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European Journal of Therapeutics (Eur J Ther) is the double-blind peer-reviewed, open access, international publication organ of the Gaziantep University School of Medicine. The journal is a quarterly publication, published on March, June, September, and December. The journal publishes content in English.

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Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Methods, Results, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

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Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

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Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

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When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including

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Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

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Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

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Review

Nosocomial Parasitic Infections

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ABSTRACT

Nosocomial infections develop a minimum of 48 h after hospital admission in patients who are free from infections at the time of admission. In addition to other agents that cause infection, the etiology of nosocomial infections involves various parasites. In light of literature data, the aim of this review was to address the agents that cause nosocomial parasitic infection.

Keywords: Hospital-acquired infections, nosocomial infection, parasites

INTRODUCTION

Nosocomial infections develop a minimum of 48 h after hospital admission in patients who are free from infections at the time of admission. Nosocomial infections extend the hospitalization period and increase patient costs (1). The agents that cause nosocomial infection are reported to be bacterial, viral, and fungal agents in many studies, whereas parasitic agents are generally ignored.

Waterborne Nosocomial Parasitic Agents

There can be many sources of nosocomial infections in a hospital. The most prominent among the important and controllable causes of nosocomial pathogens is the water supply of the hospital. Waterborne contagion can occur in hospitals due to showering, drinking the water, and using contaminated medical equipment washed with tap water. Hospital water sources include water tanks, showers, and tap water. There are some protozoans that run the risk of causing waterborne transmission or that have actually caused outbreaks in hospitals. Major outbreaks of waterborne *Toxoplasma gondii* have already been reported. Therefore, *T. gondii* can be an agent that potentially causes waterborne nosocomial parasitic infection (2). Diarrhea cases were seen, due to *Encephalitozoon intestinalis*, in the ward of immunosuppressed children in Spain between 2012 and 2013, and protozoans were subsequently isolated from the hospital's water tank (3). In another study conducted in South Africa, free-living amoebae, at a rate of 79.4%, were isolated from water and biofilm samples collected from various departments and units of a hospital. Therefore, free-living amoebae could be a potential nosocomial agent for both immunosuppressed patients and hospital employees (4). Another protozoan that can be transmitted by water is *Cryptosporidium*. Just how severe an infection can be is shown by an outbreak caused by chlorine-resistant *Cryptosporidium* oocysts in the public water supply in Milwaukee in 1993. The outbreak affected 403,000 individuals and caused 69 deaths (5). Immunosuppressed patients in hospitals are easy targets for *Cryptosporidium* infection. *Cryptosporidium* infections can become chronic in immunosuppressed patients. This can lead to severe extraintestinal complications (6). Nosocomial *Cryptosporidium* infections can cause outbreaks as *Cryptosporidium* can be transmitted by food, direct contact, and, occasionally, hospital equipment. They generally affect patients with human immunodeficiency virus (HIV), transplant patients, patients with malignancies, and children (7). In an outbreak in China that involved 6284 pediatric patients who were admitted to three different hospitals with non-gastrointestinal complaints between 2007 and 2009, *Cryptosporidium* species were detected in 102 cases. However, the source could not be identified (8). To prevent the risk of *Cryptosporidium* oocyst, drinking water can be kept at a temperature of ≥72.4°C, or water treatment systems with a 1 µm filter can be used (9).

Transfusion-Transmitted Nosocomial Parasitic Agents

Another possible cause of nosocomial contagion is transmission by transfusion. The most well-known blood parasite that can be transmitted via transfusion is the *Plasmodium* species. Increasing the number of journeys to endemic areas results in an increased risk of transfusion-transmitted malaria (10). In Turkey, donors are tested for certain viral diseases and syphilis, and, as per law no. 2857, it has become obligatory to test for agents that cause malaria in blood donors. However, some limitations were implemented in the circular of the General Directorate of Treatment Services (dated October 8, 1997), and it was deemed appropriate to continue testing for malaria parasites only in donors who have a risk of contracting malaria (11). There are no recent reports of transfusion-transmitted malaria in Turkey. In a study conducted

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in 2012, only 2.97% of the 202 donors who were rejected due to the risk of malaria were found to be malaria positive (12). *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium falciparum*, and *Plasmodium ovale* in investigating the agents that cause transfusion-transmitted malaria globally were, until recently, reported as the agents, whereas the presence of transfusion-transmitted *Plasmodium knowlesi* was reported in recent years in endemic areas (13). In some regions in America, *Babesia microti*, which is a blood parasite transmitted by ticks, is the most frequently seen microbial agent that is transmitted by transfusion. A total of 160 transmission cases due to transfusion were reported in the USA between 1979 and 2009 (14). *T. gondii* is another protozoan that can be transmitted by transfusion. In a meta-analysis conducted in Iran, the seroprevalence of *T. gondii* was reported to be 34.4% in a blood donor group of 4538 individuals (15). *Leishmania* spp. and *Trypanosoma* spp. are protozoans that are rarely transmitted by transfusion. There are reports of transfusion-transmitted *Trypanosoma* infections in endemic areas within Central and South America, as well as Mexico (16). In addition, there are a few reported cases of kala-azar that are thought to be have been transmitted by transfusion. The majority of the kala-azar cases are pediatric patients (17). One case in the advanced age group, which comprises a few patients, was reported in Greece in 2012. A 77-year-old patient with chronic renal failure who was treated in an intensive care unit died, and the postmortem biopsy showed amastigotes in the bone marrow. Upon investigation of the etiology, it was found that the patient had undergone cholecystectomy 3 months previously and received two units of blood transfusion. One of the donors was *Leishmania* positive according to the serological test result conducted; therefore, it was concluded that the infection was transmitted by transfusion (18). The use of leukocyte reduction filters to prevent the transmission of *Toxoplasm*a, *Trypanosoma*, and *Leishmania* by transfusion in hospitalized patients is recommended (16, 19, 20).

Transplantation-Transmitted Nosocomial Parasitic Agents

Transmission by transplantation is another cause of the nosocomial transmission of parasites. Cases of malaria have been reported after kidney, liver, heart, and bone marrow transplants. The malaria agents were reported to be *P. vivax*, *P. falciparum*, *P. ovale*, and *P. malariae* (21). *T. gondii* infections are parasitic infections that can also be seen in the recipient after solid organ transplantation. The highest rate of transmission from a toxoplasma seropositive donor to the recipient is seen after heart transplants (50%), followed by liver (20%) and kidney transplants (<1%) (22). The mortality of *T. gondii* infections seen in the recipient in the post-transplantation period is high. This is because the recipient usually develops a disseminated infection. The rate was reported to be 64.5% in the follow-up of patients after kidney transplantation and 50% after heart transplantation (23, 24). There are some reports of leishmaniasis cases after transplantation. Leishmaniasis cases are usually associated with kidney transplantation (77%). However, there are also several reports of cases occurring after liver, heart, lung, pancreas, and bone marrow transplantation (25). *Strongyloides stercoralis* is a rare parasitic agent that is transmitted after transplantation. There are a few reports involving donor-derived *S. stercoralis* infection in the recipient. These infections, which result in a high mortality rate, are mostly transmitted from donors that come from areas where *S. stercoralis* is endemic (26). One of the known transmission routes of *Trypanosoma cruzi* is by transplantation (27). However, successful transplantations with the administration of prophylactic treatment from a *T. cruzi* seropositive donor to a seronegative recipient have been reported in recent years. Salvador et al. (28) reported that *T. cruzi* DNA is negative 6 months after the completion of prophylaxis in a seronegative patient who received benznidazole prophylaxis following lung transplantation from a seropositive donor.

Hospital Equipment-Acquired Parasitic Agents

Nosocomial parasitic infections can sometimes be acquired from contaminated hospital equipment. There are reports of *Plasmodium*, a genus of protozoans, being transmitted by injectors, contaminated gloves, and contacting bedside glucometers (29-31). *S. stercoralis* has also been reported to be transmitted from contaminated endoscopes (32). Therefore, hospital staff should rigorously check to prevent transmission from hospital equipment.

Parasitic Agents in the Etiology of Nosocomial Diarrhea

In the etiology of nosocomial diarrhea, in addition to bacterial and viral agents, intestinal parasites have also been reported at various concentrations. In a study conducted in Saudi Arabia, protozoans have been reported at a rate of 19.8% in the etiology of nosocomial diarrhea in patients admitted in surgery wards. *Cryptosporidium parvum*, *Blastocystis hominis*, *Giardia lamblia*, and *Entamoeba histolytica* were found at the rates of 6.6%, 6.6%, 3.5%, and 3.1%, respectively (33). In another study, *C. parvum* and *E. histolytica* were isolated at the rates of 2.5% and 6.2%, respectively, from the stool samples of children aged <5 years admitted to the pediatric ward of a hospital in Iraq with nosocomial diarrhea (34). There are other studies that investigate intestinal parasites in hospitalized patients. Intestinal parasites were detected in 18.8% and 4.8%, respectively, of asymptomatic male and female patients who were admitted to a psychiatric hospital in Ghana. These parasites were reported to be *E. histolytica*/*dispar* cysts, *G. lamblia* trophozoites, *C. parvum* oocysts, *Hymenolepis nana* eggs, *Trichuris trichiura* eggs, *Ascaris lumbricoides* eggs, and *S. stercoralis* larvae (35). In a study conducted in Turkey by Östan et al. (36) in 2004, nosocomial parasitic agents, including *Enterobius vermicularis*, *Giardia intestinalis*, *B. hominis*, *E. histolytica*, and *Dientamoeba fragilis*, were detected in 33.3% of the patients who were admitted to some wards and the intensive care unit in Manisa Public Hospital.

Nosocomial Transmission of Ectoparasitic Infection Agents

There are several infestations that occur due to ectoparasites in hospitals. Scabies, which is an ectoparasitic infection caused by *Sarcoptes scabiei*, is among these infestations. Infestation occurs by close contact, sexual intercourse, and, more rarely, due to sleeping in the same bed. Scabies typically clinically manifests with skin lesions and pruritus that aggravates at night. The form of scabies seen in patients receiving immunosuppressive treatment, patients with HIV infection, and patients with mental retardation is usually Norwegian scabies or crusted scabies (37). The host has 5–15 microorganisms in typical cases of scabies, whereas the host may have millions of microorganisms

in Norwegian scabies (38). There are many studies that report outbreaks of nosocomial scabies. One of these outbreaks is the scabies outbreak that affected 460 patients and 185 hospital employees in a university hospital in the Netherlands in 2015 (39). Another outbreak was reported in the dementia ward of a geriatric hospital in Japan. A patient with senile dementia staying in the dementia ward was diagnosed with scabies, and during the following 288 days, scabies was seen in 20 patients among 65 individuals in the same ward (40). In Switzerland, a skin rash in a patient with acquired immunodeficiency syndrome who was admitted to the intensive care unit with pneumonia and sepsis diagnosis was thought to be a delayed hypersensitivity reaction due to antibiotic treatment. The patient was then diagnosed with crusted scabies in the rehabilitation center to which he was transferred 7 weeks later. The 1640 individuals who were possibly exposed to the agent during the 7-month period after this patient was diagnosed with crusted scabies were administered prophylactic scabies treatment. The scabies agent was detected in 19 individuals that consisted of hospital employees, patients, and their relatives (41). Healthcare workers play a significant role in the prevention of nosocomial scabies. These workers should not ignore unexplained skin rash and pruritus in both themselves and their patients, but consult the relevant persons upon its detection. Patients diagnosed with scabies should be isolated and treated. Healthcare workers and other patients who have come into contact with these patients should also be administered prophylactic treatment (42). If Norwegian scabies is seen in a hospital, the necessary precautions should be taken in laundry rooms in which the patient's clothes are washed. Patient's rooms should also be cleaned (37).

Myiasis is a clinical occurrence that develops as a result of the infestation of the body of an animal or human by dipterous fly larvae. Nosocomial myiasis is rare. The predisposing factors for this infestation include paralysis, debilitation, diabetes, and vascular diseases, as well as the presence of blood and mucus. Most of the cases are reported in the summer when the fly population increases. Agents that cause nosocomial myiasis were reported to be flies from the Calliphoridae, Sarcophagidae, Muscidae, Cuterebridae, and Phoridae families. Myiasis cases are generally reported during adulthood, whereas infantile nosocomial myiasis cases are rarely reported (43, 44). Flies that cause myiasis can be present due to other infestations in the hospital. In the USA, nasal myiasis caused by *Lucilia sericata* in two comatose patients in the intensive care unit was associated with a mouse infestation in the food storage areas of the hospital (45). The clinical course of myiasis cases is generally good. Removing larvae mechanically and washing the affected tissues are generally sufficient for treatment (46). However, there is a risk of penetration into the intracranial cavity in cases of risky anatomical localizations, such as nasal and auricular myiasis (47, 48). Myiasis was suspected as being the cause of death of a patient in Iran who was diagnosed with nosocomial nasal myiasis caused by *L. sericata* in the postoperative period (49). Precautions, such as placing mechanical barriers that prevent flies from entering through windows and vent holes, as well as inspecting food storage areas for other infestations that attract flies, can be taken to prevent nosocomial myiasis (50).

CONCLUSION

Although parasitic infections are commonly seen worldwide, they are usually ignored in the etiology of nosocomial infection. However, various agents that cause nosocomial parasitic infections were reported in some studies. Therefore, clinicians should definitely consider parasitic infections in the etiology of nosocomial infection, and hospital infection control committees should take measures against parasitic infections. Finally, in-hospital training sessions on this issue should be planned by the training units.

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Original Research

Prevalence and Associated Depression Risk Factors in Patients with Chronic Obstructive Pulmonary Disease in Qazvin, Iran (2014)

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ABSTRACT

Objective: The prevalence of depression in patients with chronic obstructive pulmonary disease (COPD) varies from country to country, and even across various geographic regions within a country. The aim of this study was to determine the prevalence of depression and its related risk factors in patients with COPD in Qazvin, Iran.

Methods: This cross-sectional study included 100 patients (34–80 years old) with COPD, referred to the pulmonary diseases clinic in Qazvin, Iran, during 2014. Demographics, medical records, current symptoms, and results of the lung function tests of the participants were recorded. Moreover, the pulmonary function was evaluated. COPD was categorized according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) system. The Beck depression inventory (BDI) was completed by all participants. Data were analyzed using the independent samples t-test, chi-squared test, and linear regression analysis.

Results: Of the 100 patients with COPD, 90 were male. The mean age was 57.57±14.06 years. Moreover, among the 100 patients with COPD, 75 had depression. 67% had symptoms of mild to moderate depression, and only 8% had severe depressive symptoms. There was a significant association between depression and independent variables of cigaret smoking (β, 0.384; $p<0.05$), body mass index (BMI; β, −0.383; $p<0.05$), and one-second forced expiratory volume (FEV1; β, −0.264; $p<0.05$).

Conclusion: The prevalence of depression in patients with COPD was high in this study. Smoking, BMI, and FEV1 were associated with depression. Effective interventions should be developed to address this clinical concern.

Keywords: Body mass index, chronic obstructive pulmonary disease, depression, smoking

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive disease with a prevalence of 5%–13% (1, 2). COPD is characterized by symptoms such as dyspnea and limited airflow reversibility (3). In some patients, systemic manifestations progress and result in the disruption of peripheral muscle function, exercise limitation, and malnutrition (1, 4). The documents show that approximately 5% of the world's population is affected by the disease. In 2012, the disease was the third most common cause of mortality and morbidity in the world (5). According to researchers' predictions, COPD is expected to become the second cause of mortality and morbidity, and in terms of burden, the world's fifth-highest ranking disease by 2020 (6, 7). The burden of this disease is now higher in Asian countries than in Western developed countries. This seems to be related to tobacco exposure and the indoor and outdoor air pollution in Asian countries (8). If intervention is not taken to reduce the COPD risk, the mortality rate is projected to increase by 30% in the next decade (9).

Chronic obstructive pulmonary disease affects mental health significantly because of its effect on sleep and social life (10). Patients with COPD develop depression during their illness, and their daily activities are severely impaired due to chronic psychological stress, physical pain, and frequent hospital admission. De-

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pression is one of the factors that worsen social performance and the quality of life, and it is associated with dyspnea and disease progression (11, 12).

Depression is a major global public health problem. The disease is often associated with other chronic diseases. The impact of depression on COPD is a complex and bi-directional issue.

It is believed that depression indirectly contributes to the development of COPD because depressed people are less likely to quit smoking (13, 14). The presence of depression in chronic illnesses exacerbates the adverse effects of these diseases and leads to noncompliance with treatment, loss of disease control, lower quality of life, increased use of health resources, and increased mortality and morbidity.

The combination of these two diseases in the coming decades can create significant health problems for individuals and society (7); thus, the diagnosis of depression in patients with COPD is of great importance. Information on the prevalence of depression varies from country to country, and even across geographic regions within a country. Systematic reviews on various studies have failed to make a conclusion (6, 15). In addition, depression in patients with COPD leads to more health care use and admission, as well as to further return of patients to emergency rooms, resulting in high economic burden. Therefore, screening and timely treatment of the symptoms of depression in these patients are very important. The aim of this study was to determine the prevalence of depression and its related risk factors in patients with COPD in Qazvin, Iran.

METHODS

This cross-sectional study was conducted on 100 patients (34–80 years old) with COPD referred to the pulmonary diseases clinic in Qazvin, Iran, during 2014. The study was confirmed by the ethics committee of the Qazvin University of Medical Sciences (decision no: 796, date: 2013.11.23). The study participants gave their written informed consent.

The inclusion criterion was the COPD diagnosis confirmed by a single pulmonary diseases subspecialist. The exclusion criteria were asthma or any chronic pulmonary disorder other than COPD; COPD exacerbation; and confirmed mental illness.

The COPD diagnosis was based on the criteria provided by the American Thoracic Society and European Respiratory Society (16). For this purpose, medical records, current symptoms, and results of the lung function tests of the participants were used. The pulmonary function was evaluated by the spirometer model 701. COPD was categorized according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) system based on the one-second forced expiratory volume (FEV_1) (17).

Demographics were recorded. The Beck depression inventory (BDI) was completed by all participants. Beck's questionnaire includes 21 four-choice items, in which each choice in the range of 0–3 shows the highest severity of depression. The questionnaire has a maximum score of 63, in which the score of 0–15 indicates normal status, 16–30 mild depression, 31–46 moderate depression, and 47–63 severe depression (10, 18).

Statistical Analysis

The data were presented using the frequency and percentage for categorical variables and the mean±standard deviation for continuous variables. An independent t-test was used to compare the continuous variables, while the chi-squared test was used to compare the categorical variables. Linear regression was used to investigate the relationship between depression and several explanatory variables. Then, a multiple linear regression analysis was used to investigate the relationship between all the risk factors and depression. In both the regression models, the independent variables included gender, body mass index (BMI), age, work status, occupational exposure to airborne particles, cigaret smoking, and age at the COPD onset, FEV_1, COPD duration, family history, education level, and the GOLD stage. All the statistical analyzes were performed using the Statistical Package for the Social Sciences software version 19 (SPSS IBM Corp.; Armonk, NY, USA). A $p<0.05$ was considered to be statistically significant.

RESULTS

Of the 100 patients with COPD, 90 were male. The mean age was 57.57±14.06 years. There was only one young patient (a 34-year-old man) who was a heavy smoker from the age of 14. However, genetic deficiency was ruled out in this particular case by measuring alpha-1 antitrypsin. Table 1 shows the demographic and clinical characteristics of patients. The groups with an education level less than 12 years and illiteracy had the highest frequency. The highest frequency of work status was related to unemployed patients and workers. The mean BMI was 22.28±4.27 kg/m^2. Among the 100 patients, 16 (16%) were underweight, and 11 (11%) were obese. Moreover, 69% of the patients with COPD had a history of smoking. COPD was severe or very severe in 46% of the patients based on the GOLD criteria. Only age was significantly different between the male and female patients ($p<0.05$).

In addition, 75% of patients with COPD had depression. Table 2 shows the relationship between the COPD severity and depression. Of the 100 patients, 67% had symptoms of mild to moderate depression, and only 8% had severe depressive symptoms. The mean BDI score among the patients was 15.45, 25.79, 27.25, and 33 in the GOLD Stages I, II, III, and IV, respectively. It was also found that with increasing COPD severity of, the mean depression score increased as well.

The results of the linear regression analysis are presented in Table 3. There was a significant and negative association between depression and the independent variables of FEV_1 and BMI ($p<0.05$). On the other hand, depression had a positive relationship with cigaret smoking and the GOLD stage ($p<0.05$). In a multiple regression analysis, the results did not fundamentally change, except for the GOLD stage.

DISCUSSION

The presence of unknown depression in patients with COPD is a challenging issue. Therefore, it is very important to diagnose

Table 1. Demographic and clinical characteristics of patients with chronic obstructive pulmonary disease (COPD)

Variable	Total	Male (n: 90)	Female (n: 10)	p
Age	57.57±14.06	58.77±13.6	46.7±14.11	0.0093
Education level				
Illiterate	37 (37)	34 (38)	3 (30)	0.71
<12 years	38 (38)	35 (39)	3 (30)	
12–14 years	18 (18)	15 (17)	3 (30)	
>14 years	7 (7)	6 (7)	1 (10)	
Work status				
Unemployed	39 (39)	38 (42)	1 (1)	0.19
Employee	10 (10)	9 (10)	1 (1)	
Self–employed	17 (17)	15 (17)	2 (20)	
Worker	34 (34)	28 (31)	6 (60)	
BMI	22.24±4.77	22.50±4.78	19.9±4.17	0.091
Smoking				
No smoking	31 (31)	27 (30)	4 (40)	0.75
Former smoker	29 (29)	26 (29)	3 (30)	
Current smoker	40 (40)	37 (41)	3 (30)	
GOLD stage				
Mild	11 (11)	11 (12)	0	0.45
Moderate	43 (43)	37 (41)	6 (60)	
Severe	40 (40)	36 (40)	4 (40)	
Very severe	6 (6)	6 (7)	0	
Beck depression score	25.67±13.74	25.15±14.04	30.3±10.13	0.26
COPD duration	9.17±6.26	9.31±6.33	7.9±5.72	0.5
Age at COPD onset	56.52±15.23	56.63±15.58	55.5±12.25	0.82

BMI: body mass index; GOLD: the global initiative for chronic obstructive lung disease; COPD: chronic obstructive pulmonary disease

Table 2. Association between COPD severity and depression

		Depression				
COPD Severity by GOLD	Score	No	Mild	Moderate	Severe	p
Mild	15.45±16.17	8	0	2	1	0.037
Moderate	25.79±14.51	12	10	19	2	
Severe	27.25±9.95	4	28	5	3	
Very severe	33±19.04	1	1	2	3	

COPD: chronic obstructive pulmonary disease

and determine the prevalence of depression in patients with COPD (1). In this study, the prevalence of depressive symptoms in patients with COPD was 75%. In other words, approximately three-quarters of these patients suffered from some degree of depression, which is remarkable and greater than the high prevalence of depression in the general population of the country (20%–30%) (19).

