Designs in the software developed; a definitive system has been established for Case Presentation, Case Series, Correlational (Ecological), Cross-Sectional Research, Case / Control, Cohort, Field Intervention, Clinical Intervention, Ethnography, Phenomenology, Grounded Theory and Qualitative Case Studies. For this purpose, questions are asked to the researcher to determine which research design to use. This software has been developed using the Python programming language. For this purpose, the dash library in Python was used.
Results: Determining the research design before starting a study is a very important step. Although there are some differences in the grouping of epidemiological studies in various sources, the characteristics of the methods are basically the same. It is thought that the software developed in this study will allow researchers to determine the correct research design by eliminating these differences. The developed software can be accessed at http://biostatapps.inonu.edu.tr/EATY/.
Conclusion: It is thought that the web-based software developed, free and with Turkish / English language options, will guide and contribute to researchers in determining epidemiological research designs.
Key words: Epidemiological Research Designs, Observational Studies, Experimental Studies, Qualitative Research, Python

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Introduction

In order to contribute to science, researches carried out by collecting, interpreting and evaluating data in a planned and systematic manner are called scientific research. The results obtained from a small group of scientific researches are transferred to the society and new information is created about the reliability of diagnosis, treatment and applications. For this reason, the researcher must determine the scientific study subject, plan it and determine its methodology before starting the research (1).

The purpose of Epidemiology is to investigate the distribution, frequency and causes of health problems or events in human populations, and these purposes are planned and achieved with various types of epidemiological research. Epidemiology is one of the basic disciplines of public health. Measuring disease or health problems is important in epidemiology. Data belonging to societies are collected in certain criteria and presented in graphics and tables. The health problem is presented with some criteria such as disease criteria (incidence, prevalence), death criteria (mortality rates), risks, rates, percentages, and comparisons are made with statistical methods (2, 3).

In health sciences, epidemiology is mainly; It is used to determine the causes of diseases and health problems, to reveal the natural development of diseases, to determine the health levels of societies, to examine and compare with other societies, to evaluate clinical research results, to evaluate the effectiveness of health services and to determine the risks of people facing certain health problems It is important to investigate the distribution and determinants of health-related conditions or events within specific populations and to use the results of these studies to control health problems. They differ in terms of research design, methods/analyzes used and interpretation because they are conducted on communities. In this sense, they differ from basic medical research conducted at the individual or even cellular level in order to explain the mechanisms of health-related events. Therefore, determining the research design is a very important step before starting a research (2-4).

The aim of this study is to develop web-based and free epidemiological research design software that can automatically determine the epidemiological research design by asking specific questions to the user. The software includes English and Turkish language options. The developed software can be accessed at http://biostatapps.inonu.edu.tr/EATY/.

Methods

Hypothetical examples
Calculations for determining epidemiological research designs in medicine and other health fields were made with the web-based software proposed in this study.

In the study has determinant calculations for observational and experimental studies from epidemiological research designs. Observational studies are examined under two headings as descriptive and analytical. Experimental studies are divided into two as clinical and field intervention studies. The epidemiological research designs found in the developed software are described below.

Quantitative Research

Observational Studies
The event examined in Observational Epidemiological studies, which is one of the epidemiological research types, is observed in its natural course and no intervention is made by the investigator to the course of the event. In other words, factors (such as age or gender) and events (such as any factor or treatment method) examined by the researcher are not under the control of the researcher and cannot be changed by the researcher. Except for the examined factor or event, all variables cannot be kept constant. Randomization can be used limitedly in some cases. The cause-effect (factor-disease) relationship may not always be determined precisely and clearly. This level of clarity may differ depending on the subject and research method used (5).

Descriptive Studies
Descriptive type of research from observational epidemiological studies are studies conducted to define the occurrence and frequency of a certain health problem or disease in a society (6). Descriptive Studies are examined in three groups as Case Presentation, Case Series and Correlational (Ecological).

Case Presentation Studies
Case Presentation is a type of study in which a rare disease picture or a different clinical form of a known disease is described in detail with clinical and laboratory findings. As the name implies, there is "one case (or 1-2 cases)" in a case report study and therefore no statistical analysis is required (7).

Case Series Studies
In case series studies, interesting findings observed in the rare case (patient) group are recorded and definitions are made for the data obtained. Such a study does not aim to examine the cause-effect relationship or to discuss whether a treatment is superior or not. Such studies are guiding studies for further studies (cross-sectional, retrospective (case-control), prospective (cohort), etc.). It is not appropriate to make inferences about the universe in case series studies; because there is no sample that represents the universe (6).

Correlational (Ecological) Studies

Correlational research, also called ecological research, is like the first step of epidemiological studies. These types of studies are fast, inexpensive, often obtained from data that are routinely collected for another purpose. Here, individual people are not examined, but the data of the society are used. Data about the whole society are compared and correlated with each other. These types of studies are mostly the early examinations of the diet-disease relationship. For example, the relationship between per capita meat consumption and colon cancer was compared in various countries, and it was observed that as meat consumption increased, colon cancer also increased. However, this definition does not prove that high meat consumption increases colon cancer. In societies where meat consumption is high, fiber may be consumed less or animal fat may be consumed too much (8, 9).

Analytical Studies

Analytical epidemiological studies reveal whether the relationships between a health problem and various factors thought to cause this health problem are real (10). Analytical Studies are divided into three as Case-Control, Cross-Sectional and Cohort studies.

Case-Control Studies

Since the causality relationship is examined retrospectively in case-control studies, these studies are also called "retrospective" studies, which means "backwards" in Latin. First, a group of cases is taken, then a similar control group is selected, and the backgrounds and characteristics of the people in both groups are examined and compared, trying to understand and interpret similar and different characteristics (11).

For example, if a hypothesis has been created that smoking may be associated with lung cancer in the light of the results obtained from lung cancer screening, a group of patients with lung cancer is selected first in the case-control study to be planned to test this hypothesis. Then, controls with similar characteristics to those in this group are selected from among people without lung cancer. The meaning of similar features means that the relationship of the two groups is similar in terms of all features except the variable to be examined. In other words, apart from smoking habits, attention is paid to be similar in terms of gender, profession, age and similar characteristics that may be associated with the development of lung cancer. The better this method called "matching" is designed, the more meaningful the results will be. After the cases and controls are determined, all the characteristics of the people in both groups related to their health are examined. A more detailed examination is made on the variable chosen for causation. In other words, apart from asking whether or not people have been smoking, details such as how long and how much they have smoked, whether they have smoked in the past, quitting and restarting, and their presence in smoking environments, are **discussed**. If a good match is made in terms of other features that may play a role in the formation of lung cancer, the relationship between smoking and lung cancer can be demonstrated by making risk calculations (12).

The calculation of risk in case-control studies is called "estimated relative risk" or, more technically speaking, "odds ratio". If the estimated relative risk for lung cancer development is found to be 4, for example, the interpretation of this is that "past or current smoking increases lung cancer risk by an estimated 4 times compared to people who have never smoked". The most important drawback of these studies is the difficulty of collecting reliable information about the past. Failure to collect reliable information about the past, sometimes due to the memory factor, sometimes due to lack of recording means that the resulting relationship will always be a controversial and "predictive" relationship. However, since these studies can be done in a short time and do not bring much cost in every sense, they are of a quality that can shed light on many causality relationships if they are well designed (13, 14).

Cross-Sectional Studies

Cross-sectional studies are studies conducted in the form of collecting data from a specific section of society in a specific time period. All screenings related to health or diseases are considered cross-sectional in this sense. For example, by conducting a screening for lung cancer in any community, those with and without lung cancer can be identified and various characteristics related to them. During the screening, some cases that are already known to have lung cancer may be encountered, as well as new cases that are found to be sick with this screening for the first time. The prevalence of lung cancer is the prevalence obtained by dividing the old and new cases by the number of people screened. Since prevalence can be calculated in cross-sectional studies, these studies are also known as prevalence studies (15, 16).

Cohort Studies

In Cohort studies, a cohort group to represent the society is selected first. Cohort literally means

"individuals with common features, a community of units". Later, this group is monitored in terms of the disease that is the subject of research. Depending on the natural course of the disease, the time required for the emergence of the disease and its death or healing, follow-up is performed for days, months, or even years. Regular and detailed data are collected about whether the monitored people encounter various risk factors that may cause the disease, and the changes in their health. During these follow-up, when there are individuals who leave the study or disappear, the initial cohort size should be well calculated, since it will not be possible to replace them. As a result, the rate of disease occurrence between individuals who have been exposed to various factors and individuals who have not encountered these factors is calculated. Cohort studies are also known as incidence studies, because the name of the disease prevalence occurring within a certain period of time is "incidence" and incidence can be calculated in these studies. The difference between the disease incidences the group that encountered the factor and the group that did not encounter the factor is called "risk attributed", and the ratio between incidences is called "relative risk" or "risk ratio" (17).

For example, in a cohort study that will be planned to examine the relationship between lung cancer and smoking habits, the cohort group should be composed of people who do not have lung cancer, that is, this must be the common feature. Later, this group is divided into subgroups in terms of smoking habit and started to be followed. Examination data regarding the development of lung cancer are collected at regular intervals from all individuals in the cohort group. In addition, smoking habits and other characteristics are recorded. This type of research continues for years, as lung cancer takes years to emerge and end. As a result, it is determined that some individuals among smokers and some individuals among non-smokers have the disease and lung cancer incidence is calculated for both groups. The causality relationship between smoking habit and lung cancer is interpreted by looking at the difference between incidences and the ratio between incidences. For example, if the incidence of cancer in smokers is 0.4%; If it is found to be 0.1% for non-smokers, the relative risk is 4, and this result is interpreted as "smokers are 4 times more likely to develop lung cancer in the future than non-smokers". Since the risks calculated in these studies are not affected by the memory factor as in case-control studies and there is no estimated risk, they are considered to be a more precise indicator of causality. The high costs in terms of time, money and manpower of these research

types, which have superiority in terms of causality, are their weaknesses (18-20).

Experimental Studies

In experimental studies, factors and events (such as any factor or treatment method) examined by the researcher are under the control of the researcher and can be changed if desired. For example, a researcher can give a drug to various groups with predetermining characteristics (age, gender, etc.) in various doses and evaluate their effects. All variables other than the factor or event examined can be kept constant, or the participants or methods can be randomly divided into intervention (experimental) and control groups. This is called randomization. In addition, the cause-effect relationship can be determined completely and accurately (21).

Intervention Studies

Intervention studies are types of research that are planned in order to determine cause-effect relationships or to determine control methods. It is examined in two groups as clinical and field intervention studies (22).

Clinical Intervention Studies

Clinical trials are generally epidemiological studies planned to evaluate the effectiveness of diagnosis and treatment methods. These are mostly done to determine the efficacy and safety of various drug or treatment methods. Although it is used to refer to studies that go through the stages known as Phase I, II, III and IV, it refers to all studies conducted to test any treatment or prevention method using epidemiological methods among those who come to the clinic. Consisting of these methods, clinical epidemiology has become a sub-branch of its own scientifically. Clinical experimental studies can be designed as "parallel or synchronously controlled", "cross-controlled", "randomized controlled", "externally controlled" or, in very special cases, "uncontrolled" studies. Although there are many different design forms, the main feature of these studies is that a drug or treatment method, whose effectiveness and safety will be examined, is given to a group of patients with defined clinical characteristics and compared with a control group with the same disease who received another treatment or placebo. If the groups are selected well, the controls are matched, and the research design and data collection process are done well, it becomes possible to say to what extent the differences are dependent on the new drug or treatment method. Although various velocity, ratio and risk calculations

are made in order to examine causality in these studies, the way of making and interpretation of these calculations is different from the calculations and interpretation of the results of observational research on communities (23, 24).