In this study, cigaret smoking, BMI, and FEV_1 were significantly related to depression. However, depression had no significant relationship with age, gender, work status, and the education level.

In Iran, there is little information about the prevalence of depression in COPD patients. In a study by Adeli et al. (20), 83.3% of COPD patients suffered from varying degrees of depression.

Table 3. Linear regression analysis of depression and the independent factors

	Linear		Multiple	
Variables	**β**	**p**	**β**	**p**
FEV_1	−0.228	0.022	−0.264	0.021
BMI	−0.37	<0.001	−0.343	0.001
Gender	−0.113	0.264	0.017	0.871
Age	−0.007	0.946	0.058	0.53
Work status	0.012	0.907	−0.084	0.626
Occupational exposure to airborne particles	0.056	0.581	0.019	0.916
Smoking	0.282	0.004	0.384	<0.001
Age at COPD onset	−0.188	0.061	−0.138	0.131
COPD duration	0.061	0.549	0.038	0.67
Family history of COPD	−0.053	0.601	−0.281	0.053
Education level	0.024	0.816	0.046	0.615
GOLD	0.253	0.011	0.009	0.931

BMI: body mass index; GOLD: the global initiative for chronic obstructive lung disease; COPD: chronic obstructive pulmonary disease

The incidence of depressive symptoms varies from 6% to 56% in COPD patients. This prevalence variation can partly be attributed to the use of different scales to examine depression (21, 22).

After the inclusion of all the factors influencing depression in the regression model, other than the GOLD stage, the results did not substantially change, and in both the models, depression was associated with FEV_1, BMI, and smoking. A few studies in Iran have considered all these associations. Different studies in the literature confirm the findings of this study. For example, De et al. (23) showed in a study that depression progressed significantly with the progression of COPD. This finding is consistent with our study.

In the present study, smoking had a direct association with the prevalence of depression in the COPD patients, which is in line with the study of Wagena et al. (24). Research shows that a few minutes after taking the last cigaret, the amount of nicotine in the body begins to decrease, which also causes anxiety in a smoker and has a very close relationship with depression. Thus, permanent changes in the nervous system resulting from the use of cigarets lead to depression that may remain throughout the life of a smoker and is very difficult to overcome (25).

In this study, there was a significant reverse correlation between BMI and depression, as depression was lower in patients with higher BMI. Such a connection has also been shown in other studies (26, 27). In line with previous studies, FEV_1 had an inverse relationship with depression (26, 28). Studies show that increased dyspnea is significantly associated with the development of depressive symptoms. Reduced physical activity due to dyspnea is probably the main cause of these psychological complications (29).

Evidence suggests that low alcohol use has a significant effect on reducing the prevalence of depression (21). In this study, consumption of alcoholic beverages was not included among the variables in the model. The reason for this was the legal prohibition of alcohol in the country and that the participants never mentioned of alcohol consumption.

Contrary to this study, Hanania et al. (30) recognized the female gender as an effective factor in depression. Since only 10% of the patients in this study were female, this could not result in a reliable comparison. In a study by Zhang et al. (7), similar to our study, gender was not considered to be a significant moderator in depression. Moreover, contrary to the current study, in a study conducted by Bhowmik et al. (6), the education level was a risk factor for depression. The reason for this contradiction is the impact of cultural, ethnic, and genetic factors on the lifestyle, which can affect the observed relationships.

One of the strengths of this study, compared to the previous studies, was the use of statistical tests that controlled the confounding factors. In this research, the regression test was used for this purpose. This study had some limitations, including its cross-sectional design and reliance on self-report questionnaire for determining depression; thus, further studies are needed to determine the causal relationship between the factors of the study. Obstructive sleep apnea, which may affect depression, was not evaluated in this study. To achieve a more comprehensive examination, clinical diagnostic criteria need to be used to investigate depression. Moreover, this study examined people living only in one of the cities in Iran. Therefore, these findings cannot be applied to the whole country. To achieve such a goal, further studies should be undertaken at a wider level.

CONCLUSION

This study showed that the prevalence of depression in patients with COPD was high in comparison with general population. In a more detailed study, it was found that smoking, BMI, and FEV_1 were three important risk factors. Effective interventions should be developed to address this clinical concern, and the impact of these interventions should be evaluated by self-reporting measures. One of the suitable strategies for this task is cognitive and behavioral therapy, which requires an examination of all the influential factors that were considered to the extent possible in this study.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Qazvin University of Medical Sciences (decision no: 796, date: 2013.11.23).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Original Research

The Pain in the Canon of Medicine: Types, Causes, and Treatment

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ABSTRACT

Objective: Avicenna (980–1037 AD) was a renowned physician and philosopher. This study aimed to elaborate on the presented information in The Canon of Medicine about pain, its causes, types, and treatment methods in the pain-related specific chapters and compare it with today's information.

Methods: The information in the pain-related chapters in The Canon of Medicine was examined. This information was compared with the information in the English translation of the book. The information obtained by the correlation between the two works was compared with the current knowledge.

Results: The pain was defined as abnormal condition seen in an animal's body. The causes of pain were examined as sudden and irregular abnormalities in temperament and interruption of continuity. Avicenna categorized pain and developed hypotheses about the cause of each type of pain. The application of Avicenna's pain treatment is based on the use of methods that act in opposition to the elements that cause loss of temperament and continuity. He prescribed analgesic agents, anesthetics, and antispasmodics for the pain relief.

Conclusion: Although the effect of the pain-related theories of Hippocrates and Galen are also visible in The Canon of Medicine, his work contains much more detailed information about the definition, types, causes, and treatment methods of pain. The definitions he made in The Canon of Medicine about the classification of pain are found in many of the pain assessment scales used today. His descriptions of drug and dose selection are similar to those of modern pharmaceutical principles.

Keywords: Avicenna, canon of medicine, pain

INTRODUCTION

Avicenna (980–1037 AD) was a renowned physician and philosopher. He wrote many works in the field of medicine. The most important work of Avicenna is The Canon of Medicine (known as El-Kânûn Fi't-Tibb in Turkish, al-Qānūn fī al-Ṭibb in Arabic) that consists of five volumes. In the first of these volumes, general medical topics and human anatomy are explained. In the second, basic drugs and their preparation are explained. In the third volume, which is the most comprehensive volume, organs and medical ethics are discussed. The fourth volume deals with some infectious disease (such as leprosy, plague, and smallpox), skin diseases, animals, and poisonous plants. The fifth volume lists all known medicines at that time and information on their dosage. The Canon of Medicine was used as a textbook for many years in the Eastern and Western world and translated into languages such as Latin, Persian, English, Hindi, Spanish, Portuguese, German, and French (1). The first volume of the work was translated into contemporary Turkish by Kahya E. (2) in 1995, and the translation of the other volumes was completed and published in 2015 (3). The influence of the teachings of Hippocrates (469–399 BC), Aristotle (384–322 BC), and Galen (131–200 AD) on medicine can be seen in The Canon of Medicine in a systematic order (4).

Pain has been a fact in the life of human beings for more than 50,000 years. It is described as an unpleasant, sensory, and emotional experience that can be attributed to present or possible tissue damage (5). There have been theories about the formation of pain and its pathophysiology since the time of Hippocrates (6). The examination of pain-related doctrines in the book, The Canon of Medicine, provides a clearer understanding of pain-re-

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lated hypotheses and definitions. Avicenna separately examined the definition of pain, its causes, types, treatments, and effects on body under specific chapters in the first volume in The Canon of Medicine.

This study aimed to elaborate on the presented information in The Canon of Medicine about pain, its causes, types, and treatment methods in the pain-related specific chapters in first volume and compare it with today's information.

METHODS

In this context, information in the pain-related chapters (Chapters 19–22) in second subsection (specific reasons subsection) in the second part (Etiology) of the Health and Disease section in Turkish translation of the first volume of The Canon of Medicine was examined. The Turkish translation was based on Beyrut printed edition (1st book) and Süleymaniye Library, Turhan Sultan 265, handwritten editions by Kahya E. (7). This information was compared with the information in the English translation of The Canon of Medicine. The English translation was based on the Latin editions published at Venice in 1595 and 1608, and supported by Arabic edition printed at Rome in 1593 and the Bulaq edition (8). The information obtained by the correlation between the two works was compared with the current knowledge. Because this study was evaluated as a historical medicine study, there was no need to take any ethics report or patient approval form.

RESULTS

Definition of Pain

The definition of pain, its causes, types, treatment modalities, and effects on body were separately examined under four chapters in the first volume. The definition of pain was explained in the "General Reason of Pain" section. He defined pain as "[a]n abnormal condition seen in an animal's body", and stated that discomforts in the body are perceived as pain (7).

Causes of Pain

The causes of pain were examined under two headings: sudden and irregular abnormalities in temperament; and interruption of continuity.

Sudden and Irregular Abnormalities in Temperament

According to Avicenna, pain is caused by the transformation of a present temperament to an exact opposite temperament (e.g., the sudden transformation of hot temperament to cold temperament) by the disruption of the balance between the temperaments. He stated that the sudden imbalance between hot and cold temperaments directly creates pain, that dry temperament indirectly brings pain, and that wet temperament never causes pain (7).

Interruption of Continuity

In this heading, Avicenna refers to Galen's theory of "loss of continuity" with regard to pain formation. Avicenna criticizes Galen's theory and argues that the change in present temperaments of organs causes pain (7). In addition, Avicenna presented a pain-temperature mechanism. According to Avicenna, temperature increases with pain; and with the increase in temperature, more blood flows in the blood vessels. The increase in the blood flow leads to edema, and the tension of the tissues further increases the pain (7).

Pain Types and Causes

Avicenna categorized pain and developed hypotheses about the cause of each type of pain. It was determined that the number and sequence of pain types differ between the English and Turkish translations of the work. A total of 14 different types of pain were explained in Turkish translation (7), while 15 types of pain were defined in its English translation (8). Tashani and Johnson (9) also identified 15 different types of pain in their work on the basis of the Arabic text of The Canon of Medicine (Table 1). The Arabic text of Tashani and Johnson's (9) used was based on Kitāb al-Qānūn fī al-.-tibb printed at Rome in 1593. The types and explanations of pain in Canon of Medicine were showed in Table 1.

The Relief of Pain

The application of Avicenna's pain treatment is based on the use of methods that act in opposition to the elements that cause loss of temperament and continuity. Removal of unnecessary fluids from the body, narcotics that make patients feel sleepy, and anesthetics that give the feeling of cold to the body are used to relieve pain.

Clinical information about analgesic agents, anesthetics, and antispasmodics is described in detail in the Pain Relief section (7).

Analgesic agents are pain relievers that show their effects by changing temperament. As an example of analgesic agents, opium, mandrake seeds and roots, seeds of black and white poppy, hyoscyamus, hemlock, oleander, and cucumber seeds are prescribed. In the English translation of the work, in addition to these items, there are also deadly nightshades and lettuce seeds. Ice and cold are also exemplified as substances with analgesic properties (7, 8).

Anesthetics are defined as substances that relieve pain by disrupting the activity of the affected organ with their toxic properties or causing extreme cold on it. It is suggested that a piece of sweet smelling moss or agar wood should be put in wine to make someone lose consciousness (7).

Antispasmodics are described as pain relief substances by dissolving and scattering matters that accumulate in an organ. Dill, linseed, melilot, chamomile seed, celery seed, and bitter almond are shown as examples of these substances (7).

Drug Selection

According to Avicenna, the pain-relieving drug may exert its effect mildly and slowly, or in some cases it may also be dangerous. For this reason, he gave detailed information about the drug's dosage and side effects. He emphasized the difficulty of choosing drugs and dosages for each disease. It was recommended to select the appropriate drug by observing the patient's pain tolerance level. The relationship between pain level and medication should be carefully controlled. He indicated that sometimes an untreated pain may result in death (7).

Table 1. The comparison of the number, sequence, and causes of each pain types in English translation (8), Tashani & Johnson's (9) study and Turkish translation (7)

	Type of the pain		
No.	**Gruner et al. (8) (English translation)**	***Tashani and Johnson (9)**	**Kâhya E. (7) (Turkish translation)**
1	Boring -Retention of gross matter or gas between the tunics of a hard and gross member	Itching -Exposure to irritating substance or salt	Itching The pain caused by cold-burning or acrid humors
2	Compressing -Confining of fluid or gas in a too small space	Coarse -Coarse substance	Burning -The pain caused by unprocessed blood
3	Corrosive -Presence of material between the muscle fibers and their sheets	Pricking -Something stretches membranes	Stabbing -The transverse tension of membrane interrupted of continuity by a humor
4	Dull -Too cold temperament -Occlusion of the pores -Overfulness of the cavities	Compressing	Tension - A humor or gas stretching to nerve or muscle fibers
5	Fatigue pain -Unnecessary effort -A humor producing tension -A gaseous substance producing inflative weakness -Ulcerative	Stretching -Bloat or muscle or nerve stretch	Compressing -The pain caused by pressure of humor on the organ
6	Heavy pain -Inflammatory process in insensitive organs like lung, kidney, or spleen	Disintegrating -A substance disintegrate inside the muscle and membranes	Corrosive -The humor accumulating between the muscle and membrane
7	Incisive -A humor of sour quality	Breaking -Bone change	Tearing -The fluid or gas accumulating between bone and periost
8	Irritant -A certain type of change in the humors	Soft -Muscle change	Blunt -The muscle stretched by the accumulating gas type materials in the muscle belly
9	Itching -A humor is acrid, sharp, or salt	Penetrating -A thick substance or bloat trapped in colon	Boring -The pain caused by the humor or gas in the organ
10	Pricking -The material retaining to organ	Stabbing -A substance trapped inside an organ	Pricking - The pain caused by the humor or gas in the organ, but it's harmless
11	Relaxing -The matter accumulating in and stretching the belly of muscle	Numbing -Extreme cold or vessels obstruction	Numbing -The pain caused by too cold temperament
12	Stabbing -A humor transverse stretching to membrane	Pulsating -A tumor or swelling close to arteries	Throbbing -The pain caused by hot inflammation
13	Tearing -A humor or gas between bone and periosteum	Heavy -A tumor or a swelling in lungs, kidney, or spleen	Heavy -The pain caused by inflammation in the insensible organs like lung, spleen, and kidney
14	Tension - A humor or gas stretching to nerve or muscle fibers	Tiredness	Fatigue -A humor cause to tension -It is derived from the humors like ulcers damage to tissues
15	Throbbing -The hot inflammatory process	Bitter -Ulcers	_

No.: Number of pain type; *:the authors declared using Arabic manuscript in their study

Table 2 . The similarities of Avicenna's pain definitions in Kâhya E.'s Turkish translation (7) between multidimensional pain scales widely used at the present day

	McGill Pain Questionnaire (16)			
Avicenna's pain definition (7)	**Our comments toward Avicenna's pain definitions in McGill Pain Questionnaire**	**Tashani and Johnson's (9) comments toward Avicenna's pain definitions in McGill Pain Questionnaire**	**Tursky Pain Perception profile (17)**	**Pain quality assessment scale (18)**
Itching	Itchy	Itchy, Pricking, Stinging	Itching	Itchy
Burning	Splitting, Burning	Rasping	Burning	Burning
Stabbing	Stabbing, Pricking, Stinging	Pricking, Stinging, Itchy	Stabbing, Stinging	Tingling
Tension	Tender, Taut	Tugging, Cramping, Taut	Cramping	Tender, Cramping
Compressing	Pressing, Squeezing	Squeezing, Pinching, Crushing	Squeezing, Pressure	Squeezing, Tight
Corrosive	Tearing, Cramping	_	Cramping	Cramping, Squeezing, Tight
Tearing	Sharp, Tearing, Cutting	Splitting, Tearing, Cutting	_	Sharp
Blunt	Taut	Tender	_	Dull
Boring	Boring, Stabbing	Stabbing, Lancinating, Cutting	Stabbing	_
Pricking	Pricking, Drilling Stabbing, Penetrating	Pricking, Stinging, Itchy	Stabbing	Tingling
Numbing	Numb, Drawing	Numb	Numbing	Numb
Throbbing	Pulsing, Throbbing Beating	Pulsing, Throbbing, Beating	Throbbing	Throbbing
Heavy	Heavy, Aching	Heavy, Dull, Aching	Aching	Aching, Heavy
Fatigue	Tiring, Exhausting	Tiring, Exhausting	_	_

DISCUSSION

Definition of Pain

Avicenna defined pain as an abnormal condition in an animal's body. He also expressed the discomforts in the body (7). Today, it is known that there are four stages of pain: transduction, transmission, perception, and modulation (10, 11). Avicenna's expression of discomfort as pain is consistent with the notion of perception. On the other hand, in Avicenna's medical definition, while the health and treatment phases are treated as subjects specific to humans, it is challenging to understand why he explained pain as an abnormality seen in an animal's body.

Causes of Pain

According to Avicenna, the transformation of a present temperament to an exact opposite temperament creates pain. Avicenna furthered Hippocrates and Galen's temperament and humoral theories. According to temperament theory, there are four temperaments in the nature that are balanced with each other and are the basis of nature: hot, cold, dry, and wet. In the body, there are four groups of organs as hot, cold, dry, and wet in accordance with these temperaments. According to humoral theory, humor is the main product of digested foods, and there are four basic humors in the body. These are blood, phlegm, black bile, and yellow bile. The excessiveness or insufficiency of these fluids leads to illness (12, 13). Avicenna was affected from ancient humoral theories while explaining causes of pain.

Avicenna refers to Galen's theory of "loss of continuity" with regard to pain formation. According to Galen, the real cause of pain is the loss of continuity. According to Galen's theory, particles in tissues get together depending on hot or cold temperature and are separated from their surrounding structures. The feeling that emerges as particles are separated from the surrounding structures is defined as pain. However, Avicenna criticizes Galen's theory and argues that the change in present temperaments of organs causes pain.

The temperature, blood flow and pain relation was stated by Avicenna. Roman physician Celsus first described inflammation findings (1st century BC) as rubor et tumor cum calore et dolore (redness, edema, heat, pain) (14). Avicenna appears to be influenced by Celsus in terms of the pain-temperature mechanism. Today's knowledge about the acute inflammatory process is similar to the information provided by Avicenna many centuries ago.

Pain Types and Causes

It was determined that the number and sequence of pain types differ between the English and Turkish translations of the work. The descriptions about the sequence of pain types and causes of pain in the Turkish translation (7) and Tashani and Johnson's (9)

study showed similarities. In the study of Tashani and Johnson (9), the pain caused by ulcers was called "bitter" while the pain caused by ulcers in Turkish translation was defined as "fatigue" (Table 1). We think that the differences in number, sequence, and reasons of pain types may be due to translations or may arise from differences in the versions from which the translations were made.

Today, unidimensional and multidimensional scales are used in the assessment of pain. Unidimensional pain scales are scales that determine the amount of pain intensity experienced by an individual (e.g. numeric rating scale, visual analog scale). In the assessment of complex and persistent pain, it is recommended to use multidimensional scales that assess the character of pain and its effect on daily life (15). The McGill-Melzack pain questionnaire (16), Tursky pain perception profile (17), and the pain quality assessment scale (18) are multidimensional scales based on patients' self-reports and are frequently used today. There are serious similarities between Avicenna's definitions of pain types and the definitions contained in these scales (Table 2). Because there was no definition in Tursky pain perception profile meeting the meaning of "tearing", "blunt", "boring", and "fatigue" and in pain quality assessment scale meeting the meaning of "boring" and "fatigue", no comment had been made in Table 2.

It is also apparent that Avicenna was influenced by Galen while explaining types of pain, brain anatomy, and physiology. Galen defined pain types as pulsating, lancinating, weighty, and stretching (19). Avicenna, like Galen, also stated that senses are carried to the brain and that the brain is a center receiving the senses. In addition to the sensory function of the brain, Avicenna emphasized that the brain is a cold organ and the center of movement (7). Avicenna laid the basis of the theory to be called the specificity theory after the 1800s (20). Avicenna's causal explanation for each type of pain is called physiopathological mechanism in the modern medicine. Definitions made about the types of pain in The Canon of Medicine may have emerged because of different subjective pain descriptions made by the patients.

The Relief of Pain and Drug Selection

The analgesic, anesthetics, and antispasmodics terms is described in detail in the work (7, 8). Today, analgesic drugs are defined as drugs that relieve pain without causing loss of consciousness. Medicines used for anesthesia are defined as substances that cause general sensory loss by suppressing all of the sensory functions of the central nervous system. Antispasmodics are drugs that usually have a relaxing effect on smooth and striated muscles (21, 22). Avicenna did not have separate descriptions of analgesics, anesthetics, and antispasmodics and said that all of them were painkillers. Nowadays, it is known that the definitions and mechanisms of action of analgesics, anesthetics, and antispasmodics in modern pharmacology are different from each other.

In addition, Avicenna stated that analgesic applications should be diligently done, in necessary situations and by considering their side effects. Analgesics should not be used if not necessary, and if used, the ones with the least side effects should be preferred. He talked about local or oral use of analgesics depending on the disease (7). Today, information such as indications, pharmaceutical effect, side effect, usage, and proper dose are routinely given in drug prescriptions; nevertheless, it is seen that Avicenna observed the modern pharmaceutical principles about a thousand years ago.

CONCLUSION

Although the effect of the pain-related theories of Hippocrates and Galen are also visible in The Canon of Medicine, his work contains much more detailed information about the definition, types, causes, and treatment methods of pain. The definitions he made in The Canon of Medicine about the classification of pain are found in many of the pain assessment scales used today. His descriptions of drug and dose selection are similar to those of modern pharmaceutical principles. We think that the awareness of researchers interested in the science of pain should be more aware about the teachings in The Canon of Medicine.