Field Intervention Studies

Field studies, which are among the experimental epidemiological researches, are studies planned in healthy people, unlike clinical studies. Field research is a concept that refers to experimental research on communities. The aim of these studies is to examine the efficacy and safety of any treatment or prevention method. However, unlike clinical trials, they are designed to be performed on human populations rather than on cases that come to the clinic. Communities of people can be people of a geographic area, country, settlement or any other environment. The difference is that the experimental and control groups were selected from groups, not individuals. For example, conducting various health education activities in one of two settlements with similar characteristics to control alcohol and substance addiction, and collecting and interpreting data on the change of alcohol and substance use habits in both communities over time, leaving the other on its own, is an example of a community experiment. Similarly, the chlorination and purification of the mains water of a settlement and the interpretation of the health problems here by comparing the water with another non-chlorinated settlement is a classic example of community experiment (25-27).

Qualitative Research

Ethnography

The main purpose of the ethnographic research method is to observe the participants in the cultural environment they live in and to make descriptions regarding a specific subject. What is important here is to watch the participants in their natural environment and to associate the information obtained as a result of observation with the cultural characteristics of the environment where the participants are located. The characteristics of ethnographic research can be listed as follows:

•   These studies reveal to what extent the cultures they live in affect the experiences and behaviors of individuals.

•   In ethnographic studies, relatively small sample sizes are studied.

•   The focus in ethnographic research is the group structure and cultural environment studied. The researcher is part of the cultural environment under study and is affected by this culture.

•   The basic approach followed in the data collection phase in the research is based on "unstructuredness".

•   In the analysis of the data obtained, the behaviors and verbal expressions of the individuals are interpreted (28, 29).

Phenomenology

Phenomenology aims to examine the existence of a particular phenomenon based on the participants' perception and experience of that phenomenon. Although the development of phenomenology goes back to ancient times, it first developed as a science in the first period of the twentieth century under the leadership of Edmund Husserl (30).

In phenomenological studies, expressing and examining a subject as a phenomenon varies according to the participant's position, perspective, experiences and purpose in the formation of his perception. Therefore, every issue should not be handled as a phenomenon and not analyzed (31).

According to the phenomenological point of view, there is no single reality and the existing reality may change according to how individuals perceive the relevant phenomenon and time. The fact that different individuals perceive the same phenomenon differently in the same situation forms the basis of phenomenological research. For example, the answers given by the students taking the course to the exam questions at the end of the semester will be different from each other (32).

Grounded Theory

The most important point of any research project is that it needs conceptualization. This happens in two ways. The first is to be a preparation for the research so that the reader is informed about the focus of the study. The second is carried out by making a literature review on the subject at the beginning of the research and reveals the basic structure of the subject to be used in later studies. This method, which is expressed as an embedded theory, sub-theory or grounded theory in the literature, was created by Glaser and Strauss (1967) and was especially expanded by the studies of Strauss and Corbin (1998) and Charmaz (2002). The main purpose of this research method is to define the relationship between conceptual categories and to reveal in detail in which theoretical relationships these are formed, changed and maintained. In this research method, revealing the concept depends on the systematic collection and analysis of the data. Here, it is expected that the

researcher will not start researching with any ideas at the beginning of the study and therefore define the real concept under the categories (33, 34).

Qualitative Case study

Unlike other qualitative research methods, the important point in the case study method is to focus on a specific unit of analysis, in other words, the case (case) rather than collecting and analyzing data. In case studies, the unit of analysis can be an institution, a city, a group of people, a society, a patient, a school, an application, an accident, a situation or an experience. The features of case studies can be listed as follows:

• Has a point of view that explores individual differences: Here, rather than addressing the general of the researcher, it is trying to understand a particular event with all its features.

• Considering the contextual data: The researcher handles the case together with all the subjects it covers. Therefore, certain events should be defined as the focus of the research.

• Uses the diversification method: In case studies, many data collection methods are used together in order to examine the subject in more depth.

• It has a temporary feature: The characteristics of the event examined in case studies may change over time.

• It prepares the ground for the formation of the theory: Since case studies involve making in-depth studies on a particular subject, they cover all processes and this facilitates the emergence of the theory behind the case under investigation (31).

Web Based Software

Epidemiological research design software has been developed as web-based and can be used free of charge from any device (desktop computer, laptop, mobile phone, etc.) with an internet connection. The software was developed using the DASH library in the Python programming language (35). Includes English and Turkish language options. The current software can be accessed at http://biostatapps.inonu.edu.tr/EATY/..

Results

The software consists of three main menus. First, the introduction menu (Figure 1) contains a brief description of epidemiological studies. The design determination menu (Figure 5-6-7) allows the researcher to easily determine the research design by asking a few questions for descriptive and experimental epidemiological studies. In addition,

there is a table in this menu that provides more detailed information for the designated research Examples of Intervention Studies

An example for the Clinical Intervention Study:

For example, suppose a new antibiotic or cancer drug is being researched. Whether a drug used twice a day would have the same effect with less side effects should be investigated. The aim here is to determine which of the two treatment methods is more effective.
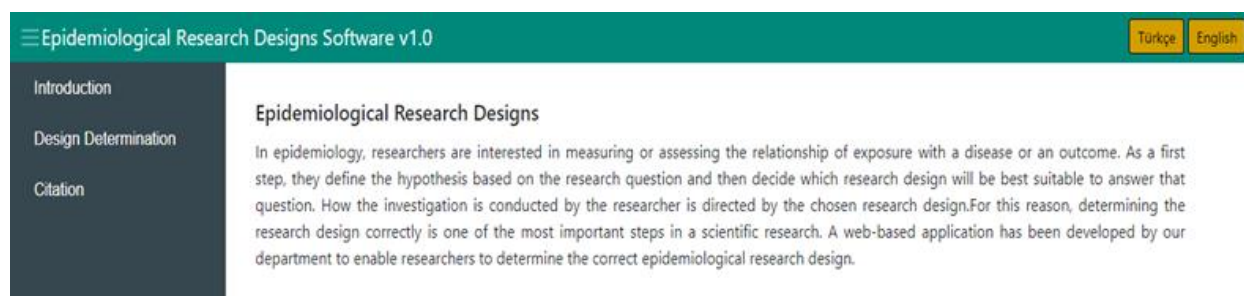
The type of research in this study is quantitative, there is an intervention (active substance is being tested) and the main aim of the study and the route followed is the effectiveness and safety of the treatment. Therefore, the related study is a clinical intervention study. When all these options are selected in the software, the criteria (Relative Effectiveness, Protectability dimension) obtained from the research appear automatically. The steps to determine the type of this study in the software are as in Figure 4.design. This table can be accessed by clicking the "Click for Detailed Information on Proposed Research Design" button that appears after the questions are answered in the design determination menu. The following examples are made to demonstrate how the software works and its principle.

Examples of Descriptive Studies

An example for the Case Series Study:

If the type of research in the relevant study is quantitative, if there is no attempt, no hypothesis and the research unit include more than one person, the relevant study is the Case Series. The steps for determining the type of this study in software are as in Figure 2.

Examples of Analytical Studies

An example for the Cohort (Follow-up) Study:

A cohort type study was conducted to examine the relationship between lung cancer and smoking. For this purpose, 2000 cigarettes selected from the society. A smoker group and a non-smoker group of 2000 people were selected and followed for a certain period of time, and as a result of this follow-up period, lung cancer prevalence was found in both groups.

The type of research in this study is quantitative, there is no intervention (there is a period of follow-up), there is a hypothesis (what is the risk of lung cancer in smokers compared to non-smokers), and the direction of the research is forward. Therefore, the related study is a Cohort study. When all these options are selected in the software, the criteria obtained from the research (Incidence Rate, Relative Risk, Attributable Risk, Preventability Rate, Dose-

response relationship) automatically appear. The steps to determine the type of this study in the software are as in Figure 3.

Examples of Intervention Studies

An example for the Clinical Intervention Study:

For example, suppose a new antibiotic or cancer drug is being researched. Whether a drug used twice a day would have the same effect with less side effects should be investigated. The aim here is to determine which of the two treatment methods is more effective.

The type of research in this study is quantitative, there is an intervention (active substance is being tested) and the main aim of the study and the route followed is the effectiveness and safety of the treatment. Therefore, the related study is a clinical intervention study. When all these options are selected in the software, the criteria (Relative Effectiveness, Protectability dimension) obtained from the research appear automatically. The steps to determine the type of this study in the software are as in Figure 4.

Examples of Analytical Studies

An example for the Case Control Study:

In a study planned to determine whether there is a causal relationship between Hodgkin's disease and previous tonsillectomy; case group with Hodgkin's disease and control group intact. In this study, it is aimed to compare the probability (risk) of developing Hogkin's disease in those who have had tonsillectomy in the past compared to those who did not have tonsillectomy.

The type of research in this study is quantitative, there is no intervention (there is a backward scan), and there is a hypothesis in the research (whether there is a causal relationship between Hodgkin's disease and previous tonsillectomy), and the direction of the research is backward. Therefore, the related study is a case-control study. When all these options are selected in the software, the criteria (Odds ratio) obtained from the research appear automatically. The steps to determine the type of this study in the software are as in Figure 5.

Figure 1. Introduction Menu

Figure 2. Results Screen in Software for Case Series Studies

Figure 3. Results Screen in Software for Cohort (Follow-up) Studies

Figure 4. Results Screen in Software for Clinical Intervention Studies

Figure 5. Results Screen in Software for Case Control Studies

Discussion

Today, in the field of health, information is developing rapidly and physicians have to know the most accurate and reliable way to reach. It is possible to continuously and regularly research, interpret, and conduct research to improve and improve healthcare services. Proper planning of all scientific research in the field of health; an epidemiological research design is needed in order to give unbiased, reliable and realistic results and to evaluate the results correctly (1, 4).

In any society (this society may be a country, it can be a region, province, district of the country, employees of a factory, school students, or any social group) what the health status is, the most seen, the most killing and the most Epidemiological and biostatistical methods are used to define the quantity and quality of health problems that cause social burden. It is tried to reach some statistical findings based on the data that existed first. When this is insufficient, clearer information about diagnosis can be obtained by planning a research with epidemiological methods. For the treatment of societies whose health status has been examined and problems have been identified, health education studies are conducted at the community level to control risk sources and to change the health behaviors of individuals positively. Therefore, it may be necessary to plan and organize services to solve the problems, as well as to be successful in solving the problems by better management of the existing health system (36, 37).

Determining the correct research design is a very important step in epidemiological studies. Because each research design has strengths and weaknesses relative to each other. These research designs depend on the purpose of the research, its hypothesis, the number of people included in the research, the direction of the research, the criteria to be obtained from the research, etc. varies according to. There are different information in different sources in the literature for the classification of epidemiological studies. The software developed in this study can enable researchers to determine the correct epidemiological research design before starting their studies.

Conclusion

As a result, it is thought that the software will prevent information differences and misclassifications in the literature in determining the research design.

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Determining the Effects of Women's Fertility Awareness Levels on Obstetric History

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Abstract

Objective: This study was conducted using the Google Forms platform to determine the effects of women's fertility awareness on their obstetric histories.

Methods: The sample of this cross-sectional study consisted of 365 women between the ages of 18 and 49 who visited three family health centers in eastern Turkey. The data has been collected via Google Form. Data were collected using the Personal Information Form and the Fertility Awareness Scale (FAS). Descriptive statistics (n, %, mean, standard deviation, min-max), Cronbach alpha, Pearson correlation, chi-square and independent sample t-test were used in statistical analysis.

Results: 365 women participated in the study. The women with a mean age of 34.25 ± 6.82 had a mean score of 38.74 ± 6.45 in the Bodily Awareness dimension of FAS, a mean score of 32.14 ± 5.28 in the Cognitive Awareness dimension of FAS, a mean total score of 70.89 ± 10.50 in FAS, and they were determined to have a high level of fertility awareness (61.1%). The participants' mean scores of Bodily Awareness were determined to decrease with their age of marriage and age of first childbirth ($p<0.05$). The mean FAS total and dimension scores of the women who were employed, those who had a high level of education, those who had a good economic status and those who used modern family planning methods and trust these methods were determined to be higher ($p<0.05$). The women who had sexually transmitted diseases and reproductive system infections in the past were determined to score higher, while the women who had problems during the conception process and pregnancy were determined to score lower ($p<0.05$). Among women surveyed, it was determined that miscarriage, abortion, stillbirth and having a dead child did not affect fertility awareness.