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Original Research

Comparison of Treatment Outcomes in Patients with Rectal Cancer

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ABSTRACT

Objective: The aim of the present study is to evaluate survival results and acute chemoradiotherapy toxicity in patients with rectal cancer who underwent preoperative chemoradiotherapy (CRT), postoperative CRT, and non-operative CRT.

Methods: The records of 139 patients with rectal cancer were analyzed retrospectively. Out of these, the data 9 (6%) patients who died during or immediately after treatment and 2 (1%) patients who gave up the treatment were not used in the survival analysis.

Results: Postoperative CRT was applied to 57 (44%) patients, preoperative CRT to 47 (37%) patients, and non-operative CRT to 24 (19%) patients. Non-operative CRT group was the oldest patient group (median age: 70). There was a difference between the treatment groups regarding tumor localization ($p<0.001$), pathological stage ($p<0.001$), lymphovascular (LVI, $p<0.004$), and perineural invasion (PNI, $p=0.017$). A difference was determined between the groups regarding median follow-up and the postoperative CRT group had the longest median follow-up ($p<0.001$). A difference was also determined between the groups regarding local recurrence and distant metastasis ($p=0.467$ and $p=0.901$, respectively). The three-year overall survival and disease-free survival rates were 78% and 78% for the postoperative CRT group, 76% and 73% for the preoperative CRT group, and 48% and 41% for the non-operative CRT group ($p<0.001$ and $p<0.001$, respectively). However, the difference between preoperative and postoperative CRT regarding overall survival and disease-free survival was not determined since the non-operative CRT group was included in survival analysis ($p=0.184$ and $p=0.073$, respectively). No difference found among the three groups regarding the adverse effects of chemoradiotherapy ($p>0.050$).

Conclusion: While no difference was determined between preoperative and postoperative CRT applications regarding local recurrence and distant metastasis, overall survival and disease-free survival, and adverse effects of treatment, LVI, and PNI determined in earlier pathological stage and lower frequency for the preoperative application. However, overall survival results of patients receiving non-operative CRT were worse as compared to patients receiving operative CRT.

Keywords: Non-operative chemoradiotherapy, postoperative chemoradiotherapy, preoperative chemoradiotherapy, rectal cancer

INTRODUCTION

The primary treatment of rectal cancer is surgery, however, the local and systemic failure rate increases up to 50% particularly for advanced stage tumors when treated with surgery alone (1, 2). The decreased success rate of surgery led researchers to combine treatments such as radiotherapy (RT) and chemotherapy (CT) with surgical treatment. However, at the time, studies on this combination of treatment schemes were also being done. National Institutes of Health emphasized in a consensus meeting held in 1990 that postoperative CT and RT improved local control and survival for locally advanced rectal cancers and that combined treatments are required in such cases. The use of postoperative RT and CT became common in the 1990s (3). In a meta-analysis published by the Colorectal Cancer Collaborative Group in 2001 (22 randomized studies and 8507 patients), it was revealed that adjuvant RT ensured recovery in local control. In survival analyses, this recovery was determined to be on the border (4). It was reported in the same meta-analysis that local recurrence was decreased by 37% in postoperative RT and 46% in preoperative RT (4).

Simultaneous chemoradiotherapy (CRT) in locally advanced rectal cancer has also been investigated in large-scale studies. Several studies indicated that CRT applied following surgery in rectal cancers improved the disease-free survival and overall survival rates, and regressed local recurrence rates as compared to patients who received only RT (5-10). Preoperative RT and preoperative CRT were compared in the study by Braendengen et al. (8) on the basis of complete pathological response, local control, disease-specific survival rate, and preoperative CRT was found to be more advanced. However, it was also reported to increase grade 3–4 acute toxicity. In EORTC trial22921, it was shown that while tumor down-stating was better ensured with preoperative CRT in the early results, improved survival was not seen in long-term results. However, preoperative CRT proved advantageous for local recurrence (9, 10). In French FFCD 9203 trial, results were similar to those by EORTC obtained for preoperative CRT (11).

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In a German study comparing the preoperative and postoperative CRT and in an NSABP R-03 trial, the cumulative local recurrence rates were shown to be lower in preoperative CRT patients. Moreover, 5-year disease-free survival (DFS) in the NSABP R-03 trial and grade 3–4 diarrhea in the German study were reported to be increased in preoperative CRT cases (12). Thus, it was indicated that success was achieved in both local-systemic recurrences as well as in survival outcomes of locally advanced rectal cancers with combined treatments. Nevertheless, a standard algorithm has not been created as yet to determine the application time of treatment modalities (13, 14).

The complete response following preoperative CRT can be observed in 8–30% of patients (15-18). Researchers have observed that survival outcomes were better in patients for whom the complete response was observed after preoperative CRT, and have started to develop the "wait and watch" approach after preoperative CRT (19-21).

The aim of the present study was to evaluate the survival outcomes and the level of acute chemoradiotherapy toxicity of patients with rectal cancer who underwent preoperative CRT, postoperative CRT, and non-operative CRT.

METHODS

This study was conducted at the Cumhuriyet University Medical Faculty Hospital, Turkey, in accordance with the principles of the Declaration of Helsinki (date: 19/04/2017, a decision no: 2017-04/13). The data of 139 rectal cancer patients who were treated between 2007 and 2015 at the Oncology Center of Cumhuriyet University Medical Faculty Hospital were retrospectively evaluated. The patients were examined under three groups: preoperative CRT, postoperative CRT, and non-operative CRT.

Table 1. Demographic characteristics of the patients

	Postop CRT n=57 (44%)	Preop CRT n=47 (37%)	CRT n=24 (19%)	p
Gender				
Female	38 (67)	32 (68)	20 (83)	
Male	19 (33)	15 (32)	4 (17)	0.298
Age				
Mean (year)	60.2±1.3	55.6±1.7	72.5±1.9	<0.001
Comorbidity				
No	32 (56)	29 (62)	12 (50)	
Yes	25 (44)	18 (38)	12 (50)	0.631
ECOG PS				
ECOG 0	30 (53)	22 (47)	8 (33)	
ECOG 1	25 (44)	21 (45)	11 (46)	
ECOG 2–4	2 (3)	4 (8)	5 (21)	0.123

ECOG: Eastern Cooperative Oncology Group; PS: performance status; CRT: chemoradiotherapy

The performance status of the patients was evaluated by the ECOG (Eastern Cooperative Oncology Group) scoring system at the time of metastases. Pretreatment evaluation was performed by complete blood count, biochemical profiles, serum CEA (serum carcinoembryonic antigen), colonoscopy with biopsy, abdominopelvic CT scan, EUS (Endoscopic Ultrasound), and chest CT scan. In addition to these examinations, some patients underwent pelvic MR and PET-BT. Clinical staging was performed using the above-mentioned examinations and pathological staging was performed after the surgery. The stage of disease was evaluated according to the 2010 TNM classification developed by the International Union against Cancer and the American Joint Committee on Cancer (22).

Radiotherapy was performed using linear accelerators. Eclipse (version 8.6; Varian Medical Systems, Inc. Palo Alto, CA, USA) was used as the three-dimensional conformal radiotherapy planning software program. All patients received a total RT dose of 50.4 Gy with a daily dose of 1.8 Gy. The chemotherapies administered simultaneously with RT were weekly FUFA, infusional 5FU, or capecitabine. Adjuvant chemotherapy was administered with FUFA, FOLFOX6, XELOX, and FOLFİRİ.

During the course of treatment, the adverse effects of chemoradiotherapy were evaluated weekly based on the RTOG (Radiation Therapy Oncology Groups) scoring. According to the acute radiation morbidity measurement criteria constituted by RTOG, the acute radiation morbidity ranged between grade 0 and 4 (23). Side effects of RT on patients were evaluated based on these criteria once a week during treatment and once every three months during follow-ups and weights. The ECOG performances of patients were also recorded during the evaluation. Weight loss was assessed as loss of 5% of patients' weight during CRT.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) for Windows 14.0 (SPSS Inc.; Chicago, IL, USA) was used for the statistical analysis. The mean, standard deviation, frequency, and median were used to evaluate descriptive statistics. The Kruskal-Wallis test was used to compare the average of the patients' age and the number of follow-ups. Categorical data were compared statistically using the chi-square test or Fisher's exact test. The survival rates were calculated according to the Kaplan–Meier method. P values of ≤0.05 were accepted as statistically significant.

RESULTS

Out of the 139 patients who received treatment for rectal cancer, 2 (1%) were not included in survival analysis because they gave up the treatment, 3 (2%) expired during the study (death due to pulmonary emboli, diabetic coma, and heart attack), and 6 (4%) were excluded following CRT. Total survival analysis of the remaining 128 patients was performed.

Postoperative CRT was applied to 57 (44%) patients, preoperative CRT to 47 (37%), and non-operative CRT to 24 (19%). There was a statistical difference in the mean age of the patients ($p<0.001$), where the mean age of the patients undergoing non-operative CRT was observed to be higher as compared to the other groups. Demographic characteristics of the patients were summarized in Table 1.

Table 2. Characteristics of the disease

	Postop CRT n=57 (44%)	Preop CRT n=47 (37%)	CRT n=24 (19%)	p
Rectal localization				
Proximal	18 (32)	2 (4)	1 (4)	
Medial	23 (40)	17 (36)	9 (38)	
Distal	16 (28)	28 (60)	14 (58)	<0.001
Preop. T stage				
T2	–	1 (2)	1 (4)	
T3	–	13 (28)	11 (46)	
T4	–	33 (70)	12 (50)	0.245
Preop. N stage				
Nod negative	–	20 (43)	10 (42)	
Nod positive	–	27 (57)	14 (58)	0.945
Surgery				
Low anterior resection	44 (77)	31 (66)	–	
Abdominoperineal resection	11 (19)	15 (32)	–	
Transanal resection	2 (4)	1 (2)	–	0.323
Postop. Stage				
Complete response	–	6 (13)	–	
Stage I	2 (4)	11 (23)	–	
Stage II	21 (37)	15 (32)	–	
Stage III	33 (58)	15 (32)	–	
Stage IV	3 (5)	–	–	<0.001
Extracapsular invasion				
No	41 (79)	35 (88)	–	0.278
Yes	11 (21)	5 (12)		
Surgical margin				
Negative	52 (91)	42 (89)	–	
Positive	5 (9)	5 (11)	–	0.542
Lymphovascular invasion				
No	30 (58)	31 (86)	–	
Yes	22 (42)	5 (14)	–	0.004
Perineural invasion				
No	30 (58)	30 (81)	–	
Yes	22 (42)	7 (19)	–	0.017
Grade				
Grade 1	8 (15)	10 (28)	3 (43)	
Grade 2	38 (72)	21 (58)	4 (57)	
Grade 3	7 (13)	5 (14)	–	0.244

CRT: chemoradiotherapy

Low anterior resection (LAR) was performed on 44 (77%) patients undergoing postoperative CRT, abdominoperineal resection (APR) on 11 (19%) patients, and transanal resection on 2 (4%) patients (CRT was applied after resection because these patients did not consent to advanced surgery). Metastasectomy was also added along with LAR in 3 (5%) patients. 31 (66%) patients receiving preoperative CRT underwent LAR, 15 (32%) underwent APR, and 1 (2%) underwent transanal resection. The between-group difference was not determined regarding the type of surgery performed (p=0.323). In distal tumors, LAR was applied to 5 (31%) patients receiving postoperative CRT (N=16), APR to 9 patients (56%), and transanal resection to 2 patients (13%); whereas, LAR was applied to 16 (57%) of the patients receiving preoperative CRT (N=28), APR to 11 (39%), and transanal resection to 1 (4%). No difference was found in distal tumors regarding surgical treatment (p=0.195). Complete response was determined in 6 (13%) out of 47 patients receiving preoperative CRT, partial response in 31 patients (66%), stable response in 9 patients (19%), and response to progress in 1 (2%). Table 2 shows tumor characteristics and surgical treatments of the groups.

When the general characteristics of the disease were examined; the between-group difference was not determined regarding preoperative T stage, preoperative N condition, type of surgery, extracapsular invasion, surgical limit, and tumor grade. A difference was determined between the groups regarding localization of disease (p<0.001), postoperative disease stage (p<0.001), LVI (p=0.004), and PNI (p=0.017). The patients undergoing preoperative CRT and non-operative CRT were observed to have more distal rectum localization. In the postoperative period, the earlier pathological stage was determined in patients undergoing preoperative CRT, whereas the patients receiving postoperative CRT reached a more advanced pathological stage. The LVI and PNI were also increased in patients undergoing postoperative CRT.

Table 3. Survival of the patients

	Postop CRT n=57 (44%)	**Preop CRT n=47 (37%)**	**Non-opere CRT n=24 (19%)**	**p**
Median follow-up (month)	55.4±3.8	41.5±3.4	27.7±3.4	<0.001
Local Recurrence				
No	54 (95)	42 (89)	21 (87)	
Yes	3 (5)	5 (11)	3 (13)	0.467
Local Recurrence				
No	54 (95)	42 (89)	–	
Yes	3 (5)	5 (11)	–	0.256
Distant Metastasis				
No	44 (77)	38 (81)	19 (79)	
Yes	13 (23)	9 (19)	5 (21)	0.901
Distant Metastasis				
No	44 (77)	38 (81)	–	
Yes	13 (23)	9 (19)	–	0.417
Overall Survival				
The 3-year OS	78%	76%	48%	
Median survival	Not yet	75 month	36 month	0.001
Overall Survival				
The 3-year OS	78%	76%	–	
Median survival	Not yet	75 month	–	0.184
Disease-free survival				
The 3-year DFS	78%	73%	41%	
Median survival	101 month	64 month	26 month	<0.001
Disease-free survival				
The 3-year DFS	78%	73%	–	
Median survival	101 month	62 month	–	0.073

CRT: chemoradiotherapy; DFS: disease free survival

Table 2 shows tumor characteristics and surgical treatments of the groups.

In a median 35-month follow-up (range: 1–148 months) for all patients, local recurrence was detected in 3 (5%) patients undergoing postoperative CRT, 5 (11%) patients undergoing preoperative CRT, and 3 (13%) patients undergoing non-operative CRT (p=0.467). When preoperative CRT and postoperative CRT were compared without including outcomes of the patients undergoing non-operative CRT, no difference was determined between the groups regarding local recurrence (p=0.256). Distant metastasis was determined in 13 (23%) patients undergoing postoperative CRT, 9 (19%) patients undergoing preoperative CRT, and 5 (21%) patients undergoing non-operative CRT (p=0.312). The between-group difference regarding distant metastasis was not determined when preoperative CRT and postoperative CRT were compared without including the outcomes of patients undergoing non-operative CRT (p=0.417).

Table 4. Side effects of chemoradiotherapy

	Postop CRT n=57 (44%)	Preop CRT n=47 (37%)	CRT n=24 (19%)	p
Upper Gastrointestinal System				
Grade 0	37 (65)	34 (72)	18 (75)	
Grade 1–2	20 (35)	13 (28)	6 (25)	0.580
Lower Gastrointestinal System				
Grade 0	19 (33)	12 (25)	3 (13)	
Grade 1–2	35 (62)	29 (62)	20 (83)	
Grade 3–4	3 (5)	6 (13)	1 (4)	0.161
Genitourinary System				
Grade 0	35 (61)	29 (62)	15 (63)	
Grade 1–2	21 (37)	18 (38)	9 (37)	
Grade 3–4	1 (2)	–	–	0.868
White blood cell				
Grade 0	46 (82)	38 (81)	16 (67)	
Grade 1–2	11 (19)	8 (17)	8 (33)	
Grade 3–4	–	1 (2)	–	0.357
Neutrophil				
Grade 0	52 (91)	41 (87)	21 (88)	
Grade 1–2	5 (9)	6 (13)	3 (12)	0.780
Platelet				
Grade 0	55 (97)	44 (94)	22 (92)	
Grade 1–2	2 (3)	3 (6)	2 (8)	0.644
Hemoglobin				
Grade 0	49 (86)	34 (87)	20 (83)	
Grade 1–2	8 (14)	13 (28)	4 (17)	0.202
Hematocrit				
Grade 0	55 (92)	43 (92)	22 (92)	
Grade 1–2	4 (8)	4 (8)	2 (8)	0.517
Loss in weight[1]				
No	52 (91)	41 (87)	20 (75)	
Yes	5 (9)	6 (13)	4 (25)	0.144

[1]Loss in weight during chemoradiotherapy
CRT: chemoradiotherapy

Figure 1. Treatment-based overall survival curves

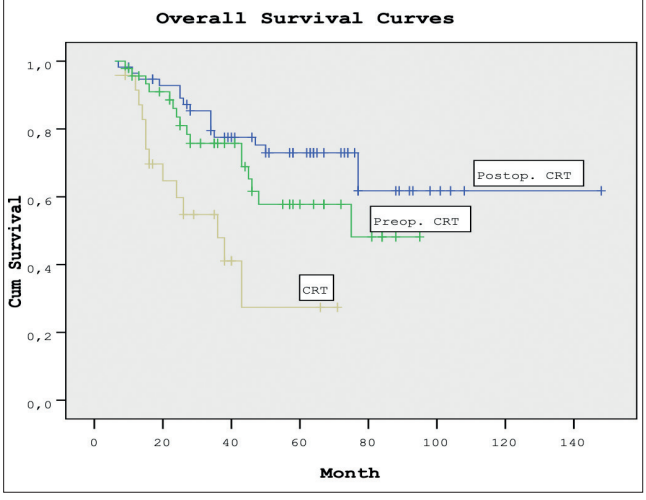
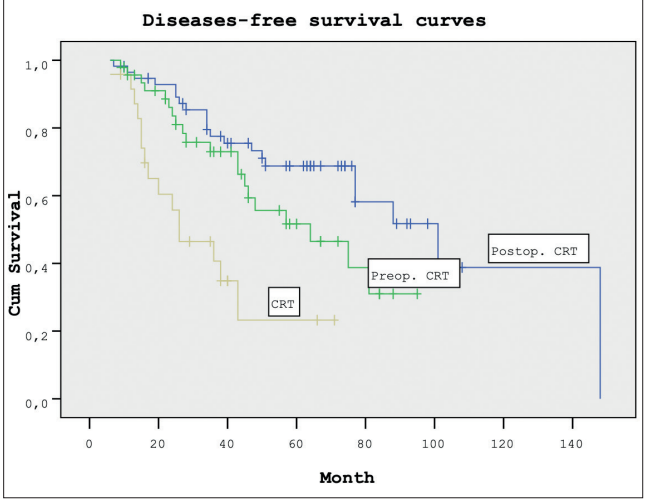


Figure 2. Treatment-based disease-free survival curves



The 3-year overall survival and median survival rates were 78% and no median survival in patients undergoing postoperative CRT, 76% and 75 months in patients undergoing preoperative CRT, and 48% and 36 months in patients undergoing non-operative CRT, respectively (p=0.001). When survival outcomes of postoperative CRT and preoperative CRT were compared without including patients undergoing non-operative CRT, no statistically significant difference was observed (p=0.184). The 3-year DFS and disease-free median survival were determined to be 78% and 101 months in postoperative CRT, 73% and 64 months in preoperative CRT, and 41% and 26 months in non-operative CRT (p<0.001). No statistically significant difference was determined when DFS outcomes of postoperative CRT and preoperative CRT were compared without including the patients undergoing non-operative CRT (p=0.073). Table 3 shows the mean follow-up, local recurrence, distant metastasis, and survival outcomes of all patient groups. According to the type of treatment, overall survival curves are shown in Figure 1 and, DFS curves are shown in Figure 2.

No significant difference was determined between the three groups when the adverse effects of patients who were evaluated with RTOG were compared. Prevalence of weight loss after the treatment also was similar between the groups. Table 4 shows the comparison of the groups regarding adverse effect and weight loss observed after treatment.

DISCUSSION

Rectal cancer is one of the leading causes of cancer-related deaths in developed and developing countries and continues to be a crucial health problem. The main objective of multiple treatment protocols of surgery, chemotherapy, and radiotherapy is to prevent a loco-regional recurrence, increase survival, and preserve the quality of life via primary tumor resection (5).

In locally advanced rectal cancers, the use of postoperative CRT improves both local control and survival (24, 25). In postoperative treatment, the pathological stage is determined after surgery and the need for adjuvant treatment is better known, which is an important advantage compared to preoperative practices and avoids unnecessary treatment or overtreatment. It was also suggested by some researchers that postoperative CRT could be more effective in determining recurrence and secondary events (26, 27). However, postoperative CRT was found to result in worse outcomes because of increased adverse effect profile, poor patient tolerance, and lesser oxygen in RT area (27). Postoperative CRT was applied to 44% of patients in the present study. Only 28% of patients receiving postoperative CRT had distal rectum localization and the follow-up of these patients was determined to be longer as compared to other patient groups. At the beginning of periods included in the study, postoperative CRT application was higher; the application tended toward preoperative treatments as time progressed.

The preoperative treatment provides an opportunity for optimum planning because the anatomy is not deformed and has more advanced tissue oxygenation, because of which the cancer tissue is more radiosensitive and low doses are more efficient. This allows surgical resection to shrink advanced cancers and enable sphincter protecting surgery in distal tumors. The predictions about it resulting in longer survival rates by allowing relatively better local control have been shown among the advantages of preoperative CRT (28, 29). A preoperative CRT treatment option that allows sphincter protection in distal and central tumors and provides an opportunity for life without colostomy should be primarily preferred. When applying preoperative CRT to 47% of patients in the present study, 60% of these were observed to have a distal rectal tumor. Preoperative treatments were recorded as preferred treatments, particularly in distal tumors.

Combination of surgical intervention along with chemoradiotherapy in rectal cancer is an accepted method of treatment. However, there is no consensus yet about the preoperative or postoperative use of CRT because both applications have disadvantages and advantages. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) R-03 study, 130 patients were evaluated in the preoperative branch, and 137 patients were evaluated in the postoperative branch. While early results of this

study reported that elevated complete pathological response was obtained with preoperative CRT application, it was also stated in reports published in 2009 that 5-year DFS was more improved in patients undergoing preoperative CRT (64.7% vs. 53.4%, p=0.011). Even though it was not statistically significant in the same study, overall survival was also reported to be higher in preoperative CRT branch (30).