Conclusion: In this study, among women surveyed, fertility awareness was observed to be affected by socio-demographic characteristics such as marriage age, first childbirth age, employment status, and economic status. It was determined that the women who used modern contraceptives and trusted these methods and the women who had sexually transmitted diseases and reproductive system infections in the past had high fertility awareness, whereas the women with low fertility awareness had health problems during the conception process and pregnancy.

Key words: Fertility awareness, Obstetric history, Women.

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Introduction

Fertility is defined as the ability of a person to give birth to offspring conceived during a cycle (1). It also refers to the biological characteristics of men and women who have the ability to reproduce (2). When the fertility rates in the world were examined, it was determined that the number of children decreased from 2.2 to 1.7 per woman in developed countries

between 1970 and 2015. This rate was also found to decrease from 5.4 to 2.6 in developing countries (3).

Technological and industrial developments today not only facilitate human life but also affect our health. These developments particularly affect the fertility and reproductive systems of people (4). Technological and industrial developments bring along harmful side effects such as radiation exposure, toxic gases and pesticides. Furthermore, due to these effects, the probability of conception during a cycle (i.e., fecundity) has decreased by 7% for sexually active individuals. This decrease is estimated to continue if the necessary precautions are not taken (5). With the changing living conditions and development of technology, the age for the first conception increased globally, and the chance of having a child started to decrease gradually, due to factors such as the inclusion of educated women into the workforce, their career focus and delay in choosing a partner (6-8). In addition to the harmful effects of technological and industrial developments, there are many factors that affect fertility. These factors are advanced age, overweight, inappropriate exercise, smoking and/or alcohol consumption, excessive caffeine consumption, and mobile phone use (9-12). Furthermore, obstetric characteristics such as risky sexual behaviors, frequent and excessive number of birthing and abortion under inappropriate conditions are known to have negative effects on fertility (12). Fertility is further affected by women's lack of sufficient knowledge about these factors affecting fertility (7). Thus, providing necessary information to women about fertility and ensuring fertility protection by implementing appropriate policies is the main goal of health organizations (13). In this context, fertility awareness is emphasized, and it is desired to gain personal responsibility (12).

Awareness means having knowledge and understanding about something, while fertility awareness refers to an individual's awareness of all things related to fertility (12, 14). Women with fertility awareness are knowledgeable about the duration and characteristics of their menstrual cycle and the physiological effects of this cycle on their bodies. With this awareness, women are able to determine their fertile periods and decide to use contraception or not (15). It is also important to have knowledge about medical problems that affect fertility. Hormonal disorders of women causing problems such as ovulation irregularity and polycystic ovary syndrome, structural disorders in the uterus (polyps, adhesions, obstructions, etc.), endometriosis, primary ovarian failure causing early

menopause, pelvic adhesions - presence of pelvic infection, postoperative abdominal or pelvic area scar tissue, and diseases such as diabetes are some medical problems that prevent fertility (12). Some negative behaviors that men and women exhibit, whether intentionally or unintentionally, may harm fertility by causing these medical problems (16). However, the fact that many negative health behaviors are modifiable, advising people on making healthy changes and raising their awareness may encourage the preservation of fertility (12, 16). In addition to the global increase in marriage and first childbearing ages, women's negative health behaviors increase the importance given to fertility awareness. In this direction, it is of great importance for healthcare professionals to closely follow the obstetric histories of women and diagnose and manage preventable health problems early. Additionally, preserving fertility along with changeable lifestyle behaviors will increase the chance of success in the infertility treatment process (2, 11). Based on this information, addressing the negative effects of fertility awareness in women on obstetric characteristics is thought to contribute to the literature. This study was conducted using the Google Forms platform to determine the effects of women's fertility awareness on their obstetric histories.

Methods

Study Design and Sampling Selection
This study was planned as a cross-sectional study to determine the effects of women's fertility awareness on their obstetric histories. Sampling, eastern Turkey between December 2020 and February 2021 three family health center was registered among women 18-49 years of age.

The inclusion criteria were as follows:
- Being sexually active,
- Having a history of at least one pregnancy,
- Being between the ages of 18 and 49,
- Considering having a child,
- Not having a psychiatric diagnosis.

Data Collection Tools
A Personal Information Form and the Fertility Awareness Scale (FAS) were used to collect the data.

Personal Information Form
Within the personal information form prepared by the researchers in line with the literature, there were 20 questions including the socio-demographic characteristics (age, marital status, place of residence, education and employment status, social security and

economic status) and obstetric characteristics (number of pregnancies, number of births, family planning (FP) method used for the longest period, most trusted FP method) of the participants (2, 6, 11, 12). This form was created by the researchers using the Google Forms platform.

Fertility Awareness Scale (FAS)

The Fertility Awareness Scale (FAS) was developed by Ozsahin among Turkish women aged 18-49 in 2020 to determine the fertility awareness levels of women. The Fertility Awareness Scale is a 5-point Likert-type scale consisting of 19 items and two dimensions. These dimensions are Bodily Awareness (items 7, 9, 10, 11, 12, 13, 15, 17, 18 and 19) and Cognitive Awareness (items 1, 2, 3, 4, 5, 6, 8, 14 and 16). Items in the scale are scored from 1 to 5 (1-Never, 2-Rarely, 3-Sometimes, 4-Often and 5-Always). There are no inversely scored items in the scale. The lowest possible score that can be obtained in FAS is 19, and the highest possible score is 95. These scores are respectively 10 and 50 in the Bodily Awareness dimension and 9 and 45 in the Cognitive Awareness dimension. The level of awareness increases with the total FAS score. In evaluation of the total score obtained from FAS, a score in the range of 19-43 indicates a low awareness level, 44-69 indicates a medium awareness level, and 70-95 indicates a high awareness level. The Cronbach's alpha reliability coefficient of the scale was calculated by Ozsahin as 0.887 (12). In this study, the Cronbach's alpha reliability coefficient was found to be 0.789.

Data Collection

Informed consent of the participants was received via Google Forms. Again, using Google Forms, data collection forms were sent to the participants and their responses were digitally collected. The data were limited to the respondents among the women who attended three family health centers. It was assumed that the answers of the participants were correct. The data collection process took approximately 5-10 minutes for each participant.

Statistical analysis

Data entry and analysis were carried out in a computer environment using the SPSS 20.0 software (Statistical Package for the Social Sciences Inc., Chicago, IL, USA). The results were evaluated in a 95% confidence interval, and the significance level was determined as $p<0.05$. The conditions for independence, randomization and quantitative data, which are parametric test assumptions, were provided. The homogeneity of variances was checked by Levene's test. It was observed that the variances in all variables were homogeneous ($p>0.05$). The normal distribution of the data was checked with Kolmogorov-Smirnov Test. Since normal distribution was provided in the variables ($p>0.05$), the analysis continued with parametric tests (independent-samples t-test, one-way ANOVA, Pearson's correlation analysis). Additionally, in the statistical analysis, percentage distribution, arithmetic mean, standard deviation and Cronbach's alpha were utilized.

Ethical issues

Ethical approval (Decision No: 2020/1229) of the study was obtained from the Health Sciences Scientific Research and Publication Ethics Committee of the Inonu University. The informed consent of the participants was also obtained via the internet before the study.

Results

365 women participated in the study.

The socio-demographic characteristics of the women participating in the study are presented in Table 1. The mean age of the women was 34.25±6.82 years, the mean age of their spouses was 37.99±7.43 years, and their mean age of marriage was 23.05±3.76 years. Among the participants, 56.2% were unemployed, 62.5% were university graduates, 92.9% had working spouses, and 84.4% had spouses who were high school graduates. Moreover, it was determined that 77.5% of the women lived in the city center, 58.1% of them had a moderate economic status, 89.3% had a nuclear family, and the participant's mean BMI was 25.69±7.15.

The distribution of the obstetric characteristics of the women is presented in Table 2. The mean age when the women had their first child was found to be 24.19±5.51, the women's mean total number of pregnancies was 1.76±0.42, their mean total number of births was 1.93±1.01, and their mean total number of children was 1.97±0.14. It was determined that, of the family planning methods used by the women for a long time, 61.6% were modern methods, the most trusted family planning methods among 76.4% of the women were modern methods, 65.5% of the women had sexually transmitted diseases before, and 55.1% had reproductive system infections in the past. It was also found that 73.7% of the women did not have a miscarriage in the past, 80.3% did not have an abortion, 97.8% did not have a stillbirth, and 83.6% did not have a deceased child. Furthermore, it was determined that 67.9% of the women had an

unplanned pregnancy in the past, 83.0% had no problems during conception, and 61.1% of them had no problems during pregnancy.

Table 1. The distribution of socio-demographic characteristics of women (n=365)

Descriptive Properties	n	%
Employment Status		
Employed	160	43.8
Unemployed/Housewife	205	56.2
Educational Level		
Literate	6	1.6
Primary school graduate	32	8.8
Secondary school graduate	34	9.3
High school graduate	65	17.8
University graduate	228	62.5
Spouse Educational Level		
Illiterate	5	1.4
Literate	2	0.5
Primary school graduate	32	8.8
Secondary school graduate	18	4.9
High school graduate	308	84.4
Spouse Employment Status		
Employed	339	92.9
Unemployed	26	7.1
Place of Residence		
Province	283	77.5
Town	72	19.7
Village	10	2.8
Income Status		
Good	130	35.6
Moderate	212	58.1
Poor	23	6.3
Family Structure		
Nuclear Family	326	89.3
Extended family	39	10.7
Total	**365**	**100.0**
	Mean± SD	
Age (years)	34.25±6.82	
Spouse's age (years)	37.99±7.43	
Marriage age (years)	23.05±3.76	
BMI (kg/m^2)	25.69±7.15	

SD= Standard Deviation

The distributions of the lowest-highest scores that can be obtained from FAS and its dimensions and the lowest-highest scores and mean scores of the women are presented in Table 3.

The participants scored a minimum of 22 and a maximum of 50 points in the Bodily Awareness dimension, a minimum of 9 and a maximum of 45 in the Cognitive Awareness dimension and a minimum of 40 and a maximum of 95 in the total FAS.

The mean score obtained from the Bodily Awareness dimension was 38.74±6.45, the mean score obtained from the Cognitive Awareness dimension was 32.14±5.28, and the mean total score in FAS was 70.89±10.50.

Table 4 presents the distribution of the mean scores of the participants based on their fertility awareness levels. The fertility awareness levels of the women were determined to be high (61.1%). The women with high fertility awareness scored a minimum of 70 and a maximum of 95 points, and their mean score was 77.74±5.20.

Table 5 presents the relationship between the women's total and subscale mean scores and their age, marriage age, first childbirth age and BMI.

It was found that the FAS total and dimension scores of the women decreased with increasing age,

but there was no statistically significant relationship between these variables (r=-0.028, p=0.589; r=-0.081, p=0.124; r=-0.058, p=0.269, respectively).

It was determined that the mean Bodily Awareness scores of the women increased significantly with increasing marriage age, there was no significant difference in terms of the Cognitive Awareness scores, and the total scale scores decreased significantly (r=0.113, p=0.031; r=0.070,

p=0.124; r=-0.105, p=0.046, respectively). The mean Bodily Awareness scores of the women were found to increase significantly with increasing first childbirth age, but this relationship was not significant in terms of the Cognitive Awareness subscale and total scale scores (r=0.114, p=0.030; r=0.044, p=0.404; r=0.092, p=0.079, respectively).