A study by the Dutch Rectal Cancer Group (code: CAO/ARO/A10-94) shows the position of preoperative CRT compared to postoperative CRT. A total of 823 patients with stage II-III rectal cancer were included in this study and the early results reported that preoperative CRT provided distinct regression of the tumor, increased local control and patient tolerance, reduced acute-late toxicity, and possibly increased sphincter protection rates in distal tumors compared to postoperative treatment (9-14). After publishing the data of the study, preoperative CRT was accepted as the standard treatment for locally advanced rectal cancer (9-14). According to the results of the same study after a median 11-year follow-up, the 10-year overall survival rates were reported to be 59.6% for preoperative CRT and 59.9% for postoperative CRT (p=0.850). Results showed no difference in overall survival or DFS and distant metastasis varied for recurrence. While the 10-year cumulative recurrence ratio was 7.1% in patients undergoing preoperative CRT, it was determined to be 10.1% in patients undergoing postoperative CRT (p=0.048) (12). The 5FU-based chemotherapies were simultaneously used with RT in both the above-mentioned studies.

In a study by Park et al. (31), preoperative and postoperative CRT was compared using capecitabine simultaneously with RT. Patients with cT4 or N+ 240 rectal cancer were evaluated, and no difference was determined between preoperative or postoperative CRT regarding 3-and 5-year overall survival, DFS, and incidence of cumulative local recurrence as a result of median 52-month follow-up. However, the study also emphasized that rates of sphincter protection were higher in the preoperative application (68% vs. 42%, p=0.008). Perineural invasion and lymphovascular invasion were reported to be less frequent as pathological characteristics for those undergoing preoperative CRT. Further, early stages were determined to be more prevalent in the patient group undergoing preoperative CRT. In the present study, on the other hand, there was no difference between preoperative or postoperative applications regarding 3-year overall survival, DFS, local recurrence, and distant metastasis for both applications. However, the location of the tumor played an important role in choosing the treatment. The early pathological stage was determined in patients undergoing preoperative CRT due to down-staging. Similar to other studies, statistically significant decreased levels of perineural and lymphovascular invasion were found in this patient group. Even though there was no difference between applications with respect to the type of surgery, APR surgery was performed in distal tumors in 39% of patients undergoing preoperative CRT and 56% of patients undergoing postoperative CRT.

The pathologic complete response can be ensured in 8–20% of cases after preoperative CRT (16-20). Researchers have started to evaluate the results of the "wait and watch" approach without radical surgery in patients whose clinical complete response following CRT was confirmed via biopsy (27). Habr-Gama et al. (26) conducted the first studies on "wait and watch" approach in patients with complete response. In their study including 365 patients, they followed-up 71 patients with complete response after preoperative CRT, performed surgery on 194 patients with incomplete response and reported that 5-year overall and DFS rate of the patients was 88% and 83% for patients underwent operation, respectively and 100% and 92% for patients who were followed-up. In their prospective study, Renehan et al. (27) determined that while the 3-year DSF outcome of "wait and watch" group was 88%, it was 78% for the group undergoing surgery (p=0.043). The 3-year overall survival was observed to be 96% in the non-operative CRT group and 87% in the surgery group (p=0.024). In the present study, the pathological complete response was achieved in 13% of the patients. We intended to also show the outcomes of the mandatory "wait and watch" group arising not from the "wait and watch" approach but from the fact that patients could not receive surgical treatment because of various reasons. Most of these patients did not accept the treatment due to either permanent colostomy or false belief. When these patients were evaluated generally, their median ages were observed to be higher as compared to other patient groups (median age: 70). Even though outcomes of preoperative treatment were not evaluated for many patients, the 3-year median survival of these patients was 48%, and median survival was 36 months. It was found that the 3-year DFS rate of the same patient group was 41% and disease-free median survival was 26 months. When outcomes of these patients were evaluated as compared to operated patients, they were observed to have statistically significant worse outcomes regarding both overall survival and DFS. However, it is important to consider that the response to treatment after preoperative CRT was required to be evaluated in the patients who were not scheduled for surgery.

Since the outcomes of treatment approaches are similar, the treatment toxicity should be evaluated for every treatment modality. All studies comparing preoperative and postoperative CRT also reported acute side effects while reporting early results of the treatment. In a German study, the existence of any grade 3–4 toxicity and side effect diarrhea were observed to be more prevalent in postoperative CRT and were found to be statistically significant (13). In this study, grade 3–4 toxicity was determined to be 27% in patients undergoing preoperative CRT and 40% in patients undergoing postoperative CRT (13). Acute toxicities generally associated with the treatment were determined to be similar for both groups in the NSABP R-03 trial (30). In the study conducted by Park et al. (31) that compared pre-postoperative CRT using capecitabine, there was no difference between the groups regarding acute adverse effects. Similar to the two surveys above, the between-group difference was not determined regarding treatment-related acute adverse effects in the present study as well. Similarly, even though patients undergoing non-operative CRT had the highest weight loss regarding weight loss during the treatment, no statistical difference was obtained for all three groups.

CONCLUSION

As a result of the present study, it was found that while no difference was determined between preoperative and postoperative CRT applications regarding local recurrence and distant metastasis prevalence, overall and DFS, and adverse effects of treatment, the earlier pathological stage and less frequent LVI and PNI was determined for the preoperative application. However, all survival outcomes of the patients undergoing non-operative CRT gave worse results as compared to operated patients. Non-operative CRT seems far from being an option of sufficient treatment, particularly in patients without complete response.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Cumhuriyet University School of Medicine (date: 19.04.2017, no: 2017-04).

Informed Consent: Due to the retrospective design of the study and some of the patients died, informed consent was not taken.

Author Contributions: Concept – E.E.; Design – E.E.; Supervision – E.E.; Resources – E.E.; Materials – B.Y.; Data Collection and/or Processing – E.E.; Analysis and/or Interpretation – B.Y.; Literature Search – E.E.; Writing Manuscript – E.E.; Critical Review – E.E.

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Original Research

Anterior Knee Pain after Intramedullary Nailing of Tibial Fractures: Medial Parapatellar versus Transtendinous Approach

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ABSTRACT

Objective: Chronic anterior knee pain has been considered as the most frequent postoperative complication of tibial nailing surgery technique. Surgical approaches used for tibial intramedullary nailing include medial parapatellar, transtendinous, and lateral parapatellar techniques, but lateral parapatellar approach is less preferred. The aim of the present study was to determine the role of medial parapatellar and transtendinous approaches on anterior knee pain of patients with tibial diaphyseal fractures treated with intramedullary nail.

Methods: A total of 132 patients who were admitted to our emergency clinic with tibial shaft fracture between January 2015 and January 2017 were evaluated retrospectively. Of the 132 patients, 45 patients who were treated with intramedullary nail were included in the present study. Medial parapatellar approach was used in 20 fractures, and transtendinous approach was used in 27 fractures.

Results: The mean follow-up period of the patients was 12 (6–15) months. The mean union time of fractures was 5 (3–15) months. Severity of anterior knee pain was assessed by Visual Analog Scale (VAS). There was no statistically significant difference between the medial parapatellar method and the transtendinous method according to proximal nail entry exposures in anterior knee pain (p=0.927).

Conclusion: In conclusion, although tibial nailing is a highly successful procedure for fracture healing, anterior knee pain remains the main disadvantage of it. Although our data showed no differences between the groups, the groups were relatively small to accept this null hypothesis with full confidence.

Keywords: Anterior knee pain, intramedullary nailing, tibial shaft fractures

INTRODUCTION

Tibia shaft fractures are mostly caused by high-energy trauma, such as motor vehicle accidents, sports, and falls from a height (1). Intramedullary nailing of tibial diaphyseal fractures has been used frequently and accepted as a superior technique in the treatment of tibial diaphyseal fractures recently due to the high union rates, good functional and predictable results, and low infection and deformity rates (2-5). Chronic anterior knee pain has been considered as the most frequent postoperative complication of this technique (2, 3, 6-10). Anterior knee pain is a commonly reported problem, with an incidence ranging from 10% to 70%, with most series reporting an average incidence of approximately 50% (9, 11). The cause of this complication is still controversial, and it has been argued that it occurs due to the height of the nail, entry point of the nail, heterotopic ossification, infrapatellar branch of saphenous nerve trauma, traumatization of the tendon or the fat pad, postoperative muscle weakness, malalignment, and age (12, 13). Surgical approaches used for tibial intramedullary nailing are medial parapatellar, transtendinous, and lateral parapatellar techniques, but lateral parapatellar approach is less preferred. Some authors have reported that a transtendinous approach for nail insertion is associated with a higher rate of anterior knee pain than a medial paratendinous approach (14, 15).

The aim of the present study was to determine the role of medial parapatellar and transtendinous approaches on anterior knee pain of patients with tibial diaphyseal fractures treated with intramedullary nail.

METHODS

One hundred thirty-two patients who were admitted to our emergency clinic with tibial shaft fracture between January 2015 and January 2017 were evaluated retrospectively. Of the 132 patients, 45 patients who were treated with intramedullary nail were included in the study. The study included 14 female and 31 male patients. At the time of surgery, the mean age of the patients was

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33 (17–64) years. Nine patients had type I open fracture according to the Gustilo–Anderson classification, and two of them had bilateral tibial fractures. The types of injury were falls (10 fractures), motor vehicle accidents (28 fractures), sport activity (5 fractures), and gunshot injury (4 fractures). All of the operations were performed by two orthopedic surgeons with the same implants in the same operating room and standard operating table but different surgical exposures (medial parapatellar and transtendinous approaches). Medial parapatellar approach was used in 20 fractures, and transtendinous approach was used in 27 fractures.

All patients were informed about the types of treatment and the corresponding surgical technique. Patients were treated according to the ethical standards of the Declaration of Helsinki and were invited to read, understand, and sign the written informed consent form. Ethics committee approval was received for this study from the Ethics Committee of Gaziantep University (Research Protocol Code:328).

The mean follow-up period of the patients was 12 (6–15) months. The mean union time of fractures was 5 (3–15) months. Anterior knee pain complaint was assessed by Visual Analog Scale (VAS) while performing rest, walking, squatting, long-term sitting, kneeling, running, stair ascending, and stair descending at the time of 6 months in all patients.

Surgical Technique

All patients underwent spinal anesthesia with a tourniquet in the supine position. A longitudinal incision of approximately 4–5 cm was used over the patellar tendon when the knee was at 90° flexion. Medial parapatellar or transtendinous exposure was selected according to the surgeon's preference.

After first entry with awl and closed reduction of the fracture, with the intramedullary guide, remerization was made in all fractures. After the fluoroscopy control, the nails were placed with two proximal and distal locking screws. The mean operation time was 42 (28–125) min. Partial weight-bearing mobilization was allowed to all patients except two who had bilateral fracture, and isometric quadriceps exercises have been started immediately.

Statistical Analysis

Statistical tests were performed using Statistical Package for the Social Sciences version 22.0 software (SPSS IBM Corp.; Armonk, NY, USA). Student's t-tests were used to compare continuous variables between patients with and without knee pain postoperatively. A p value of <0.05 was considered statistically significant.

RESULTS

The mean follow-up period of the patients was 12 (6–15) months. The mean union time of fractures was 5 (3–15) months. Severity of anterior knee pain was assessed by VAS while performing rest, walking, squatting, long-term sitting, kneeling, running, stair ascending, and stair descending (16). According to the scale, a score of 0 means no pain, <33 mild pain, 33–66 moderate pain, and >66 severe pain.

When patients were assessed by VAS for anterior knee pain, no pain was detected in 18 (38.2%) of 47 extremities, including all functional activities. There were 21 (44.6%) patients with mild anterior knee pain, 6 (12.8%) patients with moderate pain, and 2 (4.5%) patients with severe pain according to the mean VAS score (Table 1). Activities that mostly cause anterior knee pain are kneeling and squatting according to the VAS scores.

There was no statistically significant difference between the medial parapatellar method and the transtendinous method according to proximal nail entry exposures in anterior knee pain (p=0.927) (Table 2).

Table 1. Distribution of the incidence and severity of anterior knee pain according to the VAS in two surgical approach groups

	Transtendinous approach group (n=27)		Medial parapatellar approach group (n=20)	
	Incidence	Mean VAS	Incidence	Mean VAS
No anterior knee pain	10	0	8	0
Mild pain	13	17.35	8	15.15
Moderate pain	3	49.58	3	49.79
Severe pain	1	71.25	1	70.62

VAS: visual analog scale; n: number of fractures

Table 2. Statistical analysis of two approaches according to mean VAS scores

	n	Mean VAS	Standard deviation	Standard error mean
Medial parapatellar approach	27	132.0370	154.67248	29.76673
Transtendinous approach	20	136.5000	174.16039	38.94345

VAS: visual analog scale; n: number of fractures

t=−0.093; p=0.927

DISCUSSION

The causes of the postoperative knee pain complication, developed after tibia nailing surgery, are thought to be multifactorial, although it is not known exactly today. The cause of this complication is still controversial, and it has been argued that it occurs due to the height of the nail, entry point of the nail, heterotopic ossification, trauma to the infrapatellar branch of the saphenous nerve, traumatization of the tendon or the fat pad, postoperative muscle weakness, malalignment, and age (12, 13).

In a review of 20 clinical studies, independent of the approach used, Katsoulis et al. (11) reported the incidence of anterior knee pain prevalence as 47.4%. In our study, 39 (83%) extremities had no or mild anterior knee pain, whereas 8 (17%) extremities had moderate or severe anterior knee pain.

Court-Brown et al. (9) and Keating et al. (14) identified younger patients as being at greater risk for chronic anterior knee pain and reported that younger patients are more symptomatic than older patients, probably because they are more active than older patients.

Some studies noted that transtendinous approach was associated with high rates of anterior knee pain and recommended a paratendinous approach for nail insertion. In retrospective studies, Keating et al. (14) reported 50% knee pain with medial paratendinous approach. In a prospective study, Väistö et al. (13) noted that75% have knee pain when using a medial paratendinous approach. However, some authors noted that there is no any association with surgical approach and severity of knee pain (2, 6, 9, 17). In addition, in a meta-analysis of 11retrospective and 9prospective studies, a total of 1469 fractures showed that there was no statistical difference between the approaches with respect to pain. Of the 1460 patients, 629 had symptoms of anterior knee pain independent of the approach used (18). Our analysis also supports this review's results.

After tibial nailing surgery, prominence of the nail had been reported to be a risk factor of anterior knee pain. Court-Brown et al. (9) and Keating et al. (14) noted that nail prominence causes anterior knee pain. Bhattacharyya et al. (17) showed that marked superior nail prominence causes anterior knee pain while kneeling, that anterior nail prominence is associated with pain at rest, and that the nail–apex distance is associated with overall knee pain. In addition, they reported that <2.5 cm of the nail–apex distance reduces anterior knee pain.

In a cadaveric study, Hernigou and Cohen (19) dissected knees after intramedullary nailing of the tibia and revealed that the intra-articular structures that are at risk of damage during tibial nailing are the medial meniscus, the lateral tibial plateau, and the transverse ligament. Results of the study revealed that in some bones, the safety zone is smaller than the size of standard reamers and the proximal part of some nails.

Devitt et al. (20) dissected eight cadaveric knees and showed that intramedullary nailing of the tibia significantly increases contact pressures at the patellofemoral joint. They used the medial paratendinous and transtendinous approaches. With the medial paratendinous approach, a significant increase in contact pressures was found at the lateral patellar facets. The contact pressure increases were recorded on both facets with the transtendinous approach, suggesting that chondral injury is more likely with this approach.

The etiology of anterior knee pain complication after tibial nailing is unknown and probably multifactorial. Usually, pain begins several months after surgery, and implant removal does not necessarily cure the problem. However, in a study, after removal of the nail, complete resolution of symptoms in 27.4% of patients, with marked improvement in 69.3%, was seen (9).

Leliveld and Verhofstad (21) studied 136 tibia fractures with regard to anterior knee pain, and despite the low number, statistical differences were found, and they provided arguments for their hypothesis that iatrogenic injury to the infrapatellar branch of the saphenous nerve is an important cause.

Our surgical experience has shown that "the transtendinous method" has some advantages, such as easier approach to nail entry point on the tibia and more vertical placement of the nail. Lateralization of the tendon with the "medial parapatellar method" allows for more mobilization of the patella and aids the protection of tendon integrity. At the same time with this exposure, if the skin incision is taken medially, the infrapatellar branch of the saphenous nerve can also be preserved.

Our study has some limitations. First, it is inherently limited by its retrospective design. Second, the relatively less number of patients is the weak points of our study. Although the present study does not detect the exact cause of postoperative anterior knee pain, it has shown that there is no significant difference between two exposures with respect to anterior knee pain.

CONCLUSION

Although tibial nailing is a highly successful procedure for fracture healing, anterior knee pain remains the main disadvantage of it. Although our data showed no differences between the groups, the groups were relatively small to accept this null hypothesis with full confidence. Future controlled randomized studies with larger populations are required to confirm our results.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Gaziantep University (Research Protocol Code:328)

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.F.K., B.B.; Design –A.F.K.; Supervision –B.B.; Resources –A.F.K.; Materials –B.B.; Data Collection and/or Processing –B.B.; Analysis and/or Interpretation –B.B.; Literature Search –A.F.K.; Writing Manuscript –A.F.K.; Critical Review –A.F.K., B.B.

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Original Research

Effects of Regular Follow-up on Quality of Life and Warfarin Efficiency in Rural Patients

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ABSTRACT

Objective: This study aims to evaluate the effects of regular follow-up and education on warfarin efficiency, satisfaction, and the quality of life in patients from rural areas.

Methods: A total of 133 patients from rural areas taking warfarin were followed up for the mean of 17.4±0.5 months (mean age 58±13 years, 72.9% female). All patients were educated and followed up by a single cardiologist prospectively. A list and an illustrated booklet presenting foods that interact with warfarin and a follow-up chart were prepared for each patient. An illustrated scheme of pills that were to be taken every day was prepared for illiterate patients. The international normalized ratio (INR) values during and 1 year before the study were recorded from the hospital system, and the time in therapeutic range (TTR) was calculated. The Duke Anticoagulation Satisfaction Scale was conducted at the start and end of the study to determine patients' satisfaction with warfarin use. Furthermore, the Medical Outcomes Study Form 36 (SF-36) was used for determining the health-related quality of life (HRQoL).

Results: A total of 45.9% of patients were illiterate, and 33.8% were primary school graduates. The median TTR during the follow-up increased significantly compared with the previous year [40.0 (IQR 36.5) vs. 62.1 (IQR 29.3); p<0.001]. Furthermore, the number of patients with TTR>70% increased significantly (36.8% vs. 21.1%, respectively; p<0.001). Unfortunately, patients' HRQoL and satisfaction with warfarin use were found to have deteriorated significantly compared to the basal levels.

Conclusion: We found that the efficiency of warfarin increased significantly, but interestingly, HRQoL and the satisfaction with warfarin use deteriorated significantly after regular education and follow-up in patients from rural areas.

Keywords: Duke Anticoagulation Satisfaction Scale, health-related quality of life, warfarin therapy

INTRODUCTION

Warfarin is an efficient oral anticoagulant used to prevent thromboembolic events in patients with atrial fibrillation (AF) or a mechanical heart valve (MHV). The efficacy and safety of warfarin strongly depend on the anticoagulation intensity measured in terms of the international normalized ratio (INR). For achieving a high-quality, safe, and minimally complicated treatment, the time in therapeutic range (TTR) is targeted at >70 (1). Many studies have shown that TTR levels differ greatly from the desired levels in the Turkish population (2-4). Çelik et al. (4) showed that only 55% of patients taking warfarin were aware of food–drug interactions. Other studies reported that the elderly and patients with a lower education level were likelier to have lower awareness of warfarin treatment, possibly because they faced difficulties in understanding educational materials and communicating with healthcare providers (5). Therefore, the educational materials and their content, duration, and frequency of education should be selected according to the target patient population. Frequent INR controls, long waits at hospitals, dietary limitations, and bleeding-related concerns reduce the health-related quality of life (HRQoL) of patients taking warfarin (6). Two basic approaches are used for measuring the HRQoL of patients receiving anticoagulants: generic and condition specific. Ideally, both approaches should be used for evaluating patients' quality of life (7).

This study aimed to evaluate the effects of a regular follow-up and education on warfarin efficiency, satisfaction, and the quality of life in patients from rural areas.

METHODS

This prospective, observational study was performed in a secondary-level hospital in a rural region of Turkey (Nizip State Hospital, Gaziantep) from January 2016 to June 2017. It was approved by the Gaziantep University ethical committee (30.05.2016/180), following which recruitment started in January 2016. All patients

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who gave their verbal or written consent to participate in the study were recruited. All patients were educated and followed up by a single cardiologist during the study. Patients who agreed to participate and were recruited had been taking warfarin for any reason for at least 1 year and were regularly followed up in the same hospital (n=137). The inclusion criteria were age ≥18 years, volunteering to participate in the study, and being followed up at the same hospital for at least 1 year. The single exclusion criterion was the gap of more than 59 days between two prospective follow-ups. Hypertension (HT) was defined as repeated blood pressure measurement >140/90 mmHg or chronic treatment with antihypertensive medications. Diabetes mellitus (DM) was defined as a previous diagnosis and/or fasting blood glucose >126 mg/dL or the use of antidiabetic medications. Hyperlipidemia was defined as low-density lipoprotein cholesterol (LDL-C) >200 mg/dL or the use of lipid-lowering medications (8). Cigarette smoking was defined as smoking ≥1 cigarette a day for at least 1 year without any attempts at quitting. Ischemic heart disease was defined as having previous percutaneous transluminal coronary angioplasty and/or stenting, coronary bypass grafting, or stable coronary artery disease. All patients were informed in detail on initial visit about why they were taking warfarin, how they would take it, how doses would be adjusted, and what the frequency of follow-up visits was. All patients were also informed about food–drug interactions. A list of frequently consumed local foods that interacted with warfarin was given to all patients, and a booklet with pictures of these foods was provided to illiterate patients. A follow-up chart was prepared for all patients, and the daily number of warfarin pills, INR values, and next visit details were recorded. For illiterate patients, the daily numbers of warfarin pills were illustrated for each day of the week. The therapeutic range in patients with warfarin for AF or aortic valve replacement was considered as the INR levels of 2.0–3.0. For patients with the mitral valve or two-valve (mitral and aortic) replacement, the INR levels were considered as 2.5–3.5. All INR levels during the study and 1-year period prior to the study were recorded from the hospital laboratory database, and the TTR was calculated using Rosendaal's algorithm (9). The annual INR after the follow-up was calculated as (all INR levels in follow-up × 12)/(duration of study in months). All adverse events during the study period were recorded. Ischemic stroke was defined as neurologist-confirmed symptomatic ischemic cerebral infarction with an apparent brain lesion in imaging studies. Transient ischemic attack was defined as a neurologist-confirmed transient episode of neurologic dysfunction without a brain lesion in imaging studies. Major bleeding was defined as symptomatic bleeding in a critical organ, transfusion of two or more units of blood, or decrease in the hemoglobin level of at least 2 g/L. All other bleeding was defined as minor bleeding.