Table 2. The distribution of obstetric characteristics of women (n=365)

Obstetric Characteristics	n	%
The Longest Used Family Planning Methods		
Modern Methods[*]	225	61.6
Traditional Methods[**]	140	38.4
The Most Trusted Family Planning Methods		
Modern Methods	279	76.4
Traditional Methods	86	23.6
Sexually Transmitted Disease Experiencing Status		
Yes	126	34.5
No	239	65.5
Reproductive System Infection Experiencing Status		
Yes	164	44.9
No	201	55.1
Miscarriage Making Status		
Yes	96	26.3
No	269	73.7
Abortion Making Status		
Yes	72	19.7
No	293	80.3
Stillbirth Making Condition		
Yes	8	2.2
No	357	97.8
Status Having a Deceased Child		
Yes	60	16.4
No	305	83.6
Unplanned Pregnancy Living Status		
Yes	117	32.1
No	248	67.9
Problem Experiencing Situation During the Conceiving Process[***]		
Yes	62	17.0
No	303	83.0
Problem Experiencing Situation During the Pregnancy		
Yes	142	38.9
No	223	61.1
Total	**365**	**100.0**
	Mean± SD	
First Child Birth Age (years)	24.19±5.51	
Total Number of Pregnancies (units)	1.76±0.42	
Total Number of Births	1.93±1.01	
Total Number of Children	1.97±0.14	

[*] Modern Methods: Condom, Oral contraceptive, Intrauterine Device (IUD), Injections, Subcutaneous implant
[**] Traditional Methods: Withdrawal, Calendar method, Breastfeeding, Methods based on fertility awareness (the length of your menstrual cycle, daily readings of your body temperature, cervical mucus)
[***] Late conception or conceiving with treatment

Table 3. The distribution of the lowest-highest scores that can be obtained from the FAS and its sub-dimensions, and the lowest-highest scores and the mean scores of the women (n=365)

Scales	The lowest and highest scores that can be obtained	The lowest and the highest scores obtained	Mean of the scores obtained (Mean± SD)
Physical Awareness Sub-dimension	10-50	22-50	38.74±6.45
Cognitive Awareness Sub-dimension	9-45	18-45	32.14±5.28
FAS Total	19-95	40-95	70.89±10.50

FAS= Fertility Awareness Scale
SD= Standard Deviation

Table 4. Distribution of Women's Mean Scores by Fertility Awareness Levels (n=365)

Fertility Awareness Levels	n	%	Mean± SD
Low	4	1.1	42.25±1.50
Middle	138	37.8	60.64±6.57
High	223	61.1	77.74±5.20

SD= Standard Deviation

Table 5. The relationship between Fertility Awareness Scale total and sub-dimension mean scores of women between age, marriage age, first child birth age and BMI (n=365)

Variables	Physical Awareness r; p	Cognitive Awareness r; p	FAS Total r; p
Age (years)	-.028; .589	-.081; .124	-.058; .269
Marriage age (years)	**.113; .031** [a]	.070; .182	**-.105; .046** [a]
First Child Birth Age (years)	**.114; .030** [a]	.044; .404	.092; .079
BMI (kg/m²)	**-.125; .017** [a]	**-.174; .001** [a]	**-.164; .002** [a]

FAS= Fertility Awareness Scale   [a] $p<0.05$ r= Pearson correlation Coefficent analyze

It was found that the FAS total and all dimension mean scores decreased significantly with increasing BMI scores (r=-0.125, p=0.017; r=-0.174, p=0.001; r=-0.164, p=0.002, respectively).

Table 6 presents the comparison of the FAS total and dimension mean scores of the women based on some obstetric and demographic characteristics of theirs.

It was determined that the women who used modern contraceptives for a long time and stated that the most reliable family planning methods were modern methods had significantly higher mean scores in the total FAS and both dimensions (p<0.05). It was also found that the women with previous sexually transmitted disease and reproductive system infection histories had significantly higher mean scores (p<0.05).

The FAS total and dimension scores of the women who had problems during conception and during pregnancy were found to be significantly lower (p<0.05). There was no statistically significant difference for the women who had a history of unplanned pregnancy, miscarriage, abortion, stillbirth or a deceased child (p>0.05).

The FAS total and dimension mean scores of the employed women were statistically significantly higher than those of the unemployed women (p<0.05). When the FAS total and dimension mean scores were compared based on the education levels of the participants, there was a significant difference in the Bodily Awareness dimension scores between the participants with elementary school and those with university degrees, as well as between the participants with middle school-high school and those with university degrees. There was a significant difference in the cognitive awareness dimension scores between the graduates of high school and university. There was also a significant difference between the graduates of middle school-high school and university in terms of the total mean FAS scores (F=8.517; p=0.000; d>a,b; c>b; F=3.747; p=0.000; d>c; F=7.118; p=0.000; d>a,b, respectively).

When the FAS total and dimension mean scores of the women were compared based on their economic status, there was a statistically significant difference between those with low and middle-high economic statuses and between those with middle and high economic statuses in the Bodily Awareness dimension, whereas there was also a statistically significant difference between those with low and middle-high economic statuses in the Cognitive Awareness dimension.

Table 6. Comparison of fertility awareness scale total and sub-dimension mean scores in terms of some obstetric and demographic characteristics of women (n=365)

Variables	Physical Awareness Mean± SD	Cognitive Awareness Mean± SD	FAS Total Mean± SD
The Longest Used Family Planning Methods			
Modern Methods*	39.85±5.73	32.86±5.249	72.72±9,71
Traditional Methods**	36.35±7.14	31.00±5.149	67.95±11.08
t; p	**4.26; 0.000**	**3.320; 0.001**	**4.31; 0.000**
The Most Family Planning Methods			
Modern Methods	39.70±5.79	32.62±5.21	72.33±9.73
Traditional Methods	35.61±7.48	30.60±5.22	66.22±11.5
t; p	**5.328; 0.000**	**3.132; 0.002**	**4.861; 0.000**
Sexually Transmitted Disease Experiencing Status			
Yes	39.77±5.96	33.27±5.12	73.05±9.83
No	38.20±6.65	31.55±5.27	69.75±10.69
t; p	**2.230; 0.026**	**2.999; 0.003**	**2.959; 0.004**
Reproductive System Infection Experiencing Status			
Yes	39.67±5.88	32.76±5.10	72.43±9.71
No	37.98±6.80	31.64±0.39	69.63±10.97
t; p	**2.507; 0.013**	**2.015; 0.045**	**2.558; 0.011**
Unplanned Pregnancy Living Status			
Yes	38.23±6.99	31.16±5.47	69.42±11.26
No	38.98±6.19	32.59±5.13	71.58±10.07
t; p	-1.045; 0.297	-2.378; 0.018	-1.836; 0.067
Problem Experiencing Situation During the Conceiving Process			
Yes	35.27±6.85	29.33±5.57	64.61±11.10
No	39.45±6.15	32.72±5.04	72.17±9.92
t; p	**-4.781; 0.000**	**-4.729; 0.000**	**-5.358; 0.000**
Problem Experiencing Situation During the Pregnancy			
Yes	37.01±6.49	30.67±5.45	67.69±10.41
No	39.84±6.20	33.08±4.95	72.93±10.07
t; p	**-4.177; 0.000**	**-4.351; 0.000**	**-4.785; 0.000**
Abortion Making Status			
Yes	38.55±6.57	31.34±5.24	69.89±10.45
No	38.81±6.43	32.43±5.27	71.24±10.52
t; p	-0.341; 0.733	-1.742; 0.082	-1.083; 0.279
Status Having a Deceased Child			
Yes	38.18±7.15	31.28±5.17	69.46±10.44
No	38.85±6.3	32.31±5.29	71.17±10.50
t; p	-.737; 0.462	-1.389; 0.166	-1.151; 0.251
Stillbirth Making Condition			
Yes	38.62±8.15	29.5000±5.07	68.12±11.55
No	38.74±6.43	32.2073±5.27	70.95±10.49
t; p	-0.053; 0.958	-1.436; 0.152	-0.753; 0.452
Miscarriage Making Status			
Yes	37.70±7.05	31.12±5.78	68.83±11.66
No	39.00±6.29	32.39±5.13	71.39±10.161
t; p	-1.523; 0.129	-1.840; 0.090	-1.863; 0.063
Employment Status			
Employed	39.85±5.29	33.06±4.72	72.86±8.72
Unemployed/Housewife	37.87±7.12	31.47±5.59	69.35±11.49
t; p	**2.933; 0.004**	**2.767; 0.006**	**3.203; 0.001**
Educational Level			
Literate	36.83±36.83	30.66±7.393	67.50±17.25
Primary school graduate	36.56±36.56[a]	31.62±5.434	68.18±10.80[a]
Secondary school graduate	34.14±34.14[b]	30.58±6.89	64.73±13.38[b]
High school graduate	37.90±37.90[c]	30.58±5.43[c]	68.49±11.95[c]
University graduate	40.02±40.02[d]	32.93±4.74[d]	72.96±8.67[d]
F; p	**8.517; 0.000**	**3.747; 0.005**	**7.118; 0.000**
	d>a,b; c>b	d>c	d>a,b
Income Status			
Good	33.69±8.00[a]	28.13±6.24[a]	61.82±13.76
Moderate	38.02±6.49[b]	31.99±5.19[b]	70.02±10.18
Poor	40.80±5.29[c]	33.10±4.90[c]	73.91±9.18
F; p	**16.211; 0.000**	**9.290; 0.000**	**15.862; 0.000**
	c>b>a	c>b>a	c>b>a
Place of Residence			
Province	39.103±9.10[a]	32.21±5.15	71.31±10.12
Town	38.12±7.13[b]	32.00±5.53	70.12±11.30
Village	33.00±7.91[c]	31.40±7.29	64.40±13.76
F; p	**4.828; 0.009**	0.149; 0.862	2.350; 0.097
	a,b>c		

t= Independent simple t test   F=One-way anova test,

* Modern Methods: Condom, Oral contraceptive, Intrauterine Device (IUD), Injections, Subcutaneous implant

** Traditional Methods: Withdrawal, Calendar method, Breastfeeding, Methods based on fertility awareness (the length of your menstrual cycle, daily readings of your body temperature, cervical mucus)

***In the Anova Test, The Duncan Test, one of the post-hoc pairwise comparison tests, was used for pair group comparisons.

There was also a statistically significant difference between those with low and middle-high economic statuses and between those with middle and high economic statuses in terms of their total mean FAS scores (F=16.211; p=0.000; c>b>a; F=9.290; p=0.000; c>b>a; F=15.862; p=0.000; c>b>a, respectively).

When the FAS total and dimension mean scores of women were compared based on their place of residence, there was a significant difference between those living in villages and districts and those living in the city center in the Bodily Awareness dimension scores, while there was no significant difference in terms of place of residence in the Cognitive Awareness dimension scores (F=4.828; p=0.009; a,b>c; F=0.149; p=0.862; F=2.350; p=0.097, respectively).

Discussion

The findings obtained from this study which was conducted to determine the effects of the fertility awareness levels of women on their obstetric history are discussed in this section in accordance with the relevant literature. Postponement of having children is caused by many personal, social and economic factors (6-8). This actually shows that planning pregnancy or using contraception is not always an informed action (17). For this reason, all women of reproductive age should get information about factors such as the appropriate time to conceive, using contraception and modifiable issues affecting fertility (age, sexually transmitted diseases, BMI) (8, 17). Preventable risk factors are emphasized for the protection and care of fertility in high-income countries (18). Fertility care may be provided by increasing fertility awareness via emphasizing preventable risk factors (18).