Questionnaires

Two questionnaires were administered to all patients to evaluate their HRQoL and satisfaction with warfarin use at the start and end of the study. The Duke Anticoagulation Satisfaction Scale (DASS) questionnaire was used to assess the satisfaction with warfarin use (10). Furthermore, the Medical Outcomes Study Form 36 (SF-36) questionnaire was used to assess HRQoL (11). The validity and reliability of the Turkish versions of both scales have been reported previously (12, 13). SF-36 comprises eight subscales that reflect both physical health (physical functioning, role-physical, bodily pain, and general health) and mental health (vitality, social functioning, role emotional, and mental functioning). The scores range from 0 to 100, where higher scores indicate better functions (11). The DASS scale includes 25 questions. The pattern of the questions is arranged to roughly correspond to three possible dimensions pertaining to anticoagulation: limitations (e.g., fear of bleeding, dietary restrictions); displeasure and burden (regular return to medical visit and wait for blood test results), and positive psychological impact. Patients respond to these questions on a 7-point Likert scale. Lower scores indicate higher satisfaction. The overall score varies from 25 to 175. The instrument is divided in three domains: limitations (score from 9 to 63), displeasure and burden (score from 8 to 56), and psychological impact (score from 8 to 56). The subscales were analyzed by adding the answers to the items (varying from 1 to 7 for each item) in each domain, and the total score was obtained by adding up all questionnaire items.

Statistical Analysis

The variables were investigated using the Kolmogorov–Smirnov test to determine whether they were normally distributed. The mean and standard deviations of normally distributed variables and the IQR of non-normally distributed variables were calculated. The TTR values and questionnaire results (DASS and SF-36) computed at the start and end of the study were compared using the paired sample t-test and Wilcoxon test. The proportions of patients with TTR values >70% at the start and end of the study were presented as a percentage, and the change was compared using the McNemar test. A p-value <0.05 was considered to indicate a statistically significant result. All data were analyzed using the Statistical Package for the Social Sciences Version 22.0 (SPSS IBM Corp.; Armonk, NY, USA) software for Windows.

RESULTS

A total of 137 patients were recruited for the study. Four patients with irregular follow-up were excluded; the remaining 133 patients (72.9% female, mean age 58.1±12 years) were followed up for a mean of 17.4±0.5 months. Table 1 summarizes the demographic characteristics of patients. The primary indication of warfarin use was MHV and AF (72.9% and 27.1%, respectively). The majority of the study population was either illiterate or had graduated from primary school (45.9% and 33.8%, respectively). The median duration for which patients had been taking warfarin was 7.0 (IQR 6) years, and 60.2% of patients had been taking warfarin for >5 years. The most frequent comorbidities were HT, heart failure, ischemic heart disease, and DM. Approximately 22.5% (n=30) of patients had a previous history of bleeding (40% [n=12] had history of major bleeding), and 9.0% (n=12) of patients had a history of ischemic events (8 and 4 had history of transient ischemic attack and ischemic stroke, respectively). The median TTR levels during the follow-up increased significantly compared with those in the previous year (40.0 [IQR 36.5] vs. 62.1 [IQR 29.3]; p <0.001] (Figure 1). Moreover, the ratio of patients with TTR levels ≥70% increased significantly (21.1% vs. 36.8%; p<0.001) at the end of the study (Table 2). The basal demographic and clinical characteristics of patients who with

Table 1. Basal Demographic and Clinical Characteristics of Study Population

Parameters	Values	TTR≥70% (n=49)	TTR<70% (n=84)	p
Age years, mean±SD	58.1±12.8	57.3±13.3	58.4±12.7	0.630
Female n, (%)	97 (72.9)	31 (63.3)	66 (78.6)	0.550
BMI (kg/m^2)	28.7±4.6	29.1±4.6	28.3±4.6	0.330
Time of warfarin use years, median (IQR)	7.0 (6)	5.0 (6.5)	8.0 (5.0)	0.032
Hypertension n, (%)	55 (41.4)	19 (38.8)	36 (42.9)	0.645
Diabetes mellitus n, (%)	32 (24.1)	13 (26.5)	19 (22.6)	0.611
Heart failure n, (%)	45 (33.8)	15 (30.6)	30 (35.7)	0.549
Cerebrovascular events n, (%)	12 (9.0)	2 (4.1)	10 (11.9)	0.129
Ischemic heart disease n, (%)	31 (23.3)	14 (28.6)	17 (20.2)	0.273
Smoke n, (%)	10 (7.5)	2 (4.1)	8 (9.5)	0.251
Chronic kidney disease n, (%)	12 (9)	4 (8.2)	8 (9.5)	0.792
All bleeding n, (%)	30 (22.5)	6 (12.2)	24 (28.6)	0.030
Major bleeding n, (%)	12 (9.0)	2 (4.1)	10 (11.9)	0.129
Non steroid anti-inflammatory drug use n, (%)	82 (61.7)	30 (61.2)	52 (61.9)	0.724
Antiplatelet use n, %	12 (9)	3 (6.1)	9 (10.7)	0.373
Education				
Illiterate n, (%)	61 (45.9)	20 (40.8)	41 (48.8)	
Primary school n, (%)	45 (33.8)	17 (34.7)	28 (33.3)	0.139
High school n, (%)	19 (14.3)	6 (12.2)	13 (15.5)	
University n, (%)	8 (6)	2 (4.1)	6 (7.1)	

BMI: body mass index; IQR: interquartile range; SD: standard deviation; TTR: time in therapeutic range

Table 2. Comparison of Time in Therapeutic Range Pre- and Post-study

Parameters	Pre-study	Post-study	p¶
TTR %, median (IQR)	40 (36.5)	62.1 (29.3)	<0.001
TTR ≥70% n,%	28 (21.1)	49 (36.6)	0.001*
Annual number of INR, median (IQR)	8.5 (4.2)	12 (2.6)	<0.001

INR: international normalized ratio; IQR: interquartile range; TTR: time in therapeutic range
¶ Wilcoxon test; *McNemar test

TTR≥70% and TTR<70% at the end of the study are summarized at Table 1. There were no significant differences between the two groups, expect the median time of warfarin use and history of all bleedings. The ratio of all bleeding was significantly higher in patients with TTR<70, and median time of warfarin use was significantly higher in patients with TTR≥70%. The median annual INR in the follow-up also increased significantly (11.7±2.8 vs. 8.8±4.0; p<0.001). During the follow-up, 17 (12.8%) patients suffered bleeding events (5 suffered major bleeding), 2 patients had transient ischemic attack, and 1 had ischemic stroke. No deaths occurred during the follow-up. Table 3 shows the difference between the DASS scores at the start and end of the study. The median of the DASS score and its subscales that were evaluated separately increased significantly at the end of the study (p<0.001 for all). Similarly, the role physical, physical functioning, mental functioning, bodily pain, general health, social functioning, vitality, and role emotional scores of the SF-36 scale decreased significantly at the end of the study (p<0.001 for all) (Table 3). Moreover, there were no significant differences between patients with TTR≥70 and TTR<70 in terms of both the DASS score and SF-36 subscales.

DISCUSSION

The present study provided two major results. First, the TTR level of patients from rural areas who were uneducated or had a low education level were significantly low; however, they improved dramatically after regular education with appropriate materials and follow-up. Second, patients' satisfaction with warfarin use and HRQoL unfortunately worsened significantly after regular education and follow-up.

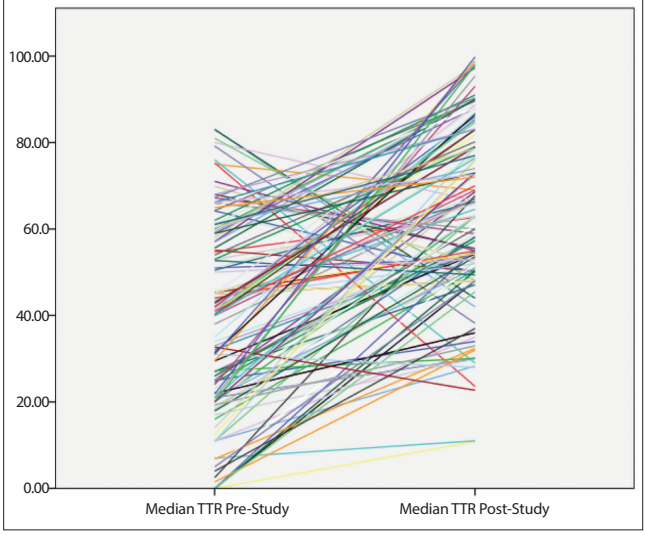
Previous studies showed that the mean TTR level was low in the Turkish population. In the AFTER study (epidemiology of AF in Turkey), only 41.3% of patients showed efficient INR levels (3). Turk et al. (2) conducted a multicenter prospective study and found that the mean TTR level was 42.3±18%. Similarly, the WARFARIN-TR (Awareness, Efficacy, Safety, and Time in Therapeutic Range of Warfarin in the Turkish population) study reported

Table 3. Comparison of Duke Anticoagulation Satisfaction Scale and Medical Outcomes Study Form 36 Pre–and Post–study and Between TTR≥70% and TTR<70%

Parameters	Pre–study Median (IQR)	Post–study Median (IQR)	p*	TTR≥70% (n=49)	TTR<70% (n=84)	p
DASS						
Total, mean±SD	82.7±18.1	135.2±15.6	<0.001¶	135.4±8.5	137.1±11.1	0.349
Limitations	31 (48)	52 (21)	<0.001	52.5±4.3	52.2±4.4	0.557
Displeasure and burden	30 (47)	49 (45)	<0.001	48.8±3.9	49.6±7.1	0.464
Positive psychological impact	24 (22)	35 (18)	<0.001	34.5±3.2	34.9±3.4	0.451
SF–36						
Role physical	32 (26)	26 (23)	<0.001	25 (30)	26 (30)	0.771
Physical functioning	65 (30)	50 (30)	<0.001	54 (22)	48 (16)	0.080
Bodily pain	67.5 (54)	57.5 (35)	<0.001	55 (42)	60 (40)	0.177
General health	35 (25)	25 (50)	<0.001	25 (50)	25 (80)	0.158
Social functioning	62.5 (50)	50 (50)	<0.001	50 (37.5)	50 (25)	0.721
Vitality	45 (35)	35 (25)	<0.001	37.5 (20)	35 (25)	0.585
Role emotional	35.1 (33)	20 (33)	<0.001	20 (30)	20 (25)	0.897
Mental functioning	58 (49)	44 (35)	<0.001	46 (25)	43 (30)	0.786

DASS: Comparison of Duke Anticoagulation Satisfaction Scale; IQR: interquartile range; SD: standard deviation; SF–36: Medical Outcomes Study Form 36
¶ Paired samples t–test; * Wilcoxon test

Figure 1. Pre- and Post-study Median Level of Time in Therapeutic Range (TTR) for Each Participant



that the 1-year average TTR level was 49.5±22.9% (4). Furthermore, a subgroup analysis of the WARFARIN-TR study showed that themean TTR levels differed significantly across different geographical regions of Turkey (14). In this analysis, the mean TTR level in the Southeastern Anatolia region was found to be 44.3±23.5%; this was significantly lower than the mean for Turkey. Similarly, our study in the Southeastern Anatolia region of Turkey reported low TTR levels (38.7±22.03) for patients in the period before the study. However, after regular education and follow-up, patients' TTR levels improved significantly. Moreover, the number patients with TTR ≥70 increased significantly. The INR monitoring can be performed in hospitals, general outpatient clinics, and specialized INR outpatient clinics, as well as through self-monitoring (15-18). The highest TTR can be achieved through self-monitoring; however, the most significant limitations in this regard are the patient's compatibility, ability to use necessary medical devices, and awareness of required drug dose to be set (17, 19). Self-monitoring was not applicable for our patients because most of them were illiterate or were at most primary school graduates. However, we showed that the TTR level could be improved significantly through a regular follow-up at, for example, specialized INR outpatient clinics. The main difficulties faced in warfarin use are frequent food–drug interactions and the need for lifetime use. Moreover, frequent hospital visits, long waits at hospitals, and bleeding-related worries are among the primary difficulties faced in warfarin use that affect patients' quality of life and satisfaction (20-22). Although there are methodological differences between studies, long-term warfarin use was found to have significant and negative effects on the quality of life (23, 24). Previous studies revealed that the mean DASS scores were different among populations (7, 25). The mean of the scale for the Turkish population (85.0±25.1) was found to be higher than those of the original scale scores (55.0±17.6) and the scores determined in the Brazilian–Portugal validation (57.9±16.5) (7, 12, 25). This result shows that the treatment satisfaction of Turkish patients is lower than that of other populations, and they perceive more problems. Our results show that although the mean DASS (82.1±18.1) of patients before the study was similar to that of Turkish population, it unfortunately increased at the end of the study. Meanwhile, the SF-36 subscale scores decreased. These re-

sults show that, unexpectedly, patients' satisfaction with warfarin use and their health-related quality of life deteriorated after regular follow-up and education. This can be attributed to factors like a regular follow-up, development of awareness about the effect mechanism and adverse events related to warfarin use, dietary limitations, worries about drug interactions, and more frequent hospital visits. Shifting from a solitary and snugger (without being careful about the diet or going for follow-up visits by their own choice) follow-up pattern to a more regular and systematic follow-up design that also includes the participation of the physician might have negatively affected their quality of life. In addition, although warfarin protects patients from serious complications such as thromboembolism, it does not provide a symptomatic improvement, and it also imposes additional burdens such as bleeding risk, dietary limitations, drug interaction, and regular follow-up; these factors may explain the decreases in the patients' quality of life (26). New-generation oral anticoagulants that can be applied as alternatives for patients taking warfarin for nonvalvular atrial fibrillation have come into use recently. These drugs have similar efficacy to previous ones and afford significant advantages such as not requiring a close follow-up, the absence of food–drug interactions, and causing less bleeding (27-30). New-generation oral anticoagulants can be preferred to warfarin in patients who have a low TTR level or are dissatisfaction after a regular follow-up. Moreover, for patients who use warfarin due to MHV, appropriate interventions should be done considering the special conditions of the patients.

The main limitations of our study are its single-center design, a low number of patients, and short follow-up. In addition, the pre-study INR measurements were obtained from hospital records, and we cannot exclude the possibility of other measurements at another facility. Another limitation is that because most patients were uneducated or had a low education level, they may have responded incorrectly to the questionnaires.

CONCLUSION

The present study showed that an appropriate educational material and follow-up can significantly increase the TTR levels of patients from rural areas who are mostly illiterate or primary school graduates. However, only one-third of patients had TTR levels >70%, suggesting that different approaches should be used to increase the efficiency of warfarin use. Finally, deteriorations in HRQoL can be explained by the increased awareness and additional burden that comes with a regular follow-up.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Gaziantep University (30.05.2016/180).

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Original Research

Choroidal Thickness Change in Central Serous Chorioretinopathy after Photodynamic Therapy Using Optical Coherence Tomography

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ABSTRACT

Objective: This study aimed to evaluate the change in choroidal thickness and subanalyze Haller's and Sattler' layer in patients with central serous chorioretinopathy (CSC) following low-fluence photodynamic therapy (PDT) using enhanced depth imaging optical coherence tomography (EDI-OCT).

Methods: In this retrospective study, medical records of the patients with CSC were reviewed. Patients with a diagnosis of CSC and a history of decreased visual acuity for more than six months and treated with half-dose PDT with verteporfin were included in the study. Patients who received previous PDT for chronic CSC or had evidence of choroidal neovascular membrane were excluded. Main outcome measures were the change in choroidal thickness and subanalysis of Haller and Sattler layer after treatment.

Results: A total of 13 eyes of 13 patients were included in the study. The mean age of the patients was 49±11 years (range 40–68). The mean subfoveal choroidal thickness decreased significantly from 310.60±89.16 μm at baseline to 308.41±90.03 μm after PDT ($p<0.05$). The mean Haller's layer thickness decreased significantly from 203.40±86.37 μm to 200.20±81.55 μm ($p<0.05$). The thickness of Sattler' layers did not differ significantly after PDT treatment ($p>0.05$).

Conclusion: Half-fluence PDT for CSC resulted in thinner subfoveal choroidal thickness after PDT treatment. Sattler's layer had similar thickness in eyes with active CSC and after PDT. This study finding suggested that subfoveal choroidal thickness changes after half-dose PDT were likely due to the changes in Haller's layer.

Keywords: Central serous chorioretinopathy, choroidal thickness, optical coherence tomography, photodynamic therapy

INTRODUCTION

Central serous chorioretinopathy (CSC) is a sporadic disease that is characterized by serous neurosensory retinal detachment often affecting middle-aged men (1). Although it can heal spontaneously without treatment, it can show recurrent and chronic characteristics and lead to progressive visual loss (2).

A number of theories have been proposed concerning the pathophysiology of CSC, but its mechanism is still not fully understood. Theories related to retinal pigment epithelium (RPE) dysfunction and choroidal vessel abnormalities currently dominate the literature (3). In indocyanine green angiography (ICGA), it is stated that vascular anomalies in choroidal vessels, and increased venous dilation and hyperpermeability in patients with CSS, is more intense compared to RPE leakage (4).

Currently, monitorization, laser photocoagulation, anti-vascular endothelial growth factor (anti-VEGF) inhibitors, mineralocorticoid receptor antagonists, and photodynamic therapy (PDT) are applied for the treatment of CSC (3, 5-7). PDT has been shown to treat subretinal fluid accumulation and increase visual acuity (7). Although the treatment mechanism is unknown, it has been suggested that it reduces choroidal hyperpermeability, causing damage in the choriocapillaris and resulting in resolution of leakage in the RPE (8).

Optical coherence tomography (OCT) is a noninvasive diagnostic imaging technique that provides high-resolution and cross-sectional imaging of the retina and the choroid using light waves. Conventional spectral-domain OCT devices cannot adequately image the choroid layer due to the shadowing effect of the RPE and the choroidal vascular structure. Today, choroidal vascular structure can be visualized with the EDI-OCT technique developed by modification of the spectral-domain OCT technology (9). The choriocapillaris/Sattler's layer, which is known as the choroidal small and medium-sized vessel network just below the Bruch membrane, and the Haller's layers, which are composed of the larger vessels that are located more deeply, can be distinguished by using new technology devices.

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Studies evaluating choroidal thickness with EDI-OCT have reported increased choroidal thickness in patients with CSC and decreased choroidal thickness in patients who spontaneously recovered, and in patients treated with PDT compared to healthy individuals (10, 11). In a study evaluating the choroidal sublayers with EDI-OCT, a significant increase was observed in the subfoveal Haller's layer in patients with CSC compared to healthy subjects, but there was no change in the choriocapillaris/Sattler's layer (12). As far as we know, no study shows the effect of PDT on Haller's and Sattler's layers in patients with CSC.

This study intends to evaluate changes in the choroid layer, choriocapillaris/Sattler's and Haller's layers with EDI-OCT in patients with chronic CSC who have undergone PDT treatment.

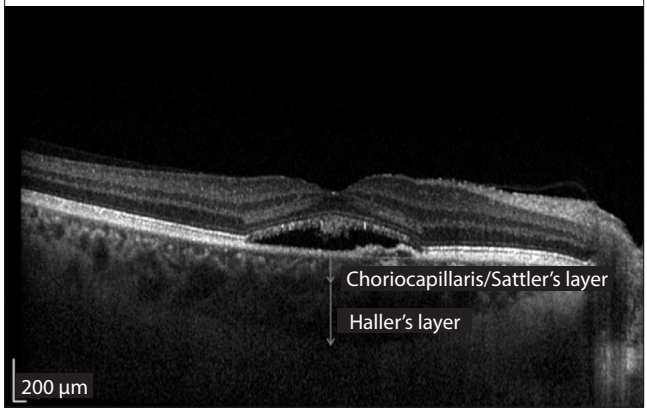
METHODS

Patients admitted to Ankara Atatürk Training and Research Hospital's Retina Clinic between March 2016 and September 2017 with a diagnosis of CSC were retrospectively reviewed on the basis of the file records. Patients who had symptoms of decreased visual acuity for a period of longer than six months receiving PDT treatment were included in the study. Patients with retinal diseases, such as age-related macular degeneration, degenerative myopia, polypoidal choroidal vasculopathy, and diabetic retinopathy, were excluded from the study. Patients with refractive errors of more than 6 diopters and patients with relapsed CSC who had previously undergone PDT and laser photocoagulation or intravitreal injection treatments were also excluded. Patients who did not attend regular follow-ups or have their EDI-OCT measurements were also excluded from the study. The diagnosis of CSC was made on the basis of subretinal fluid in the macular area in the OCT and idiopathic leaks detected via the fundus fluorescein angiography (FFA).

All patients received PDT at low energy levels according to the classical protocol (13). Verteporfin (Visudyne; Novartis, Basel, Switzerland) was calculated according to the body surface area of 6 mg/m^2 and administered intravenously for 10 min. After 15 min of beginning of the injection, the 689 nm diode laser was applied to the lesion site at a dose of 300 mW (half of the conventional dose of 600 mW) for 83 s.

Figure 1. Calculation of choriocapillaris/Sattler's layer and Haller's layer in EDI-OCT

EDI: enhanced depth imaging; OCT: optical coherence tomography;



During all control examinations, a detailed ophthalmologic examination including EDI-OCT measurements was performed on all patients. A visual acuity examination was performed with a Snellen eye chart. An FFA evaluation was performed on the first examination visit. The pre-PDT control examination records of patients and their post-PDT examination records at month 1 were evaluated.

A single technician performed the OCT measurements of the patients in the EDI mode using the Heidelberg spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) device. The same person (Mücella Arıkan Yorgun) manually measured the choroidal thickness in the linear measurement mode of the device over the OCT section across the subfoveal area. After each measurement, the manual additions were deleted and the measurements were repeated three times at different times. The mean values were used for the analysis. Total choroidal, choriocapillaris/Sattler's layer, and Haller's layer measurements were performed at intervals of 500 µm and at a nasal and temporal distance of 1500 µm from the subfoveal point. The distance between the outer border of the retina pigment and the outer border of the choroidal vascular bed was accepted as the "total choroidal thickness". The innermost border of large choroid vessels and the space between the choroid-scleral line were recorded as "Haller's layer". The difference between the total choroidal thickness and Haller's layer was accepted as representing the "choriocapillaris/Sattler's layer" (Figure 1).