In this study, 61.1% of the women were found to have a high level of fertility awareness (Table 4). Furthermore, while the rate of the women with moderate fertility awareness levels was 37.8%, the rate of those with low fertility awareness levels was 1.1% (Table 4). Besides this, in the literature, it is seen that the fertility awareness levels of women have been reported to be low or moderate (7, 16). The finding in this study that the rate of the women with low fertility awareness levels was not compatible with the literature may be associated with the fact that the vast majority of the participants in this study were university graduates. When it comes to fertility awareness, the first thing that comes to mind is planning or postponement of having a child. Fertility awareness also requires bodily awareness (frequent pregnancies, abortions, advanced maternal age,

sexually transmitted infections, reproductive system infections, and their harm to fertility) (19-21), as well as cognitive awareness, as in recognizing the symptoms of the individual's own body (22). In this study, the mean Cognitive Awareness dimension score of the women was found as 32.14±5.28, whereas their mean Bodily Awareness dimension score was 38.74±6.45 (Table 3). In a study, participating women with low fertility awareness levels were found to not have enough information about their fertile periods and be misinformed (23). However, it was also stated that, with effective counseling, women may get to know their bodies, and their cognitive knowledge could increase (17, 23). In this study, fertility awareness was found to be a variable associated with a negative obstetric history. For example, it was found that the mean score of bodily awareness decreased with decreasing ages of marriage and first childbearing (Table 5). It is understood that women who marry at a young age do not know their bodies well. Women who do not know their bodies well and use natural family planning methods experience more anxiety about unwanted pregnancies (24). Studies have shown that the education levels of women with a younger age of marriage and a younger age of first childbearing are lower (25-27). It was a similar finding to the literature in this study that, as the age of marriage and first childbearing in the participating women decreased, their mean Bodily Awareness scores decreased (Table 5). What is more, there was a statistically significant negative correlation between BMI and FAS total and dimension scores (Table 5). BMI was observed to increase as the fertility awareness mean scores of the women decreased. In a study, it was found that individuals with a high level of education paid more attention to their nutrition (28). Studies have demonstrated that the need for training increases with increasing BMI (28-30). The negative relationship between the BMI and fertility awareness levels observed in this study was consistent with the literature and showed that women with low fertility awareness levels have higher BMI.

The World Health Report states that unwanted pregnancies are among the most common causes of maternal deaths in developing countries (31). The failure to use family planning methods effectively is the culprit in this issue (32, 33). Although most women are aware of modern and natural family planning methods, they have insufficient knowledge about details such as protection periods, return of fertility when these methods are stopped and benefits of methods other than contraceptives (33). In this regard, it is essential to increase the awareness levels

of women. The total FAS scores and the mean Bodily Awareness and Cognitive Awareness dimension scores of the women who stated that the FP method they used the longest and the most reliable FP method were "modern methods" (Table 6) were higher. This finding indicated that women with high fertility awareness levels use modern contraceptive methods more.

The result that the women with a history of a sexually transmitted diseases or reproductive system infections had higher levels of fertility awareness was a striking finding of this study (Table 6). It may be argued that a history of infection increases the importance of fertility awareness for women, and the bodily and cognitive awareness of women increases after such a negative experience. Reproductive system infections are among the most common health problems faced by women (34). Infections in the reproductive organs may prevent conception or the healthy continuation of a pregnancy. It is stated that most women need education and counseling for preventing reproductive system infections (34). Especially considering the negative consequences of sexually transmitted diseases, it is essential to increase the awareness levels of women on this issue. From this point of view, it may be concluded that fertility awareness is a significant variable in terms of sexually transmitted diseases and reproductive system infections.

In this study, the mean age of the participating women was found to be 34.25±6.82 (Table 1). Considering "planning to have a child", which was one of the criteria of this study, it may be seen that the age of becoming a mother had advanced. It is seen worldwide that the age of maternity is being postponed. Advanced maternal age is associated with lowering the chance of having the desired number of children (8), low-quality follicles, prolonged conception, abortion and increased obstetric diseases (17). In a study, it was stated that the possibility of conception decreased with increasing age for women (35). Women need to be informed about the consequences of advanced maternal age (8, 36). Therefore, advanced maternal age should be taken into consideration in pregnancy planning and counseling (37). According to Turkish Statistical Institute 2019 data, the rate of women who graduated from high school or faculty is 18.5% (38). In this study, the rate of women who graduated from high school or faculty is 62.5%. The difference between the findings is striking. The fact that the Google Forms method was used in this study may have resulted in reaching more university graduate women and limited number participant. When the fertility

awareness mean scores of the participants were compared based on their descriptive characteristics, it was found that the relationship between their employment status, economic status and education levels and their scale total and dimension mean scores was statistically significant (Table 6). The mean total fertility awareness scores and the mean dimension scores of the women who were employed, those who had higher education levels and those who had a good economic status (Table 6) were found to be higher. Furthermore, it was found that the mean bodily fertility awareness score of the women living in the city center was higher than those living in villages and districts. When the literature is examined, it may be observed that place of residence, education level and economic status are among the significant factors that affect women's contraceptive preference, marriage age and their risk of having an STD and/or a reproductive system infection (21, 32, 39). Beekle and McCabe found that contraceptive preference was affected by the sociodemographic characteristics of women. Salari et al. reported that women living in rural areas are in need of increasing their fertility awareness (21, 32). Dogru et al. determined that education level is effective in the choice of a contraceptive method. These results have shown that the findings of this study were compatible with the literature (21, 32, 40).

Conclusion

In this study, among women surveyed, fertility awareness levels were determined to be affected by their age of marriage, age of first childbearing, employment status, and economic status. The women who were employed, those who had a higher education level and those who had a good economic status were observed to have a higher Bodily and Cognitive awareness subscale mean scores. Midwives and other healthcare professionals should take into account the sociodemographic and obstetric characteristics of women while considering reproductive planning in meetings with women of reproductive age.

Limitation

As this study was carried out with women living in eastern Turkey, its results may not be generalized to the entire society. The small sample size of the study was another limitation. Additionally, the fact that the study was conducted using the Google Forms platform led more university and high school graduate women to respond to the data collection forms. This situation may prevent one from making a

comment on the fertility awareness levels of women with low educational levels.

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CASE REPORT

A Case with Sneddon Syndrome Combining with Preeclampsia and Intrahepatic Cholestasis of Pregnancy

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Abstract
Sneddon's syndrome (SS) is a rarely seen thrombotic vasculopathy characterized by the combination of ischemic cerebrovascular disease with livedo racemose (LR) and mainly affects young women in the third decade of life. We present a case of an 32 year old women diagnosed with SS 17 years ago, admitted to our emergency department when she was 37 weeks pregnant, and diagnosed as having superimposed severe preeclampsia and intrahepatic cholestasis of pregnancy, who had an emergency cesarean section. There are very few case reports presenting the relationship between pregnancy and SS and a possible relationship between this syndrome and preeclampsia or cholestasis has not yet been shown. We think that our case presentation may become important to contribute literature.
Keywords: Sneddon Syndrome, Pre-Eclampsia, Cholestasis

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Introduction

Sneddon's syndrome (SS) is a rare non-inflammatory thrombotic vasculopathy of small and medium-sized arteries characterized by the combination of ischemic cerebrovascular disease with livedo racemose (LR) defined as net-like, patchy, violaceous, skin discoloration (1). It has been estimated that the incidence of SS is 4 per 1 million per year and mainly affects young women with a mean onset in the third decade of life, between the ages of 20 and 42 years (2). SS is an episodic or chronic, slowly progressive syndrome that was first described in 6 patients who had several common symptoms such as lacunar, subcortical, ischemic cerebral infarcts and widespread livedo eruption (3). LR may progress over the years and the trunk and/or buttocks are involved in nearly all patients. Recurrent cerebrovascular events are mostly secondary to ischemia including transient ischemic attacks and cerebral infarct (4). On the other hand; headache, cerebral hemorrhage, seizures, vertigo, cognitive and psychiatric disturbances, can be seen as neurological symptoms (5). Approximately 80% of patients with SS have an antiphospholipid antibody marker and other manifestations of primary antiphospholipid syndrome (1). It can be diagnosed by general LR with typical histopathological findings on skin biopsy and focal neurological deficits (1,2). The pathogenesis of SS is associated with hypercoagulability and intrinsic small-vessel vasculopathy. The optimal therapy of SS remains an unresolved problem and long-term anticoagulation is recommended for cerebral ischemic events. But there is controversy about the treatment of SS with immunomodulatory agents (4). The relation of pregnancy and SS has been reported rarely and to our knowledge, there is no data to be found in the literature about the relationship and coexistence between SS and pregnancy complicated with preeclampsia and cholestasis. We aimed to contribute to the literature by presenting a rarely seen case of a pregnant woman with SS, complicated by preeclampsia and cholestasis.

Case

We report the case of a nulliparous 32-year-old pregnant woman who has SS since she was 15. She experienced one ischemic attack at the time of her diagnosis. She was admitted to the emergency room of the obstetrics and gynecology department at her 37 weeks of pregnancy due to increased blood pressure and lack of variability in her nonstress test (NST). General examination showed erythematous macular eruption on her skin involving the abdominal region. Her symptoms were headache, palpitation, itching, dryness in her mouth, swelling in her feet, increasing pain in her hand, wrist, and knee. According to her last menstrual period, she had a pregnancy of 37 weeks and 1 day. In the fetal examination, a 37-week fetus with the head presentation was observed, her amniotic fluid index and fetal doppler findings were normal. There was no fetal demise detected. At the time of her admission to the hospital, her blood pressure was 170/100 mmHg, platelet count was 153000 /microL, liver enzymes were elevated (AST:70 U/L ALT:63 IU/L LDH:580 U/L). The serum total bile acid concentration was 72 micromol/L, bilirubin levels were normal. In her urine sample (++) albumin was seen. The antiphospholipid antibodies were negative. Her electrocardiogram was normal. In echocardiography, ejection fraction was in the normal range, minimal aortic failure was noted. She had a history of chronic hypertension presumably due to the SS. The medication she was using; alpha-methyl-dopa 250 mg tb 3x2 per oral (P.O)., methylprednisolone 2 mg tb 2x1 P.O., azathioprine 50 mg tb 2x1 P.O, ursodeoxycholic acid 250 mg tb 2x2 P.O., enoxaparin sodium 40 mg 1x1 subcutaneously (S.C.). In her previous visits, her blood pressure was in normal range with medical therapy Due to known chronic hypertension, headache, and high levels of protein in her urine; superimposed preeclampsia was diagnosed. Additionally, her liver enzymes and bile acid level were elevated. Cholestasis of pregnancy was added to our diagnosis. Due to our findings, pregnancy termination was planned. A consultation was made to her specialist in the department of rheumatology. Due to the risks of thromboembolism and stroke during the stages of normal vaginal labor, the rheumatologist recommended labor with cesarean section. Her blood pressure remained above 160/110mmHg. The patient remained suffering from severe headaches. The non-stress test showed decreased variability. Magnesium sulfate protocol was initiated immediately, and the pregnancy was terminated with cesarean section. After the operation magnesium sulfate infusion was continued for 24 hours. The patient was re-evaluated by the rheumatology specialist postoperatively. The post-operative second day her blood pressure increased to 180/100mmHg. We manage to control the blood pressure after giving 5 mg of hydralazine. Nifedipine 30 mg P.O. and Enoxaparin sodium 60 mg S.C. was added to her routine treatment. The patient was observed in the hospital until the postoperative fourth day. She was discharged after her blood pressure remained regulated for 48 hours. During the patient's follow-up until postpartum 6th month, we did not observe any thromboembolic events.

Although we had informed consent from the patient to make a case report, we cannot make a photo presentation because the patient did not allow us to take photographs of the skin lesions due to her religious beliefs.

Discussion

SS is a rare disease of unknown etiology with dermatological manifestation and recurrent strokes. It can be classified as, antiphospholipid syndrome associated, systemic lupus erythematosus related or idiopathic if there is no causative factor identified (4). In our case, it was classified as idiopathic because of no relation to SLE or antiphospholipid syndrome. Besides cutaneous and neurologic symptoms, systemic hypertension, valvular and ischemic heart disease, renal disease, retinopathy, Raynaud phenomenon, and fetal loss are also commonly seen in SS (1,4). In our patient, there were no signs of cardiac, renal, or ophthalmic disease but she had chronic hypertension and no abortion history. The optimal management of patients with SS is yet an unresolved problem, there have been no prospective controlled studies to guide therapy because of the rare incidence of the disease. The main goal is to prevent further cerebrovascular events and to reduce skin symptoms. Antiplatelet therapy and anticoagulation both decrease the risk of secondary ischemic events. Recent research suggests that the prognosis of stroke recurrence might be better compared to the historical data due to the increasing use of antiplatelet/antithrombotic agents for secondary stroke prophylaxis (1). Also, our patient had one cerebral ischemic attack, no history of recurrent ischemic attacks and cerebral infarct due to the beneficial effect of anticoagulant therapy. Although it has been suggested that anti-inflammatory or immunosuppressive therapies are beneficial, because of the presence of an inflammatory phase in the early stage of SS, it has been shown that these therapies such as corticosteroids and azathioprine are generally not beneficial (1). But our patient was receiving corticosteroids and azathioprine and had used it throughout her pregnancy. When it comes to rare diseases; we believe that the relevant studies should be followed closely by the related branches and the previous experiences in the treatment should be taken into consideration. Since SS is seen frequently in women and in their fertile period; pregnancy, complications related to pregnancy and their management become important. In addition, the case reports presenting the relationship and prognosis of pregnancy and SS is very limited (6-8). Dikova et al. (6) claimed an increase in abortion, similar to that

Baleva et al claimed an increase in recurrent abortion. In our patient, she did not experience any risk of abortion and it was her first pregnancy. She had regular follow-up throughout her pregnancy and underwent antihypertensive treatment because of a history of chronic hypertension. Her blood pressure levels were within normal limits until her emergency admission. Dietl et al. (8) presented a case of 31-year-old pregnant women with SS in 1991. She developed episodes of cerebral ischemia with multiple neurological deficits in the 24th week of pregnancy. The symptoms were associated with the dermatological signs of LR. In the 36th week of pregnancy, delivery was made by cesarean section and it resulted in a major improvement of the neurological signs and symptoms. The immunosuppressive therapy with cortisone and cyclophosphamide was planned but due to the persistent improvement in the patient's condition, it was not instituted. Our patient was 32 years old, diagnosed as SS at the age of 15, had a cerebral ischemic attack without any neurological disability that responded to anticoagulant therapy. She had been given enoxaparin sodium 40 mg 1x1 subcutaneously during pregnancy. When she was admitted to our emergency room, she had a 37-week pregnancy. She was diagnosed with high blood pressure, proteinuria, headache, edema in the hands and feet, pruritus due to bile acid elevation. She was diagnosed with superimposed severe preeclampsia and cholestasis, and the pregnancy was terminated with a cesarean section. On postpartum day four, blood pressure was under control and she was discharged. The limitation of our case report is the lack of photograph presentation. Nevertheless, to our knowledge, this is the first report presenting a pregnant woman with SS complicating with superimposed severe preeclampsia and cholestasis. Therefore, we think that it will contribute to the literature data. Despite insufficient data, it is known that pregnancy with SS is a high-risk pregnancy and the risk of abortion increases. Due to increased coagulability and vasculopathy in small vessels, the risk of preeclampsia and cholestasis may be increased as seen in our case. Our patient had been receiving anticoagulant treatment since diagnosis and she had no recurrent ischemic attacks. As anticoagulant therapy decreases cerebral ischemic attacks by reducing thrombosis it can also decrease the risk of abortion and preeclampsia. However, more study data is needed in this subject.

Conclusion

We believe that pregnancy with SS is a high-risk condition and it should be followed with caution by experienced clinicians. Anticoagulant therapy can be considered during pregnancy until delivery as it may be helpful to decrease complications. Pre-eclampsia and cholestasis can increase mortality and morbidity therefore during these pregnancies suspicion and cautiousness are necessary.

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CASE REPORT

Pleomorphic Adenoma: Report of Two Cases with an Unusual Presentation

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Abstract

Pleomorphic adenoma is the most common salivary gland tumor. Pleomorphic adenoma is also known as benign mixed tumor. Most commonly affected site is the parotid gland. It may also occur in other major salivary glands (submandibular and sublingual glands), lacrimal glands and minor salivary glands. Pleomorphic adenoma arises as a painless, firm swelling, slowly growing in the oral cavity. Pleomorphic adenoma is a benign triphasic salivary gland tumor that occurs in epithelial, myoepithelial, and chondromyxoid stroma. Complete surgical resection with negative margins is the main treatment method in pleomorphic adenoma, insufficient resection for treatment causes local recurrence.

It is an entity that should be considered in oral cavity lesions. Here, cases of pleomorphic adenoma with maxillary localization are mentioned.

Keywords: pleomorphic adenoma, salivary gland tumor, oral cavity

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Introduction

Pleomorphic adenoma (PA), also known as a benign mixed tumor, is the most common salivary gland tumor in both children and adults. It is most frequent in women in the fourth decade of life, but it can be seen in patients of all ages and genders. Benign triphasic salivary gland neoplasm is composed of epithelial cells, myoepithelial cells and chondromyxoid stroma (1). Most commonly affected site of pleomorphic adenoma (PA) is the parotid gland. It may also occur in other major salivary glands (submandibular and sublingual glands), lacrimal glands and minor salivary glands.

Clinically, they are observed as a slow growing, painless, well circumscribed mass that involves the salivary gland. Radiological findings may be useful in clinical diagnosis (1). Definitive diagnosis is made histopathologically.

Here, cases of PA with maxillary localization, where is a rarely reported region, are presented.
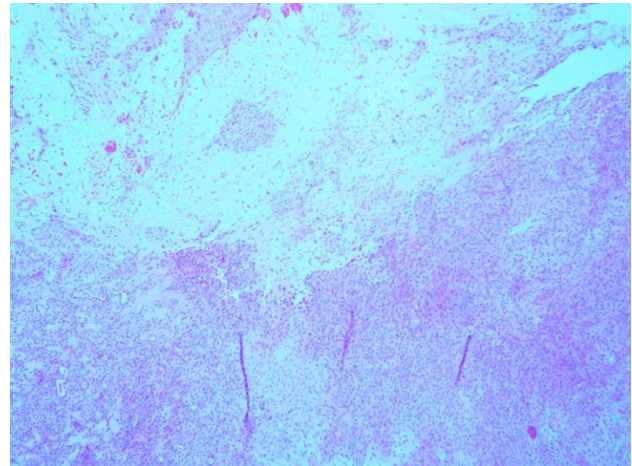
Case 1

In the examination of a 56-year-old female patient who applied to the dental clinic, a solid mass of 3 cm in diameter was detected in the right maxillary premolar region. The lesion was observed close to the buccal mucosa, with the appearance of expanding in the vestibular sulcus. The lesion that could not be clearly evaluated radiographically was considered as a lipoma and an excisional biopsy was taken.
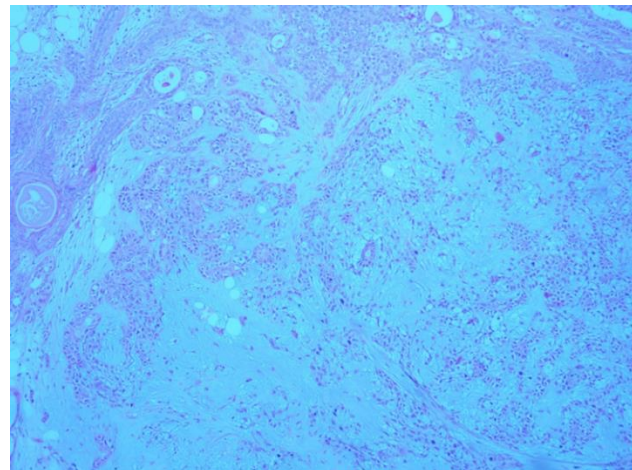
Case 2

In the examination of a 74-year-old female patient who applied to the dental clinic, a solid mass of 2,5 cm in diameter was detected in the foramen pallatinum in the right posterior maxilla. The mass was observed as elevated from the surface and caused bone resorption radiologically. An excisional biopsy was taken considering peripheral giant cell granuloma.

Histopathologic findings of the two cases were similar. In the microscopic examination of both cases, epithelial and mesenchymal cells were observed in the chondromyxoid stroma. Therefore both cases were diagnosed as PA in our pathology department (Figure 1-2).

Figure 1. PA (Case 1), HEX100, on the lower side cellular area is seen, on the upper side chondroid stroma is seen.

Figure 2. PA (Case 2), HEX100, chondromyxoid stroma is seen.

Discussion

Pleomorphic adenoma is the most common neoplasm of the large salivary glands and mostly affects the parotid gland, less often the accessory salivary glands. It takes its name from the architectural pleomorphism seen under the light microscope (2).

The palate corresponding to the small glands is the most common site for a mixed tumor.

Another area frequently affected by this tumor is the lips. A small minority of tumors are also found in the oral cavity, neck and nasal cavity (3). Both of our cases were located in the maxillary region. Clinically, it is seen as a slow-growing, painless, well-circumscribed mass that involves the salivary gland.

The most important feature of a pleomorphic adenoma of the minor salivary glands is the absence of a capsule, if present is only very thin (4). The differential diagnosis of PA includes palatal abscess,

odontogenic and nonodontogenic cysts, soft tissue tumors and salivary gland tumors (5).

Approximately 6% of these tumors turn into carcinoma ex pleomorphic adenoma (6).

In our two cases, PA was not considered clinically, and radiological findings did not help.

Diagnosis was made histopathologically in our pathology department. Thus, both cases were diagnosed as PA with light microscope examination.

Complete surgical resection with negative margins is the main treatment method in PA. An incisional biopsy must be performed first to determine the proper treatment approach. Insufficient resection for treatment causes local recurrence. Radiation therapy may be considered in symptomatic recurrent PA cases not suitable for surgical treatment (7).

For patient with gross residual disease, close or positive margins, multifocal recurrence, or with perineural invasion, postoperative radiotherapy can provide long-term local control (8).

Surgical margins in both cases were evaluated as intact. In patients diagnosed with PA, long-term follow-up should be performed after surgical treatment due to risk of recurrence and malignant transformation (9).

Conclusion

PA should be considered in oral cavity lesions. Radiology may be useful in clinical diagnosis but definitive diagnosis can be rendered on preoperative cytology or biopsy. Definitive diagnosis is made histopathologically. It is very important to know the histopathological features and locations of PAS for correct diagnosis. Correct diagnosis of PA is very helpful to direct its treatment. The main treatment method in PA is complete surgical resection with negative margins.

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CASE REPORT

Recurrent Herpes Zoster as a Sign of HIV Infection

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Abstract

Herpes Zoster is characterized with painful dermatomal blisters, which commonly seen in elderly or immuncompromised people. It is caused by varicella zoster virüs (VZV). HIV infection is known as a risk factor for herpes zoster and for developments of its complications. Cutaneous findings can be the presenting symptom for HIV infection. In the presence of HIV infection, HZ can be prolong or can complicate evet its recurrence rate increases. HZ recurrences are usually seen in immuncompromised individuals.

In the presence of HIV infection, the risk of HZ increases up to 12-17 fold. Prophylaxis with daily asiclovir decrease the risk of HZ by 68%. Vaccination for HZ was found safe and effective in HIV patients with CD4+ cell count more than 200 cells/. Skin findings are frequent in HIV patients and its diversity change according to the stages of the disease. Here we report a case of recurrent HZ which later diagnosed with positive for HIV, therefore, to mention HIV as a risk factor in cases of recurrent HZ.

Keywords: Herpes Zoster, recurrence, HIV, acylovir, shingles

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Note: The study was presented as a poster at the 19th National Family Medicine Congress.