This study was conducted in accordance with the principles of the Helsinki Declaration and was approved by the Clinical Trials Ankara Atatürk Training and Research Hospital Ethics Committee Commission on 17.01.2018 with document no. 26379996/16. Written consent was obtained from all patients.

Statistical Analysis

The Statistical Package for the Social Sciences 21.0 Windows version package program (SPSS IBM Corp.; Armonk, NY, USA) was used for the statistical analysis. The mean and standard deviation values of the data were calculated. The best corrected visual acuity (BCVA), measured with a Snellen eye chart, was converted to log MAR. The normal distribution of the data was tested with the Kolmogorov–Smirnov Test. The Student t test was used to compare quantitative data and Pearson's chi-square test was used to compare qualitative data. The p value of <0.05 was accepted as statistically significant. Thickness variations in the total choroid layer and Haller's and Sattler's layers after the photodynamic treatment were accepted as the evaluation criteria.

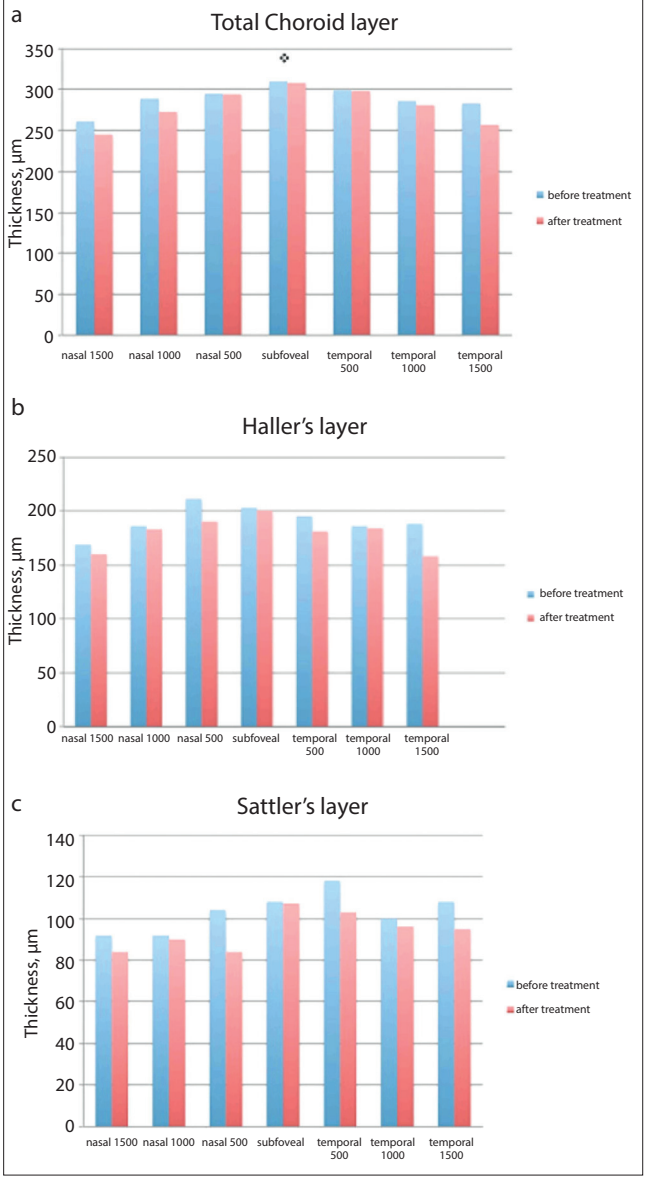
RESULTS

A total of 13 eyes of 13 patients who met the study criteria were included in the study. The average age was 49±11 years (range 40–68). The number of female cases was 5 (38%) and the number of male cases was 8 (62%). The mean symptom duration was 21.6±5.6 months. Complete relief of serous retinal detachment was observed in all patients following the first month post PDT treatment. The mean BCVA was 0.17±0.13 log MAR before treatment and 0.18±0.13 log MAR after treatment ($p=0.16$). The subfoveal total choroidal thickness before PDT was

310.60±89.16 (range 214–454), and 308.41±90.03 µm after PDT (range 183–411) (p=0.048). The subfoveal Haller's layer thickness was 203.40±86.37 µm before PDT and 200.20±81.55 µm after the treatment (p=0.032). The Sattler's layer was 108.20±33.75 µm before PDT and 107.2±17.03 µm after the treatment (p=0.147). No significant differences were found in the mean values before and after PDT in the total choroidal thickness of the nasal and temporal areas, the thickness of the Haller's layer, and the thickness of the Sattler's layer (p>0.05). Total choroidal thicknesses, choriocapillaris/Sattler's layer thicknesses, and Haller's layer thickness values before treatment and one month after treatment are shown in Figure 2.

Figure 2. a-c. (a) Change of total choroidal thickness before PDT and at month 1 after PDT, (b) change of Haller's layer before PDT and at month 1 after PDT, (c) change of choriocapillaris/Sattler's layer before PDT and at month 1 after PDT

PDT: photodynamic therapy



DISCUSSION

Today, developments in OCT technologies enable noninvasive measurement of choroidal thickness and indirect evaluation of choroidal vascular hyperpermeability, as well as investigation of the pathogenesis of diseases by distinguishing layers such as Haller's and Sattler's. In this study, in which subanalyzes of choroids and layers were performed with EDI-OCT, there was no significant change in the Sattler's layer, while a decrease in the thickness of the total choroid in the subfoveal area and the Haller's layer was detected during controls at month 1 in patients treated with PDT.

Two main theories have been proposed in the etiology of CSC: choroidal dysfunction and RPE dysfunction. In indocyanine green angiography studies, choroidal vascular anomalies causing choroidal hyperpermeability have been demonstrated (14). Choroidal hyperpermeability can be evaluated non-invasively by measuring the choroidal thickness in EDI-OCT studies. Imamura et al. (11) showed in their studies evaluating choroidal thickness with EDI-OCT that there was an increase in subfoveal choroidal thickness in patients with CSC compared to healthy individuals. Studies have reported that choroidal thickness is reduced in patients who recovered without treatment (11, 15). It is reported that there is no change in choroidal thickness in patients treated with laser, while the choroidal thickness decreases with PDT treatment (16). Maruko et al. (15) showed a reduction in the choroidal thickness with OCT in one month and a decrease in choroidal hyperpermeability with ICG in their study in which they followed up their patients with CSC who were administered a half-dose PDT for one year. Similarly, our study showed a decrease in the subfoveal choroidal thickening at month 1 after PDT treatment. Based on the results of these studies, it can be assumed that treatment with PDT causes a decrease in permeability by acting on the choroid, resulting in thinning of the choroid.

Dilatation in the choroidal vessels in the Haller's layer has been accepted as a descriptive feature of CSC disease agreed in the current literature as belonging to the group of "pachychoroid spectrum diseases" (17). Studies in which choroid layers have been evaluated by EDI-OCT showed dilation and increase in thickness of the impacted eye's vessels in the Haller's layer in CSC cases compared to the other eye and healthy subjects. It has been shown that the increase in choroidal thickness may be due to the enlargement of large choroidal vessels in the Haller's layer (8, 12, 18). No other study in the literature evaluates the choroidal lower layers using OCT after PDT treatment. However, in a study by Chan et al. (19) in which the choroidal layer was assessed through ICGA, a 32% reduction in the size of the dilated choroidal vessels was reported post-PDT in patients with CSC. In our study, a thinning of the subfoveal Haller's layer was observed after PDT treatment, but no change in the parafoveal choroidal thickness was detected. The smooth muscle cells present in the choroidal vessels are more dense in the area under the fovea and are affected by sympathetic and parasympathetic innervation, causing narrowing of the choroidal vessel wall. In the PDT protocol, the laser beam also acts on the parafoveal area circularly, as well as the subfoveal area. The lack of impact on the parafoveal area while reduction was seen in the choroidal thickness of the

subfoveal area may be due to differences in the innervation and vessel network, which are more intense in the foveal area, rather than the direct effect of the laser beam.

The retrospective nature of our study, the small number of cases, and the short follow-up periods are the main limitations of the study. At the same time, even though the OCT device used contains an EDI mode, which provides high-resolution deep-screening, factors such as optical obstructions in front of the choroid layer, eye movements, and manual segmentation may have prevented optimal choroidal stratification. Although it has been used in some experimental studies with OCT devices that provide high penetration with a wavelength of >1000 nm (20), OCT devices, which we also use at our clinic, that enable penetration at an 840 nm laser wavelength are available. Finally, although the change in the choroidal thickness was statistically significant in our study, this change in choroidal thickness may not be clinically significant.

CONCLUSION

This study demonstrates that a decrease was observed in the subfoveal choroidal thickness and Haller's layer thickness with half-dose PDT treatment in patients with CSC. We think that the results of this study will shed light on the application of PDT mechanism on patients with CSC, whose etiopathogenesis is inadequately understood. Based on our current knowledge, no study in the literature shows the effect of PDT on Haller's and Sattler's layers in patients with CSC. In this regard, studies with a wide case series and a long follow-up period are needed.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Ankara Atatürk Training and Research Hospital (date: 17.01.2018, no. 26379996/16).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The author has no conflicts of interest to declare.

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Original Research

Effectiveness of Percutaneous Drainage on the Treatment of Mesh-Induced Seroma

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ABSTRACT

Objective: To investigate the effectiveness of percutaneous treatment of mesh-related seroma to salvage the mesh.

Methods: Between October 2015 and December 2017, a total of four patients [three females, one male; mean age, 68.5±22 years (range, 61–83 years)] with repaired ventral hernia who underwent percutaneous drainage for the treatment of peri-mesh seroma were evaluated, retrospectively. In all patients, ultrasound was used to diagnose seroma and was the guiding imaging method during percutaneous procedures. General purpose pigtail-percutaneous drainage sets were used in all patients. Ethanol (96%) was used for sclerotherapy, and a fibrinolytic agent was used to destroy septa in multilocular collections. Laboratory investigations and comorbidities were evaluated in hospital data service, retrospectively. Mainly, the clinical success rates were evaluated, and technical success rates and procedure-related morbidity and mortality were also evaluated.

Results: A total of 11 percutaneous drainage sessions (median, 2; range 1–6) were performed in four patients. The mean volume of fluid collections was 807.3±3006 cc (median, 291 cc; range, 114–3120 cc). There was no significant difference between the mesh sizes. A technical success rate was 100%. There was no procedure-related morbidity and mortality. The mean of the recurrence time of the peri-mesh seroma was 3.5±11 months (median, 2 months; range, 1–12 months). In all patients, during the follow-up, seroma was accumulated repetitively.

Conclusion: Percutaneous treatment is an effective management option to salvage the mesh in patients with mesh-related seroma who are poor surgical candidates or whose mesh cannot be removed.

Keywords: Mesh-related seroma, percutaneous treatment, salvage the mesh

INTRODUCTION

Percutaneous drainage has become the first and the most effective treatment option in the management of the abdominal and thoracic fluid collection during the past three decades (1, 2). There are many reasons for fluid collection, such as an infection, inflammation, or iatrogenic and foreign body reaction. The hernia surgery technique has been modified due to new biological materials (3). There are two different construction materials of the mesh: the polypropylene (PP) and the expanded polytetrafluoroethylene (e-PTFE) mesh (4). There are some postoperative complications in hernia repair surgery using these materials. These complications are the fluid collection, mesh infections, small-bowel-related complications, spermatic-cord-and testicle-related complications, and hernia recurrence (4). The collection due to mesh used in hernia treatment may be a kind of a foreign body reaction. Fluid collections can be seroma or hematoma and can be located in front of or behind the mesh (5).

This present study examined the effectiveness of percutaneous treatment of peri-mesh seroma to salvage the mesh.

METHODS

The present study is a single-center retrospective study. Formal consent and informed consent for all individual participants included in the survey were obtained. The study was approved by the institutional ethics committee of the Karabük University (date: 07.02.2018, no: 2/7).

A total of four female patients [mean age 68.5±22 years (range, 61–83 years)], who underwent percutaneous drainage for the treatment of peri-mesh seroma after the abdominal wall hernia repair between October 2015 and December 2017, were evaluated in the present study. In all patients, non-absorbable meshes were used to repair the hernia.

All patients underwent ultrasound (US) with a 7.5 MHz linear probe (Toshiba, Minato, Japan) to diagnose peri-mesh seroma and to evaluate the feasibility of the percutaneous drainage before the procedure. The estimated volume of the seroma was calculated by the ellipsoid volume formula: $\frac{\pi}{6} \times transversediameter \times APdiameter \times longitudinaldiameter$.

A technical success was defined as an ability to drain a seroma without residue. Clinical success was defined as a preclusion of

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the mesh removal and discharge of the patient without any complaint.

Comorbidities of all patients, such as diabetes, obesity, and chronic peripheral vascular disease, were investigated. Laboratory investigations included a complete blood count and erythrocyte sedimentation rate, which are the inflammation markers, and they were noted in hospital data service, retrospectively.

Percutaneous Drainage Procedure

Peri-mesh seromas were punctured under US guidance in all patients by the same interventional radiologist. Peri-mesh seromas were drained with general purpose pigtail drainage sets (used 8F or10F) using the Seldinger technique.

A fibrinolytic agent was applied into the multilocular seromas to destroy the septa. Alteplase 20 mL (Actilyse 20 mg, Boehringer İngelheim, Rhein, Germany) was utilized for fibrinolysis (Figure 1). Ethanol (96%) 30 mL was used to destroy the walls of the fluid collection when the seroma was recurrent.

Follow-up

The US was performed on the 3rd day after the drainage procedure to assess the location of the catheter and the volume of the fluid collection in all patients by the same interventional radiologist. When the fluid discharge was less than 10 cc per day, the pigtail catheter was withdrawn.

RESULTS

All patients complained of severe pain and tension in the field of the mesh. The mesh removal was not considered due to comorbidity, and it might have been the reason for the hernia recurrence. Because of these two reasons, percutaneous drainage was performed. In Patient A, diabetes and obesity were the comorbidities. Patient B suffered from peripheral arterial disease. Patients C and D were obese. The similar sizes of the mesh were used in all patients. There was no significant difference between mesh sizes. Patient characteristics were summarized in Table 1.

In laboratory investigations, the indicator of infection was not detected in all patients. There was no evidence of mesh infection. According to these findings, peri-mesh fluid collections were diagnosed as seroma.

A total of 11 percutaneous drainage sessions (median, 2; range 1–6) were performed in four patients. The percutaneous drainage was well tolerated by all patients. Technical success rate was 100%. Sclerotherapy with 95% ethanol was performed in Patients A and C. Fibrinolytic agents were used in Patient A (Figure 1). Thus, in all patients, peri-mesh seroma was drained without residual fluid.

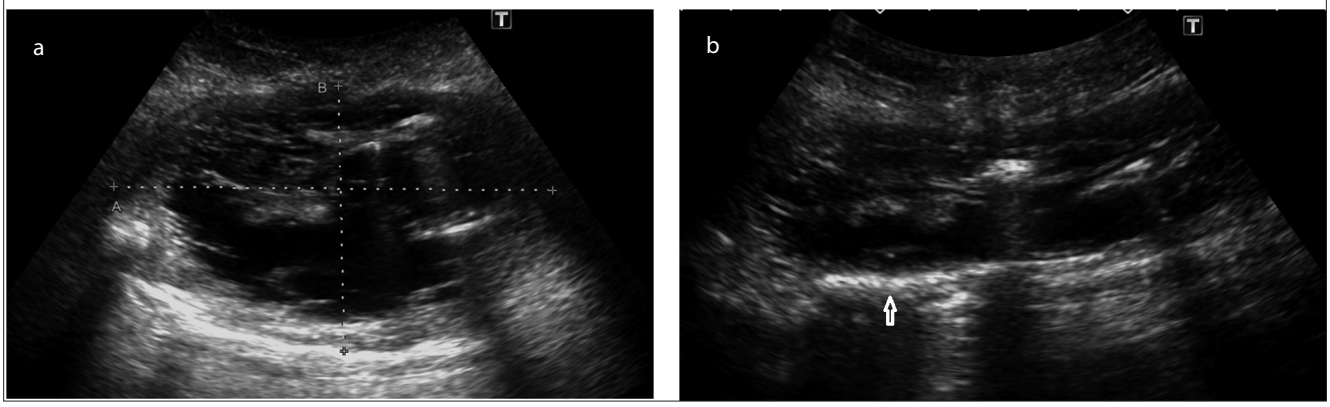
In Patient A, a total of six percutaneous drainage sessions were performed during the 1-year follow-up. Patient B did not accept recurrent drainage.

Table 1. Characteristics of patients

Patient	Age (years) and sex	Drainage number	Fibrinolytic agent	Alcohol sclerotherapy	Comorbidity	Recurrence interval (months)
A	65/F	6	No	Yes	Diabetes, Obesity	1, 2, 3, 4, 12
B	83/F	1	No	No	PAD	3
C	61/M	2	Yes	Yes	Obesity	1
D	65/F	2	No	No	Obesity	2

PAD: peripheral arterial disease; F: female; M: male

Figure 1. a, b. Peri-mesh seroma with multisepta (a) after the fibrinolytic agent was applied, (b) has shown destroyed septas , arrow have shown the mesh



The mean volume of seroma was 807.3±3006 cc (median, 291 cc; range, 114–3120 cc). The largest volume was in Patient A, and there was 3120 cc of seroma in the first drainage.

The mean recurrence time for peri-mesh seroma was 3.5±11 months (median, 2 months; range, 1–12 months). During the follow-up, the fluid collection was observed repetitively, and clinical success was achieved in all patients. There was no procedure-related morbidity and mortality.

DISCUSSION

The present study demonstrated the effectiveness of percutaneous drainage of peri-mesh seroma. There were no detected complications or mortality/morbidity. In patients with comorbidities, performing percutaneous drainage for mesh-related seroma was useful to salvage the mesh.

There is no gold standard surgical technique in hernia treatment (6). The recent involvement of new biological materials enabled a new technique of hernia surgery (3). Recently, the number of hernia repairs with mesh has increased, parallel with this condition, and mesh-related complications have become more common (4). Robinson et al. (7) showed major mesh-related complications in their retrospective study, which included 252 adverse events. The frequent mesh complications were infections (42%), while the seroma rates were at 4% and a relatively rare complication in their study. There are also articles that report seroma rates more frequently. Clinically and ultrasonographically, the presence of seroma was reported as 35% and 100%, respectively (8). In the current study, percutaneous treatment was performed in patients with clinically determined complaints, such as abdominal distention and severe pain. In an asymptomatic patient, the collection was not treated.

Salamone et al. (9) reported recurrent seroma despite the drainage in one case, and the mesh had to be removed for treatment. However, in the present study, 11 seromas in four patients were drained, and the meshes were not removed in all patients. The patients were discharged without any complaints. Susmallian et al. (8) treated four seromas with a percutaneous needle puncture without catheter drainage, and they did not prevent the accumulation of serum. Furthermore, the residual collection was observed at 100% and 50% after 30 and 90 days, respectively. In contrast, the catheter drainage was performed to treat 11 clinically symptomatic seroma in this present study, and residual collection was observed at 9% and 36% after 30 and 90 days, respectively. Our results may seem to be better. One of the reasons for relatively better results was that the catheter drainage was used instead of the needle puncture. Catheter drainage has some advantages such as forced shrinking, dilution for intense collection, and the use of ethanol or a fibrinolytic agent. Another advantage of catheter drainage is to salvage the infected mesh without the mesh removal (10). Another reason for better results may be the usage of a fibrinolytic agent to destroy the septa in the collection. Fibrinolytic agents have been used for many years as an effective and alternative treatment option incomplex seroma management (11). In our study, a fibrinolytic agent was administered in one patient who had a complex seroma. Septa of the seroma were destroyed, and the seroma was drained without residual collection.

Ethanol sclerotherapy of the renal cyst, splenic cyst, and lymphocele is a well-known, safe, and effective procedure (12-14). However, there are very few articles about the ethanol sclerotherapy of seroma in the literature. Sood et al. (15) published a comprehensive systemic review that included research articles on sclerotherapy for seroma between 1975 to 2017. This large review has revealed that there was only one patient whom Isaacson and Stavas (16) treated successfully with percutaneous ethanol sclerotherapy. Although seroma is a very common adverse effector complication after the hernia repair with a mesh, there appears to be very little information about sclerotherapy for wound seroma. This present study is unique and distinct from previous studies due to the etiology of seroma. Ethanol sclerotherapy was performed in two patients for mesh-related seroma. Recurrences of seroma were observed1month and-12months after sclerotherapy in two separate patients in our study. In our opinion, the most important reason for inadequate sclerosis is the etiology of the seroma formation. A foreign body reaction caused by the mesh may lead to seroma. The recurrence of seromas on follow-up can be considered the evidence of chronic inflammation due to a foreign body reaction.

There are some limitations to this study. Its retrospective nature and the small number of patients maybe restrictive factors. We consider that this is acceptable because a total of 11 drainages were performed despite the small number of patients. Prospective studies with a larger number of patients should be conducted.

CONCLUSION

Percutaneous treatment is an effective management option for mesh-induced seroma in a patient who is a poor surgical candidate. The use of a fibrinolytic agent may be considered in the complex seroma with septa. Although high rates of seroma recurrence are frustrating for patients, they can be acceptable for mesh salvage.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of the Karabük University (date: 07.02.2018, no: 2/7).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Original Research

Effect of Vertical Growth Pattern on Maxillary and Frontal Sinus Sizes

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ABSTRACT

Objective: The purpose of the present study was to investigate the frontal and maxillary sinus sizes of individuals with different vertical growth pattern by using lateral and posteroanterior (PA) cephalometric radiographs.

Methods: In the study conducted on 60 individuals selected from male and female patients between the ages of 15 and 17 years, lateral and PA cephalometric radiographs were divided into three groups by vertical skeletal classification. The radiographs of 20 patients with increased vertical growth [Sella–Nasion Plane and Gonion–Gnathion Plane (Sn–GoGn) >38°] were classified as Group 1, the radiographs of 20 patients with decreased vertical growth (Sn–GoGn <26°) were classified as Group 2, and the radiographs of 20 patients with normal growth (Sn–GoGn: 32±6°) were classified as Group 3. The measurements of maxillary and frontal sinus sizes were obtained via ImageJ software.