Introduction

Herpes Zoster is characterised with painful dermatomal blisters, which commonly seen in elderly or immuncompromised people. It is caused by varicella zoster virüs (VZV) (1). The risk of HZ increase with the age. In case of immunodeficiencies, HZ recurrence risk increase (1,2). HIV infection is known as a risk factor for herpes zoster, recurrences of HZ and for the developments of its complications (2,3). It is well-known that HIV is associated with increased risk of mucocutaneous manifestations. Cutaneous findings can be the presenting symptom for HIV infection. Skin diseases can occur anytime in the course of the disease. (4). Prevelance of mucocutaneous disease in HIV- infected indivudials can increase up to 90% (5). With highly active antiretroviral trerapy (HAART), survival of HIV-infected patients prolonged, resultantly, they faced more dermatological findings. The immune status of the individual and the use of HAART, are the main factors determining the mucocutaneous manifestations of HIV infection. IN HIV-infected induviduals, the skin diseases which can be also be seen in otherwise healthy populations, usually have more protracted course, they may have more severe course, they can be resistant to the treatments, besides they can recur and have atypical presentations and courses. Mucocutaneous manifestations help both in the diagnosis and staging of the disease in HIV - positive individuals (4,5). Dermatologist should be aware of mucocutaneous findings of HIV infections and should not be late to investigate the patient for the HIV infection when necassary. Here we report a case of recurrent HZ which later diagnosed with positive for HIV, therefore, to mention HIV as a risk factor in cases of recurrent HZ.

Case

49 years old male patient applied to the dermatology clinic with the painful blisters on the back and umbilical area. In dermatologic examination, there were multiple vesicles located on the erythematous base, beginning from the middle of the back towards to the umbilicus. Vesicles are grouped together and distrubuted dermatomally. Tzanck test was performed and there were multinucleated giant cells and acantholytic cells. VZV IgG was positive. After the dermatological examination and the tests performed the patient was diagnosed with HZ. Valacyclovir 1000 mg three times daily for 7 days prescribed to the patient. After at the end of the first week of the treatment the patient reevaluated. The lesions were crusted (figure 1 and 2), but the patient still had severe pain. When we

asked patient in detail the patient did not describe any stres or anxiety. The patient informed us about he had similar lesions and diagnosed with HZ six months ago. Because of the young age of the patient and the recurrence of HZ we did detailed physical examination to find out any underlying immundeficiency. The patient did not have any fever, weight loss, night sweats. He had no known any medical illness and he was not on any treatment. In physicaml examination there were no lympadenopath. Routine biochemistry, complete blood counts, viral hepatitis serology, sedimentationn level and C-reactive peptide level were within normal range but the patient was found positive for anti-HIV. The patient was consulted to the infectios diseases department. Informed consent of the patient taken prior to the publication.

Figure 1 After 1 week of treatment, dermatomally located necrotik crust and erosions (dorsal)

Figure 1 After 1 week of treatment, dermatomally located necrotik crust and erosions (abdominal)

Discussion

HZ is the result of reactivation of latent VZV in the dorsal root ganglia which ususally caused varicella during childhood period. HZ is characterised with dermatomally distrubuted painful vesicles. The overall risk of HZ was reported 20-30 % and its prevelance significantly increases after the age of 50. Even the risk reach up to 50% after 85 years old (1,3). Also HZ risk increases in the presesnce of immundeficiency (6).

It is accepted that people get HZ usually once in their life. when it recurs it is thought as the sign of immunodeficiency. The recurrence rate for HZ vary between 0,2%-12,5% in the studies. The difference between the studies can be because of study, population and total time that patients followed (7,8). Besides age and immunodeficiency the risk of recurrence of HZ increases with chronic diseases as diabetes, hypertension, dyslipidemia, chronic obstructive lung disease, depression and hypothyroidism. In addition the people who have more serious first epizode and whose pain lasts more than 30 days have more pronounced risk of HZ recurrence (9).

In the presence of HIV infection the risk of HZ increases up to 12-17 fold. HIV positive patients usually have more complicated disease, the disease can spread more than one dermatome, it has more complication such as postherpetic nevralgia and they have more recurrence risk (3,7,8). Lee et al. reported that HZ can be sign of HIV infection especially at young individuals (10). In their study Barnabas et al. showed that acylovir prophylaxis reduced HZ events in HIV-infected individuals. But acylovir prophylaxis did not prevent HZ recurrence among persons who reported previous history of HZ. HZ vaccine recommended people after age 60, but in the case of immunosupression it is contraindicated, such as HIV-infected individuals with CD4+ cell count less than 200 cell / μL (11).

Skin findings are frequent in HIV patients and its diversity change according to the stages of the disease. As a consequence skin findings can be clue for the stage of the infection (4,5). Although with administration of the antiretroviral treatment (ART) the frequency of opportunistic decreased, the risk of HZ remained same. On the contrary some studies reported as the frequency of HZ declined after ART (3). Herpes Zoster, along with extensive oral candidiasis, and oral hairy leukoplakia, as indicator of the acquired immunodeficiency syndrome (AIDS) (12).

HZ which is mild and confined to only one dermatomal region can be treated with asiclovir, valasiclovir and famciclovir in HIV-infected patients. In patients with more complicated, disseminated and severe cases, opthalmic HZ and Ramsey Hunt syndrome should be treated with intravenous asiclovir. Although the asiclovir prophylaxis decreses the prevelance of HZ in HIV+ patients, prolonged use is not recomended (13).

Conclusion

As a global health issue, HIV has a wide list of cutaneous manifestations, some of which can help in the diagnosis of HIV infection. It is known as the frequency of HZ increases steadily with age and in the presence of immunsupression. And it is also known that recurrences of HZ usually ocur in patients who have immun supression for various cause As a consequence in young patients, patients with protracted or severe disease, HZ resistant to treatment, and also recureent diseases should raise suspicion for underlying immunsupression and HIV should be kept in mind.

Herpes Zoster, Recurrence, HIV, acylovir, shingles

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Health Benefits of *Cornelian cherry* (Cornus mas L.)

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Abstract

Medicinal plants have been used for medical objectives since ancient times due to their beneficial properties, and their uses continue to this day. The *Cornelian cherry* fruit (Cornus mas L.) is considered to be one of those medicinal plants with important nutritional and therapeutic properties. It has been also used for different medical purposes in many countries in Europe and Asia for centuries due to its various important components in terms of health. *Cornelian cherry* is known to have antimicrobial, antioxidant, anticancer and anti-inflammatory effects due to its composition of phenolic compounds and ursolic acid. It is reported in the literature that This fruit is used in different countries for different purposes; for the treatment of intestinal and kidney diseases, strengthening immunity, and preventing some types of cancer and others. It is also used in traditional medicine to cure fever, cholera, kidney stones, malaria, urinary tract infections, heat stroke and bleeding. Many studies have reported the positive effect of *Cornelian cherry* in regulating blood sugar and preventing fat accumulation in the liver. Similar to many countries, it is grown in Turkey in many regions and it is consumed processed or fresh into several crops such as compote, jam, marmalade and fruit leather. This paper has reviewed the investigative studies of the health effect of cornelian cherry.

Keywords: Medicinal plants; *Cornellian cherry*; antioxidant; antimicrobial; health benefit.

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Introduction

In recent years, interest in fruits rich in antioxidant compounds has increased with the emergence of the relationship between food and health. *Cornelian cherry* is one of the fruits that grow naturally in Turkey. This fruit is a rich source of phenolic compounds, anthocyanin, and ascorbic acid. It has been reported in the literature that it has antibacterial, antihistamine, antiallergic, antimicrobial, antimalarial and anti-diabetic properties due to its antioxidant properties (1). *Cornelian cherry* fruits can be consumed dried or fresh as well as processed into marmalade, jam and fruit juice.

It is known that many factors such as developing technology, increasing environmental pollution, used pesticides, smoking and alcohol use, Ultraviolet (UV) rays, and work and living conditions all increase the stress level. These environmental and psychological factors cause the formation of free radicals in humans and the increase of the resulting radicals can trigger various diseases. These highly reactive radicals damage the cell membrane and biomolecules found in the cell structure such as proteins, enzymes, lipids, carbohydrates and nucleic acids. In some cases, the body's defense mechanism is insufficient to fight against these radicals and the oxidative stress arises in the human body (2). Oxidative stress can be a cause of aging, cancer, cardiovascular diseases, lung diseases, diabetes and cataracts. The elimination of these factors adversely affecting human health is thought to prevent the formation of such diseases and protect human life (3).

General taxonomy information and distribution

The genus Cornus L. from the Cornaceae family consists of 65 known species that grow mostly in the form of trees and bushes. Cornus L. species are widely grown in the northern hemisphere, mostly Anatolia, the Caucasus and Europe (1). Among the Cornus species found in different parts of Asia and Europe, four species are known to have edible fruits, namely Cornus officinalis, C. mas, C. kousa and C. controversa (4). *Cornelian cherry* is a type of fruit that grows on trees with a stem diameter of 25-45 cm, which can grow up to 7-8 meters in height, or bush that shed its leaves in winter.

Cornelian cherry is a type of stone fruit. It ripens in late summer and early autumn. This fruit is an elliptical-shaped, 10-15 mm long, pink-red colored, slightly sour, tasty and nutritious fruit (5,6). Average fruit weight is between 5-8 g and kernel constitutes 7.5-11% of whole fruit weight. In wild-growing species, the yield is between 2.8 and 4.8 kg per bush, while with ideal rain and sun intake, this amount can reach up to 10 kg per bush. A yield of 30-80 kg per plant can be obtained in agriculturally grown species (6).

Phytochemical Composition

It is reported that *Cornelian cherry* fruit contains up to 88% of water, and it is a wealthy source of organic acids, vitamin C, proanthocyanidin, anthocyanin, epicatechin, and catechin (7). This fruit has an impressive red color due to the anthocyanin compounds that contain. They also contain phenolic compounds which have very beneficial effects on health. The diverse phytochemicals found in different parts of *Cornelian cherry* are summarized in Table 1.

The participants with UI were evaluated in terms of quality of life. Comparisons of the participants with different types of UI are presented in Table 2A,B. Mixed incontinence patients exhibited the least satisfaction in quality of life compared to both urge and stress incontinence in our study. According to UDI-6 total and subscale scores, patients with stress incontinence were in more discomfort than patients with urge incontinence. The same results were obtained with IIQ-7 total and subscales (Table 2A,B).

Cornelian cherry contains plenty of phenolic compounds, anthocyanin, and ascorbic acid. The fresh fruit contains 101-193 mg/100g ascorbic acid (19), 223-292 mg/100g total anthocyanin expressed as cyanidin-3-O-glycoside (1) and 281-704 mg/100g total phenolic compounds (20). Anthocyanins are the most important phenolic compounds of this fruit, followed by other flavonoids, phenolic acids and tannins, respectively. The leaves are richer in phenolic compounds (11.30%) when compared to fruits. Although the leaves contain more flavonoids, they contain no anthocyanins (10). Besides, the flowers are rich source of phenolic compounds, especially flavonoids (21).

Cornelian cherry is usually consumed fresh, as jam, compote, marmalade and pestle. Recently, this fruit got interestingly importance in pharmaceutics since it contains many neutraceuticals. It displays a sour taste, since it has a high level of vitamin C. The juice is 10-fold richer in calcium than pear, plum and apple juices. The juice contains also an important level of Fe, Mn, Zn, Na, and K (22). It was reported that *Cornelian cherry* could be used for prevention remedy of coronary heart diseases and cancer thanks to its bioactive compounds. Furthermore, it exhibits antioxidant and inflammatory properties due to its high level of phenolic compounds and ursolic acid (1).

Table 1. The diverse phytochemicals found in different parts of cornelian cherry

Phytochemical group	Part of plant	Chemical constituents	References
Flavonoids	Fruits, flowers and leaves	aromadendrin 7-O- glucoside, aromadendrin 7-O- xyloside, aromadendrin 7-O- glucoside, trans-Aromadendrin, kaempferol 3-O-galactoside, kaempferol 3-O-glucuronide quercetin, quercetin 3-O-xyloside, quercetin 3-O-rhamnoside, quercetin 3-O- galactoside, quercetin 3-O-rutinoside, quercetin 3-O-glucoside quercetin 3-O-robinobioside quercetin 3-O-galactosyl 7-O-rhamnoside myricetin, naringenin 3-O-methyl ester 7,3′-dihydroxy-5,4′-dimethoxyflavanone, 4-acetoxy-5,2′,4′,6′-β- pentahydroxy-3-methoxychalcone, isorhamnetin 7-O-rhamnoside	(8-12)
Flavanols	Fruits and leaves	(+) -Catechin, (−) -epicatechin	(10)
Anthocyanins	Fruits	cyanidin 3-O-robinobioside, cyaniding 3-O-galactoside cyanidin 3-O-glucoside, cyanidin 3-O-rutinoside, delphinidin 3-O-β-galactopranoside, delphinidin-3-O-galactoside delphinidin 3-*o*-rutinoside pelargonidin 3-O-rutinoside, pelargonidin 3-O-glucoside, pelargonidin 3-O-galactoside pelargonidin 3-O-robinobioside pelargonidin 3-O- glucoside, peonidin 3-O-glucoside chloride.	(1,9,11,13)
Phenolic acids and tannins	Fruits and flowers	ellagic acid, gallic acid, quinic acid, shikimic acid,chlorogenic acid 5-O-caffeoylquinic acid 3-O-caffeoylquinic acid, ferulic acid,vanillic acid salicylic acid, p-coumaric acid	(10,14-16)
İridoids	Fruits	Loganin, loganic acid, cornuside, sweroside	(13,16)
Carotenoids	Fruits	β-Carotene, β-carotene-5,6-monoxide, lutein-5,6-epoxide, lutein, luteoxanthin (13Z, 13′Z)-lutein, (9Z, 9′Z)-lutein, (9′Z)-neoxanthin, (all-E)-neoxanthin,	(17)
Fatty acids	Fruits and leaves	Linoleic acid, oleic acid, α-linolenic acid, palmitoleic acid, palmitic acid, stearic acid,2,4-heptadienoic acid	(15)
Organic acids	Fruits and leaves	oxalic acid, maleic acid, isocitric acid, malonic acid, , succinic acid, tartaric acid, citric acid, fumaric acid	(9,15)
Vitamins	Fruits	Ascorbic acid, α-tocopherol, biotin, riboflavin	(18)

Table 2A. Beneficial effects of different parts of *Cornelian cherry*

Activity tested	Plant part	Effect	Reference
Antioxidant	fruits	Fruit extracts displayed important antioxidant activities and the FRAP value was 21–57.8 FRAP units.	(20)
	Leaves, flowers and fruits	The methanol extracts from leaves, flowers and fruit showed acceptable antioxidant activity and the IC_{50} value was 39.40, 27.58 and 251.87 μg/mL respectively.	(21)
	Fruits	All extracts displayed significant antioxidant activities with FRAP unit of 190 −200 μM/g in FRAP assay and IC50 of 3.95 −9.67 mg mL in DPPH assay.	(14)
	fruits	Showed good antioxidant activity with 1509–5954μmolFe^{2+}/100 g FRAP assay, 623–1903μmol$_{TE}$/100 in DPPH assay and 441–1475μmol$_{TE}$/100 g in ABTS assay,	(31)
Antimicrobial	Fruits, leaves	The extracts of fruits and leaves showed acceptable antimicrobial activity against different bacterial and fungal strains (*Bacillus cereus, Clostridium perfringens, Escherichia coli, Listeria monocytogenes, Micrococcus flavus, Staphylococcus aureus, Pseudomonas aeruginosa, Sarcina lutea, Shigella sonnei, Candida albicans, Salmonella enteritidis, Proteus vulgaris, Klebsiella pneumonia*)	(10)
	fruits	Showed significant antimicrobial activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The extract was killed them all in one week and there was no bacterial growth until the 28th day.	(32)
	fruits	The most efficient antibacterial effect was enounced by water and methanol extract of CM fruit against *Staphylococcus aureus* the Minimum Inhibitory Concentration value was value 0.156 mg/ml and inhibition zone was 25 mm) and just methanol extracts showed an antifungal effect.	(33)
Anti-diabetic	Fruits	It was observed to reduce high levels of low-density lipoprotein cholesterol (LDL-C), (aspartate) AST, triglycerides (TG), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) to normal levels.	(34)
	Fruits	After 6 weeks of intervention, significant increase in insulin as well as decrease in HgbA$_1$^{c} and TG levels was seen in the drug group compared to the placebo. It has been observed that daily consumption of the CM extract improves glycemic control in adults with type 2 diabetes.	(35)
	Fruits	In pre-diabetic state of animals, it was found an important decrease of glucose level after the oral implementation of CM in dose of 1000 mg/kg bw and significant limitation of water intake. It is concluded that if higher doses of CM are consumed regularly in young animals, diabetic symptoms can be prevented.	(36)

Table 2B. Beneficial effects of different parts of *Cornelian cherry*

Cytotoxic and Anticancer	**Leaves**	**Showed important cytotoxic effect against human breast cancer cells. After treatment of 72 h, it was reduced the survival of cells to 11.1% (at a dose of 750 µg/mL). It is stated that this effect is related to tannins and total polyphenols in leaves.**	**(37)**
	Fruits	Exhibited important cytotoxic effect against different tumor cells (prostate adenocarcinoma, ovarian cancer, breast adenocarcinoma and lung non small cell cancer cells by growing inhibition of 80.3%, 82.2%, 79.4%, and 78.2% respectively).	(38)
	Fruits	Showed anticancer effect against liver cancer and breast cancer cells. It was observed that the cytotoxic effect of unripe fruit was higher than that of ripe fruit.	(39)
	Fruits	The two forms of CM extract (free CM extract and encapsulated into enteric coated nanocarriers) were studied. It was determined that the encapsulated CM extract effectively preserved the antioxidant activity and increased the anticancer effect.	(40)
Protective	Fruits	Demonstrated cardioprotective effect by enhancing myocardial endogenous antioxidant enzymes (glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT)), lowering the high levels of myocardial lipid peroxides, serum creatine kinase, serum lactate dehydrogenase and fixing myocardial damage.	(41)
	Leaves	Decreased the lipid peroxidation products grades to 50.04% and showed important radioprotective effect.	(42)
	Fruits	Decreased the oxidative stress caused by methotrexate and exhibited significant dose dependent preventive effect of the sperms. Reported to have a similar effect to vitamin E.	(43)
	Fruits	Showed a protective effect on brain tissue by decreasing the levels of protein carbonyl groups and thiol groups in plasma and brain tissue and improving the activity of paraoxonase enzyme. Also improved the activity of catalase enzyme in brain tissue and showed preventive effect to the nervous system from oxidative stress.	(44)
	Fruits	At the tested doses the CM extract improved the levels of serum antioxidant enzymes and decreased the levels of urea, uric acid, serum creatinine and showed renal protective effect.	(45)
	Fruits	Increased the levels of antioxidant enzymes, decreased the elevated malondialdehyde (MDA) and showed important hepatoprotective effect. Also normalized the toxin-induced hepatic lesions.	(46)
	Fruits	Showed hepatoprotective effect by reducing the activity of, ALT, ALP, AST, Lactate dehydrogenase (LDH) and level of direct bilirubin, MDA.	(47)
	Fruits	Showed protective effect of nervous system. It was stated that CM flavonoids increased memory retention and can be used in the treatment of Alzheimer's disease.	(48)
Other	Fruits	Ethnomedical use of CM in the treatment of ulcerative colitis has been verified.	(49)
	Fruits	The extracts from fruits of CM showed important anti-amylase and anti-lipase effect. Therefore, CM can be regarded as effective inhibitors of digestive enzymes involved in the prevention or control of diseases associated with hyperlipidemia.	(50)

Health benefits

Since millennia, *Cornelian cherry* fruit, leaves and flowers are widely used in Caucasia and Central Asia as blood clotting as fruit and for the treatments of sore throat, anemia chickenpox, rachitis, and kidney-liver disorders (23,24). It is also used as an ingredient in melatonin-rich medicines since it contains a higher level of melatonin. It has antipyretic and diarrheal effects, and the juice, sherbet or compote helps for the treatment of kidney stone diseases by increasing the amount of acid in the urine (25). This fruit improves kidney and liver functions, displays neuroprotective and anti-aging effects and contributes to restoring memory and motor skills. Furthermore, the fruit has positive effects on human skin and is used in the cosmetic industry in Europe. In addition, it is used as anti-bleeding agents (25).

The health benefits of different parts of *Cornelian cherry* are given in Table 2. This fruit is used depending on the countries' traditions. In Serbia, *Cornelian cherry* is employed as a preventive and curative remedy for the treatments of intestinal diseases, diarrhea and anemia as well as to booster the immune system (26), while it is applied in the treatment of digestive disorders and hemorrhoids in Turkey and Azerbaijan (23,27). In Caucasian countries, seed oil and fresh fruits are used as cures of stomach ulcers, wounds, and colitis (24). It has been reported that fruits are used in traditional medicine as cures of intestinal inflammation, diarrhea, malaria, kidney stones, fever, urinary tract infections, cancer and sunstroke in Iran (18). *Cornelian cherry* is employed in the traditional medicine for the treatment of intestinal inflammation and digestive disorders and also the cosmetics industry in Italy (28). *Cornelian cherry* is also used to regulate kidney functions and to treat diabetes in China (29). In addition, it is commonly used in Greece to prevent gout, anemia and skin diseases as well as joint pain, metabolism disorders and tuberculosis (30).

Conclusion

Cornelian cherry is found wild or grown in many Asian and European countries. It is widely used since the positive effects on health are well-known. It has widespread uses in both gastronomy and traditional medicine. The *Cornelian cherry* produced in Turkey is rich in vitamins and minerals and have important antioxidant compounds. The fruit is considered as a valuable nutritional supplement thanks to the richness in flavonoids, carotenoids, anthocyanins, iridoids, vitamins, phenolic acids, pectins, tannins, minerals and sugars. It is used in the treatment of many diseases like obesity, diabetes, cancer, hypercholesterolemia, digestive system diseases, liver and kidney disorders. Although the action mechanism of this fruit on the mentioned diseases is not clearly determined, it is well-known that most of these diseases are caused by oxidative stress. The clinical studies on patient groups should be completed on the plants rich in bioactive components like *Cornelian cherry* used in the prevention and treatment of illnesses. Furthermore, new studies are needed to discover the unknown effects on health and to review the known effects.

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Hakan Guraslan	Bagcilar education and research hospital, Istanbul
Hatice Durmaz	Atatürk University, Erzurum
Hüseyin Bozkurt	Keçiören Training and Research Hospital, Ankara
Keziban Dogan	Dr. Sadi Konuk Education and Research Hospital, Istanbul
Kubra Yesildal Yeter	Osmangazi University, Eskişehir
Mehmet Onur Kaya	Fırat University, Elazığ
Mehmet Turan Inal	Trakya University, Edirne
Mumin Demir	Ordu University, Ordu
Murat Turkaslan	Çankırı State Hospital, Çankırı
Omer Karaman	Ordu University, Ordu
Ozkan Cikrikci	Gaziosmanpasa University, Tokat
Ozlem Ozdemir	Ordu University, Ordu
Salim Sentürk	Memorial Hospital, Istanbul
Seda Keskin	Ordu University, Ordu
Sema Rakici	Recep Tayyip Erdogan University, Rize
Serap Ozturk	Ondokuz Mayıs University, Samsun
Serpil Sener	Inönü University, Malatya
Sevgi Cirakli	Ordu University, Ordu
Seyda Tuba Savrun	Ordu University, Ordu
Songul Aktas	Karadeniz Teknik University, Trabzon
Timur Yildirim	Karatay University, Konya
Tugrul Kesicioglu	Giresun University, Giresun
Ugur Balci	İzmir Katip Çelebi University, Izmir
Umit Gurbuz	Selçuk University, KOnya
Yasemin Kaya	Ordu University, Ordu
Yeliz Kasko Arici	Ordu University, Ordu