Results: The differences between the groups for all measurements in both lateral and PA radiographs ($p>0.005$) were not statistically significant.

Conclusion: The different vertical growth pattern was not effective on maxillary and frontal sinus sizes. Future controlled trials conducted with larger samples are needed to support and extend the findings.

Keywords: Frontal sinus, lateral cephalometric radiography, maxillary sinus, posteroanterior radiography, sinus size

INTRODUCTION

The largest of the paranasal sinuses defined as bone cavities filled with air opening to the nasal cavity is the maxillary sinus. The base of the maxillary sinus is formed by the alveolar process and the hard palate, and its adjacency to the upper posterior teeth continues for life (1). The maxillary sinus reaches its mature size at the age of 12–15 years, in conjunction with the maxillary growth period (2). The frontal sinus, one of the paranasal sinuses, does not exist at birth, and it starts to develop after the age of 2 years. Its development continues until late puberty and is completed at the age of approximately 20 years (3).

The human skeleton is a balanced and dynamic system influenced by various mechanical stresses. Studies to determine the factors affecting the functions, morphologies, and sizes of the paranasal sinuses occupying space in the skull have been drawing attention for a long time (4). It is thought that the development of the maxillary sinus, which has a close relationship with the maxillary structure and the upper posterior teeth, can be affected by skeletal malocclusions (1). The frontal sinus size may be affected by different factors, such as bone density, forces of the masticatory muscles, occlusal relationships, and jaw relationships (4).

In the literature, there are various studies investigating the relationship between maxillary sinus size and malocclusion. Oktay (1) reported that female individuals with Angle Class II malocclusion have broader maxillary sinuses than other malocclusions. Tikku et al. (2) reported that the sinus size of individuals who are breathing through their mouth is smaller than that of individuals with normal respiration. On the other hand, Oksayan et al. (5) suggested that high-angle individuals have smaller maxillary sinuses than low-angle individuals. It was reported that maxillary sinus size is important with respect to providing an opinion on clinical subjects, such as the impacted upper tooth's angle and depth, determination of location in mini-implant applications, and planning orthognathic surgery (5).

The number of studies investigating the relationship between frontal sinus size and malocclusion is few. There are studies reporting that the frontal sinus may be used as an indicator for growth (6, 7) and compatible anterior occlusion (4). However, there is no study in the literature investigating the effects of vertical growth direction on both frontal and maxillary sinus sizes and assessing the correlation between them. The purpose of the present study designed on the basis of such deficiency was to investigate the frontal and maxillary sinus sizes of individuals with different vertical growth patterns using lateral and posteroanterior (PA) cephalometric radiographs.

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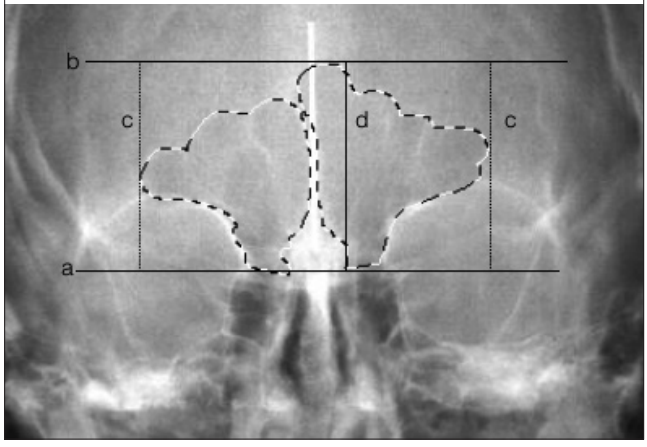
METHODS

This was a retrospective study. Lateral and PA cephalometric films with skeletal Class 1 relationship and different vertical growth patterns (A point: nasion, B point: 0–4°) obtained from systemically healthy patients without craniofacial deformities, such as cleft lip or palate, kept in the archive of the Department of Orthodontics at Gaziantep University's Faculty of Dentistry were included in the present study. The study was approved by the clinical trials ethics committee of Gaziantep University (29.03.2018/14). Written informed consent was obtained from the patients who participated in the study. The power analysis sample size determination revealed that for the analysis of variance (ANOVA) on three groups with an effect size of 0.90 for the frontal sinus area, an alpha level of 0.05, a power of 0.85, and a minimum of 19 subjects in each group were required.

The radiographs used in the study were obtained via X-ray (Planmeca EC Proline PM, Planmeca, Helsinki, Finland) at the Department of Oral Diagnosis and Radiology within Gaziantep University's Faculty of Dentistry, under standard conditions. Exposure parameters were 68–74 kVp, 12 mA, and 0.4–0.5 s. In addition, magnification ratio was 1:1. A total of 102 individuals with skeletal Class I relationship were selected randomly from male and female patients between the ages of 15 and 17 years in the department archive. The frontal and maxillary sinuses of individuals were assessed with respect to their anatomic and physiological integrity from the cephalometric radiographs. Patients with a history of orthodontics treatment or orthognathic surgery, who had experienced trauma or undergone skull surgery, and who had endocrine disorders or hereditary facial asymmetry were excluded from the study. In addition, it was taken care in the selection of radiographs that the films were acquired without rotation. After this procedure was completed, 60 individuals' radiographs were divided into three groups by vertical skeletal classification.

Figure 1. (a) A line has been drawn through the lateral limit of orbital cavities at the nasofrontal suture. (b) The line that parallels to the nasofrontal line has been drawn at the highest point of the frontal sinus. (c) Lines that delineate the maximum lateral limits of the right and left sinuses. (d) Distance between a and b lines.



The lateral and PA cephalometric radiographs of 20 patients with increased vertical growth (Sella–Nasion Plane and Gonion–Gnathion Plane (Sn–GoGn)>38°) were classified as Group 1 (high angle), the radiographs of 20 patients with decreased vertical growth (Sn–GoGn<26°) were classified as Group 2 (low angle), and the radiographs of 20 patients with normal growth (Sn–GoGn: 32±6°) were classified as Group 3 (medium angle).

Maxillary and frontal sinus size measurements were obtained using ImageJ software 1.48v (National Institutes of Health, Bethesda, MD, USA) after the images were calibrated (operated by GBB). For calibration, the ruler was used in the lateral cephalometric radiographs, and the ear rods were used in the PA radiographs. After the images to be assessed were transferred to the software using the size calculation feature, the borders of the maxillary and frontal sinuses were determined; their areas were calculated in cm^2, and their height and width were calculated in cm. Said et al.'s (4) studies for drawings of the frontal sinus area and Sidhu et al. (8) studies for drawings of the maxillary sinus area were considered as a reference. The frontal sinus was measured by calculating the average of the right and left sinus measurements obtained separately. Rectangular coordinates as described by Endo et al. (9) were selected for the assessment of the height and width sinuses. The x-axis is parallel to the Frankfort horizontal plane (Pr–Or), and the y-axis is perpendicular to the Frankfort horizontal plane through the sella. The maximum height, width, and area of the sinuses were measured in the PA and lateral cephalometric radiographs as shown in Figures 1 and 2, respectively.

Figure 2. (a) Maxillary sinus height projected on the y-axis. (b) Maxillary sinus width projected on the x-axis. (c) Frontal sinus height projected on the y-axis. (d) Frontal sinus width projected on the x-axis.

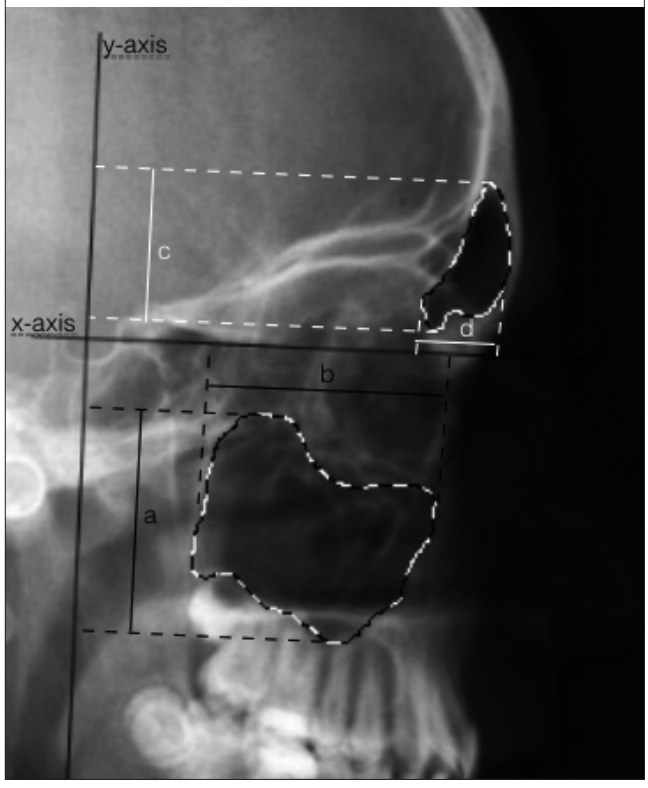


Table 1. Means, standard deviations, and p values for the lateral cephalometric radiograph measurements between the groups

	Groups			
	Group 1 (Mean±SD)	**Group 2 (Mean±SD)**	**Group 3 (Mean±SD)**	**p**
Max area (cm^2)	8.19±0.23	7.63±0.34	7.83±0.20	0.330
Frontal area (cm^2)	1.56±0.95	2.02±0.17	1.59±0.11	0.093
Max width (cm)	3.51±0.07	3.28±0.07	3.39±0.06	0.095
Max height (cm)	3.77±0.08	3.75±0.10	3.84±0.06	0.754
Frontal width (cm)	0.87±0.03	0.95±0.08	0.85±0.05	0.501
Frontal height (cm)	2.58±0.07	2.74±0.08	2.55±0.09	0.228

SD: standard deviation

Table 2. Means, standard deviations, and p values for the posteroanterior cephalometric radiograph measurements between the groups

	Groups			
	Group 1 (Mean±SD)	**Group 2 (Mean±SD)**	**Group 3 (Mean±SD)**	**p**
Frontal area (cm^2)	8.56±0.50	9.71±0.68	9.05±0.56	0.631
Frontal height (cm)	2.57±0.09	2.78±0.11	2.67±0.09	0.614
Frontal width (cm)	4.88±0.19	5.23±0.27	4.89±0.21	0.483

SD: standard deviation

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences version 21 (SPSS IBM Corp.; Armonk, NY, USA). The Shapiro–Wilk test was used to test the normality of the distribution of continuous variables. The one-way ANOVA and Least Significant Differences (LSD) test were used to compare variables between the groups when data were normally distributed, and the Kruskal–Wallis analysis was used when data were non-normally distributed. Data are expressed as mean±standard deviation. To determine the method error of five lateral and five PA cephalometric radiographs, the final records were randomly selected, retraced, and digitized at a 15-day interval by the same operator (GBB). The intraclass correlation coefficient (ICC) and 95% confidence interval were used to the test harmony of values and intra-rater reliability. ICC ranged from 0 to 1, where 0 represented no agreement and 1 indicated perfect agreement. A p value of <0.05 was considered statistically significant.

RESULTS

The average ages of individuals included in the study were 16.06±0.18 years for the high-angle group, 16.21±0.17 years for the low-angle group, and 16.09±0.16 years for the medium-angle group. The differences in average age between the groups were not statistically significant (p=0.805). The study included 13 female and 7 male patients in Group 1, 11 female and 9 male patients in Group 2, and 10 female and 10 male patients in Group 3. The difference between the groups with respect to gender was not statistically significant (p=0.627). The correlation coefficient results were >0.89 for intra-examiner reliability, showing high positive correlations and indicating the reliability of the measurements. The area, width, and height measurements of the maxillary sinus and the frontal sinus, which are the measurements from the lateral cephalometric radiographs, are provided in Table 1. The p values of comparisons among groups of these values are provided in the same table. The area, width, and height measurements of PA radiographs and statistical comparison results between the groups are provided in Table 2. According to the results, the difference between the groups in all of the measurements in both lateral and PA radiographs was not statistically significant (p>0.005). The ICC value of 0.831 suggested a high level of harmony between the frontal sinus area lateral and the PA radiograph values (r=0.831, p<0.001).

DISCUSSION

In our study aiming to assess the frontal and maxillary sinus sizes in adolescent individuals with different vertical growth patterns, both frontal and lateral cephalometric radiographs were used. In the study, the error ratio was planned to be decreased by reducing the superimposition rate, which is one of the known disadvantages of two-dimensional radiographs created through the joint use of radiographs obtained based on two different directions. This study is important as it attempts to develop a diagnosis with cheaper two-dimensional radiographs that are routinely used without the need of three-dimensional radiographs exposing the patient to more radiation.

According to our study results, the difference in the age and the gender of the individuals included was not statistically significant between the groups. When considering the effect of age and gender differences on sinus sizes (1, 10), the presence of homogenization is one of the superior aspects of the study. Therefore, by minimizing the individual differences, vertical growth patterns were provided as the only variable.

When examining studies assessing the maxillary sinus in the literature, it was seen that most used lateral cephalometric radiography as two-dimensional radiography. The difficulty of drawing the maxillary sinus with PA radiography due to superposition was given as a reason. Although this condition prevented drawing on two films, as is the case with frontal sinus values, to the best of our knowledge, this is the first study where the correlation between two sinuses is assessed by drawing two sinuses together.

According to the results of our study, a high correlation was found between the measurement values of the frontal sinus area in lateral and PA cephalometric radiographs. Preliminary information was obtained regarding the usability of one radiograph type in place of another in cases where obtaining two radiographs is not possible due to economic, physical, and other reasons.

Said et al. (4) reported that frontal sinus size is affected by vertical skeletal measurements. However, they did not observe a significant difference in the sinus sizes of individuals with different skeletal sagittal oriented malocclusions. They thought that the larger frontal sinus in individuals with open bite malocclusion resulted from the occlusal forces that were transmitted poorly along the nasal pillars associated with the reduced muscular activity in hyperdivergent individuals. Endo et al. (9) reported that there is no significant relationship between maxillary sinus size and sagittal skeletal bone, while reporting that there is a positive correlation between them and upper face height. From these findings, the effects of different vertical patterns on sinus sizes were investigated.

In our study, the statistical difference between the groups was not significant in the measurements in both lateral and PA radiographs. This result is not consistent with the study by Endo et al. (9). In parallel with the study by Oksayan et al. (5), it was suggested that the difference is the result of using the total height instead of using the upper and lower heights separately as in Endo et al.'s method (9) in determining the vertical face sizes.

Oksayan el al. (5) identified significant differences in maxillary sinus lengths and widths, contrary to our study. This is considered to be the result of the difference between the average ages of the individuals included in the groups in the two studies.

Said et al. (4), reporting that the effect of facial height on frontal sinus size is statistically significant, also considered the U1–L1 angle in the grouping of individuals. They suggested that anterior occlusion is important in the transmission of the masticatory forces to the frontal sinuses. It is thought that the difference in the results is due to the fact that this value was not standardized because of the scarcity of samples available when determining the groups in our study. It is considered that this is due to the limitations of the study. We hope that the subject can be enlightened in further detail in more comprehensive future studies in light of this article's findings.

CONCLUSION

Lateral and PA cephalometric radiographs can be used in the calculation of sinus sizes as an effective material, and no significant difference with respect to the effect of different vertical growth tendencies on maxillary and frontal sinus sizes was found.

Ethics committee approval: The study was approved by the Ethics Committee of Gaziantep University (date: 29.03.2018, no: 14).

Informed consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.G., A.G.; Design - M.G., G.B.B., A.G.; Supervision - M.G., A.G.; Resources - M.G., G.B.B.; Materials - G.B.B.; Data Collection and/or Processing - M.G., G.B.B.; Analysis and/or Interpretation - M.G. A.G.; Literature Search - M.G., G.B.B., A.G.; Writing Manuscript - M.G.; Critical Review - M.G., A.G.

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Original Research

Effects of Different Bleaching Methods on the Enamel Mineralization Level

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ABSTRACT

Objective: The aim of the present study is to evaluate the mineralization level of human enamel following bleaching treatment using a laser fluorescence device.

Methods: A total of 45 patients were divided into three groups according to the bleaching method used. In Group 1, chemical bleaching was conducted with 35% hydrogen peroxide (HP). In Group 2, we used 35% HP activated by a 980 nm diode laser. In Group 3, bleaching was conducted with ozone. Levels of mineralization were measured using a laser fluorescence device before bleaching, just after bleaching and also on the 2-weeks and 1-month following bleaching.

Results: Data were analyzed using the Kruskal–Wallis test, one-way analysis of variance, and Mann–Whitney U test. The values were significantly higher compared to initial values following bleaching and at the 2-weeks follow-up for Groups 1 and 2 ($p<0.05$). However, values were similar to the initial values at the 1-month recall ($p>0.05$). For Group 3, the values were significantly reduced following bleaching ($p<0.05$), while the values of each postbleaching were statistically similar ($p>0.05$).

Conclusion: Both chemical and laser-activated bleaching resulted in a significant reduction of the mineralization level, while bleaching with ozone did not. Bleaching with ozone seems to be safer in terms of demineralization compared to HP.

Keywords: Dental bleaching, DIAGNOdent, diode laser, ozone treatment

INTRODUCTION

Office bleaching methods have been widely used to whiten discolored vital teeth. Hydrogen peroxide (HP) at high concentrations is the most used agent for this purpose and can be arbitrarily activated by heat or light to obtain better results. This chemical leads to whitening by oxidizing organic and inorganic compounds. However, the exact mechanism of bleaching by HP is not well known. The degree of oxidation depends on environmental conditions including temperature, pH, and light. For this reason, different activation methods such as light and lasers have been used to heat HP and in this way accelerate the decomposition of oxygen to form more oxygen-free radicals (1). On the other hand, both chemical bleaching and laser-light-activated techniques have been probed due to their deleterious effects on the tooth structure (2). A previous study revealed that the structural alteration may occur in the enamel following bleaching, which is directly proportional to the concentration of HP and which result in a reduction of the enamel microhardness as a result of demineralization and loss of mineral content (3, 4).

The ozone application is a contemporary technique used for various dental treatments, including remineralization of dental hard tissues and management of dental hypersensitivity (5). This method has recently been used for bleaching to avoid undesired effects of HP (6). Bleaching with ozone acts by oxidizing. For this reason, bleaching with ozone became an alternative to bleaching with HP (7).

The DIAGNOdent device reflects the 655 nm monochromatic light to a biological substrate and recollects scattered light to detect any deviations on surfaces (8). It was first manufactured for the purpose of an early detection of the degree of demineralization (9).

It uses a scoring range from 0 to 99 as follows:

0–13: No cavities
14–20: Demineralization of enamel
21–29: Demineralization of superficial dentin
30–99: Demineralization of deep dentin (10)

The present study compared demineralization following different bleaching methods, including chemical bleaching with HP, HP activated by laser, and bleaching with ozone. The level of demineralization was measured using a DIAGNOdent pen (Kavo, Biberach, Germany).

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METHODS

The present study was approved by the ethical committee of Gaziantep University (2018/140).

Inclusion criteria were the following:

1. The presence of all maxillary and mandibular incisors, canines, and first premolars.
2. C1 or darker color shades of the relevant teeth.
3. Absence of any restoration that may interfere with the DIAGNOdent pen readings.
4. Participants with good oral hygiene were included.
5. Systemic health status of patients was also considered to be normal.

Patients with poor oral hygiene, pregnant or lactating women, and individuals who were smoking or chewing tobacco were excluded.

A total of 45 patients were divided into three groups according to the bleaching protocol (n=15).

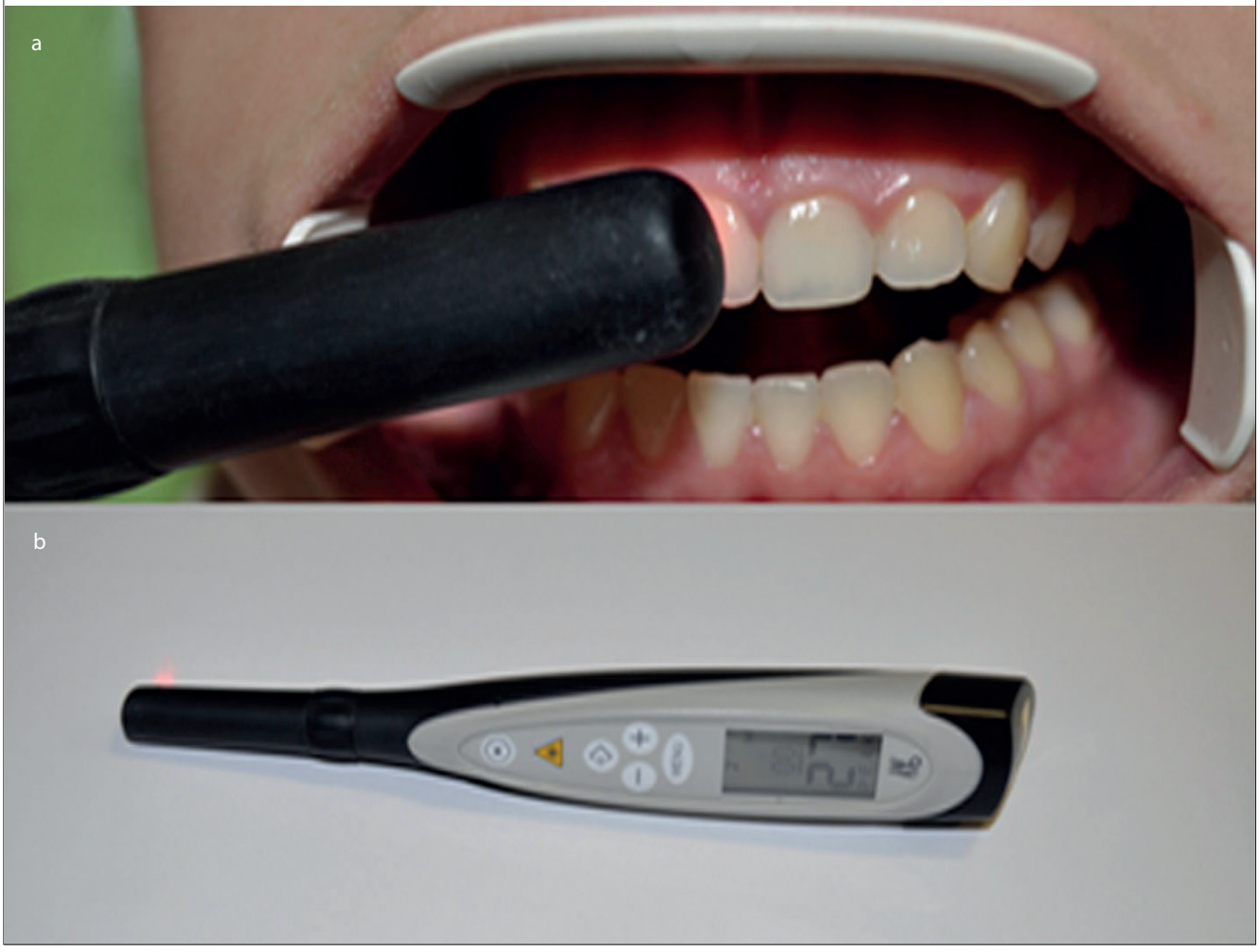
Before the bleaching procedure, the prophylaxis paste was applied to relevant teeth. Initial measurement with the DIAGNOdent pen was performed (Figure 1). Gingival tissues were isolated using a light-polymerized resin dam (Top Dam; FGM Prod., Joinville, SC, Brazil).

The bleaching procedures were conducted as follows:

Group 1: Bleaching gel containing 35% HP (Whiteness HP BLUE CALCIUM- FGM, Joinville, SC, Brazil) was coated to dried facial enamel surfaces at a thickness of 1.5 mm. The gel was kept on the teeth surface for 15 minutes and removed with air/water spray. This was repeated three times.

Group 2: Bleaching gel containing 35% HP (Whiteness HP BLUE CALCIUM-FGM, Joinville, SC, Brazil) was coated to dried facial enamel surfaces at a thickness of 1.5 mm. The gel was kept on the teeth surface for 15 minutes. During this 15-minute period, laser activation of the bleaching gel with a diode laser (980 nm, 4 W) for 2 minutes (30 seconds for each quadrant) was further achieved. For this purpose, a special bleaching handpiece was

Figure 1. a, b. (a) Measurement with DIAGNOdent pen; (b) DIAGNOdent pen device (Devices in Figures belong to Archive of Gaziantep University School Medicine - used with permission)



attached to the laser device, and irradiation was applied 6 mm away from the relevant teeth (Figure 2). Then, remnants of the gel were removed with air/water spray. This was repeated two times.

Group 3: Cast models were constructed for each patient's maxilla and mandibular and custom trays made from thermoplastic material (Easy-Vac Gasket, 3A MEDES, Gyeonggi-do, Korea) fitting both jaws of patients were prepared. The hose pipe of the

Figure 2. a, b. (a) Laser-activated bleaching; (b) Laser activation handpiece (Devices in Figures belong to Archive of Gaziantep University School Medicine - used with permission)

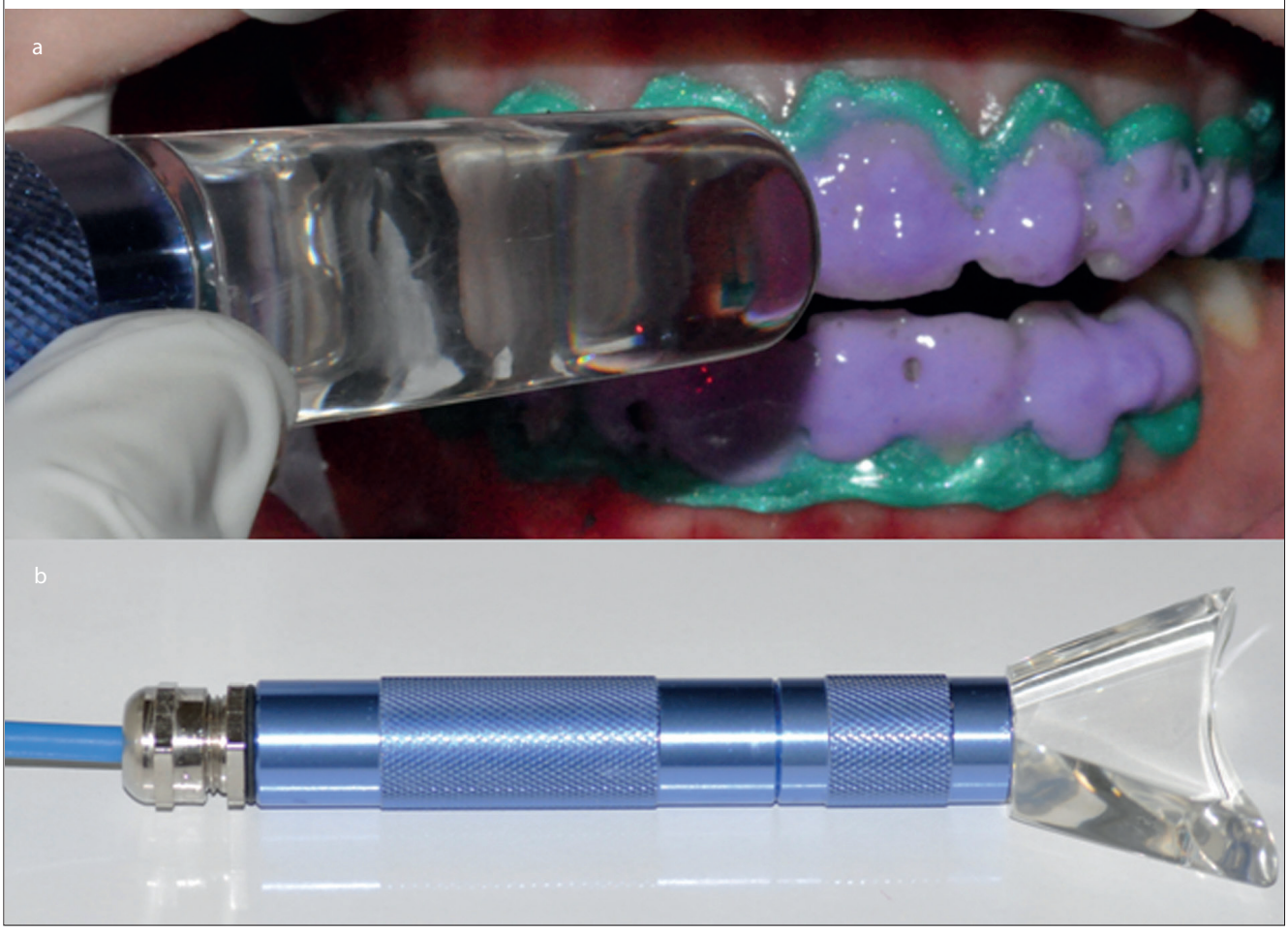


Figure 3. a, b. (a) Ozone generator device; (b) Intra-oral application of ozone for bleaching (Devices in Figures belong to Archive of Gaziantep University School Medicine - used with permission)

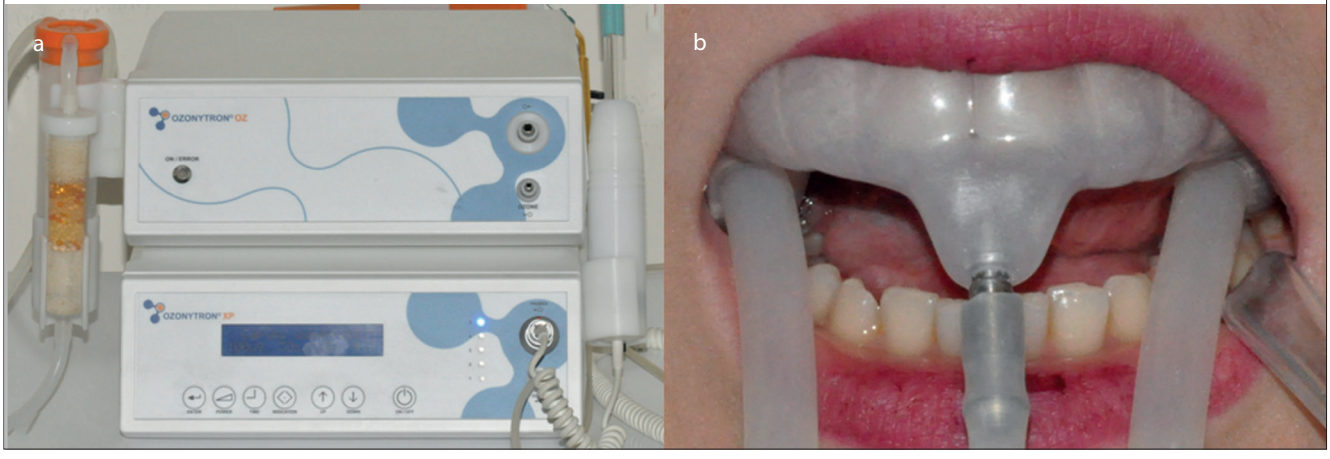


Figure 4. Graphic representing pre- and post-op mineralization levels at the four periods

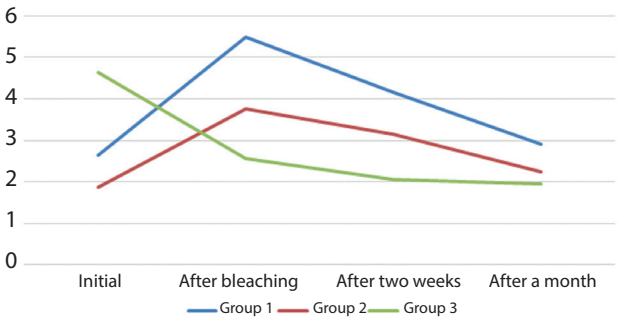


Table 1. Distribution of mineralization values following different bleaching methods

Groups	Measurement time	Mean±standard deviation
Group 1	Initial	2.65±0.18[a]
	After bleaching	5.48±0.85[b]
	After 2 weeks	4.15±0.22[b]
	After a month	2.91±0.18[a]
Group 2	Initial	1.87±0.17[a]
	After bleaching	3.75±0.35[b]
	After 2 weeks	3.15±0.21[b]
	After a month	2.25 ±0.19[a]
Group 3	Initial	4.63±0.41[a]
	After bleaching	2.56±0.33[b]
	After 2 weeks	2.05±0.13[b]
	After a month	1.96±0.1[b]

Different superscript lowercase letters indicate statistical difference for intra–group comparison

ozone-releasing machine (Ozonytyron XP-OZ MIO international, Munich, Germany) was attached to the custom tray, and ozone was applied to the external surfaces of teeth by using a special setting for bleaching (600.000 ppm). Ozone was applied to each arch for 15 minutes twice (Figure 3).

The second, third, and fourth measurements were performed just after bleaching, at the 2-weeks recall and at 1-month recall, respectively, by using the DIAGNOdent pen. The differences of values at each measurement with the initial measurement were recorded.

Statistical Analysis

Data were shown as the median, interquartile range, or frequency and percentage. Prior to statistical analysis, the normality of data was analyzed with the Shaphiro–Wilk test. Due to the non-normal distribution of the data, statistical analysis was performed using the Kruskal–Wallis one-way analysis of variance followed by the Mann–Whitney U test. The Kruskal–Wallis and Mann–Whitney U tests were used to compare the variables within the groups. (intergroup comparisons were not performed) A p-value <0.05 was considered statistically significant. The analysis was performed using the Statistical Package for the Social Sciences program version 19 (SPSS IBM Corp.; Armonk, NY, USA).

RESULTS

Mean values obtained for each group and time intervals are presented in Table 1 and graphically presented in Figure 4.

Both the chemical and laser-activated treatment (Groups 1 and 2) resulted in significant demineralization following bleaching and at the 2-weeks follow-up ($p<0.05$). However, values were similar to the initial values at the 1-month follow-up ($p>0.05$).

In the ozone group (Group 3), the samples showed significant remineralization following bleaching ($p<0.05$). Values at each follow-up visit were statistically similar ($p>0.05$). Ozone did not lead to any demineralization.

DISCUSSION

Bleaching is a cosmetic dental application that has gained popularity in recent years. Several materials and techniques have been used for this purpose. HP is one of most preferred bleaching agents. It owes its whitening effect to the oxidation reaction that destroys discoloring molecules (11).

The by-products generated following oxidation of HP can easily penetrate to enamel and dentin (12). However, the exact mechanism of bleaching with HP has not been fully understood yet because the question as to which inorganic or organic phases of the dentin and enamel are affected has not been clearly answered. On the other hand, this HP mechanism of action to is also suspected to cause some damage to dental hard tissues. Demineralization is a process that involves the loss of calcium ions in the surface of calcified dental tissues (13). A previous study by Rotstein et al. (14) revealed that 10% carbamide peroxide and 30% HP resulted in a significant reduction in the calcium-to-phosphorous ratio of dentin and caused mineral loss following bleaching. However, another study found that HP does not affect the inorganic phase and that it only destructs the organic components (11). According to the results of our study, HP-utilizing bleaching protocols (Groups 1 and 2) represented a significant decrease in the degree of the mineralization of enamel (15). Considering the results of the previous studies, we assume that this is correlated with the change in the inorganic enamel content. However, the mineralization level returned to a value close to the initial 1 month later. This is probably related to the saliva remineralization effect (16). In other words, it seems that the demineralization caused by HP is reversible. Nevertheless, dietary habits and oral care should be attended by patients during this temporary phase because of the tendency of cavities development. Potočnik et al. (17) reported that bleaching agents may lead to microstructural damages on the enamel surface

such as initial cavity lesions. Demineralization of the outer enamel means the reduction of enamel microhardness, which makes teeth less resistant to cavities (3).

Bistey et al. (4) reported that demineralization following teeth bleaching is directly proportional with the time of application and concentration of the agent. In the present study, HP was used at a concentration of 35%, which is commonly used for a bleaching treatment at a range between 35% and 40%. Duration of chemical bleaching for such agents is approximately 45 minutes according to the manufacturers' recommendations. Furthermore, the activation of chemical agents with lasers is performed to lessen the duration of treatment (18). However, in the laser-activated group (Group 2) of the present study, although HP was applied for 15 minutes less than the chemical bleaching group (Group 1), the results of both groups were similar in terms of demineralization values. This may be related with the action of mechanism during the activation of bleaching materials with a laser, which accelerates the formation of free oxygen radicals. Although this lessens the duration of the bleaching treatment, the amount of free oxygen radicals is similar to chemical bleaching alone (19). This may explain why both groups revealed a similar degree of demineralization. However, both groups returned to similar values compared to the initial ones. Justino et al. (16) reported that a 2 weeks contact with saliva provides enough enamel remineralization following bleaching. In the present study, the time required for remineralization was 1-month. This difference may be related to agents which concentration and duration of application varied.

Various techniques including visual inspection, photographic examination, fluorescent dye uptake, ultraviolet light, and laser fluorescence were used to determine the degree of enamel demineralization (20). In recent years, DIAGNOdent have also been used to detect the mineralization status of dental hard tissues (21). The device gives measurements ranging between 0 and 99. Low values indicate high mineral content, which means that the tooth structure is healthy.

Ozone is another material used in many dental procedures. Particularly, it was employed for bleaching due to its gaseous (O_3) structure (22). The oxidizing ability of ozone breaks down the chromogen molecules similar to HP and thus constitutes an alternative bleaching method (23). Requiring no light activation, lower cost and less irritation are the advantages of bleaching with ozone compared to HP (24). According to the present study results, another advantage of bleaching with ozone seems to be its remineralization effect contrary to HP. This may be related to findings by Valko et al. (25), who reported that different free radicals were produced with two different materials. Ozone produced oxygen radicals, while HP released HO_2 free radicals that are stronger than oxygen radicals. In fact, previous studies found that ozone increases remineralization in accordance with our results (26). Furthermore, Baysan and Lynch reported that ozone removes the proteins from the demineralized regions of the enamel and thus accelerate the penetration of calcium and phosphate ions (27). Furthermore, another study found that ozone provides an alkaline environment and induces remineralization using minerals from saliva (28). These statements may further explain why the ozone group of the present study did not show demineralization, but on contrary, it showed an increased degree of remineralization.

CONCLUSION

Within the limitations of this study, it was concluded that bleaching with ozone seems to be a safe bleaching method due to its remineralization effect and cavities prevention.

Ethics Committee Approval: The present study was approved by the Ethical Committee of Gaziantep University (2018/140).

Informed Consent: Written informed consents were taken from the patients.

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The author has no conflicts of interest to declare.

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Original Research

The Frequency and Clinical Associations of Interatrial Block among Patients with Heart Failure

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ABSTRACT

Objective: Heart failure is a rising global pandemic. Numerous structural and functional alterations occur within the heart in response to reduced ejection fraction and dilated chambers. The frequency and clinical associates of interatrial block (IAB) among heart failure patients with reduced systolic function were evaluated in this study.

Methods: Patients with heart failure and reduced systolic function (ejection fraction [EF] <50%) were consecutively enrolled in the study. Patients with atrial fibrillation were excluded. In total, 142 patients with sinus rhythm and systolic heart failure were included. Demographic variables and basic echocardiographic variables were recorded. The presence, absence, and degree of IAB were recorded using standard twelve-lead electrocardiography (ECG). A p wave duration of <120 ms was accepted as normal interatrial conduction. If the p-wave duration was ≥120 ms and p-wave morphology was normal in inferior derivations, it was accepted as partial IAB. A combination of a prolonged p-wave duration (≥120 ms) and biphasic p waves (positive and negative) was accepted as advanced IAB. The Kruskal–Wallis test was used to compare the variables and IAB.

Results: In total, 142 patients had heart failure (EF <50%) and sinus rhythm; 79 patients (59%) had normal interatrial conduction, 37 (27.6%) had partial IAB, and 18 (13.4%) had advanced IAB. The total frequency of IAB among patients with heart failure was 38.7%. The presence and degree of IAB were associated with advanced age (p=0.004) but not with the etiology of heart failure (ischemic and nonischemic) and gender of the patients. Also, the degree of systolic impairment, as assessed by EF, was not associated with the degree of IAB (p=0.19). The ECG P-wave duration had a significant correlation with age (p=0.002) and left atrial diameter (p=0.048).

Conclusion: Interatrial block is quite common and independent of the degree of systolic impairment among patients with heart failure. Since the clinical implication is high, frequent monitoring and a close follow-up is necessary in these patients.

Keywords: Heart failure, interatrial block, stroke

INTRODUCTION

The frequency of heart failure is increasing globally (1). An aging population and increased survival after myocardial infarction are the primary reasons for high heart failure rates. Also, transcatheter techniques developed to treat patients with advanced and inoperable valve disease increase survival and prolong life expectancy in patients with heart failure. Despite the ever-growing armamentarium of medical and device-based therapies, the mortality remains unacceptably high (2). Several structural alterations occur in the heart in response to the reduced ejection fraction (EF). Left atrial dilatation and consequent prolongation in interatrial impulse conduction frequently accompany systolic heart failure. An interatrial block (IAB) is defined as a prolonged p-wave duration (≥120 ms) and/or bimodal p waves in the inferior (II, III, and aVF) leads (3). Here, we evaluated the IAB frequency and its associates with clinical variables inheart failure patients with reduced ejection fraction.

METHODS

The ethics committee approved the study prior to patient enrollment (Gaziantep University School of Medicine, no: 348). Patients with systolic heart failure, as evidenced by reduced EF (<50%), were prospectively enrolled. Informed consent was obtained from each patient. Patients with atrial fibrillation were excluded. Standard echocardiographic examinations, including left atrial diameter, left ventricular end-diastolic diameter, and EF, were performed. The electrocardiographic (ECG) measurement was performed using SEMA Workstation 3.8.1 (Schiller AG). The ECG variables were p-wave duration and p-wave morphology in the inferior leads (II, III, and aVF). Based on these variables, patients were divided into three groups: normal interatrial conduction (p-wave<120 ms), partial IAB (p-wave≥120 ms but normal p-wave morphology in the inferior leads), and advanced IAB (p-wave≥120 ms and biphasic p waves in the inferior leads).

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Statistical Analysis

The consistency of the data for normal distribution was tested using the Shapiro–Wilk test. The Mann–Whitney U test was used to compare two groups of variables without normal distribution and Kruskal–Wallis for more than two groups of variables without normal distribution. Spearman rank correlation analysis was used to evaluate the association between numerical variables without normal distribution, and the chi-square test was used to evaluate the association between categorical variables. Numerical variables were represented as mean ± standard deviation and categorical variables as absolute number and percentages. Statistical analyses were performed using the Statistical Package for Social Sciences for Windows version 22.0 (SPSS IBM Corp.; Armonk, NY, USA). A two-sided p value of <0.05 was considered statistically significant.

RESULTS

In total, 106 male (74.6%) and 36 female (25.3%) patients with heart failure and sinus rhythm were included. The mean age of the patients was 64.74±14.28 years. The baseline characteristics of the patients are summarized in Table 1. The etiology of heart failure was ischemic in 100 patients (75.2%) and non-ischemic in 33 patients (24.8%). Based on the pwave analysis in ECG, 79 patients had normal interatrial conduction (59%), 37 had partial IAB (27.6%), and 18 had advanced IAB (13.4%). The total frequency of any degree of IAB was 41%. A sample ECG from one of the patients with advanced IAB is demonstrated in Figure 1. Also, Figure 2 is a magnified view of Figure 1, which clearly demonstrates biphasic P waves. The presence and degree of IAB were not associated with EF or left atrial diameter. However, there was a strong correlation between age and IAB. Compared to the patients with normal interatrial conduction, partial and advanced IAB were more frequent among older patients. The mean age of the patients with normal, partial, and advanced IAB was 61.22±14.26, 68.11±11.72, and 70.22±12.51 years, respectively (p=0.004). The results of the

Table 1. Baseline characteristics of the study population

Mean age (years)	64.74±14.28
Gender	Female: 24.8%
	Male: 75.2%
Mean EF (%)	34.89%
Mean p –wave duration (ms)	115.12
Frequency of IAB	Normal interatrial conduction: 59%
	Partial IAB: 27.6%
	Advanced IAB: 13.4%
	Total frequency of any degree of IAB: 41%
Etiology of heart failure	Ischemic: 75.2%
	Nonischemic: 24.8%

EF: ejection fraction; IAB: interatrial block

Figure 1. Standard 12-lead ECG showing sinus rhythm and advanced interatrial block

ECG: electrocardiography

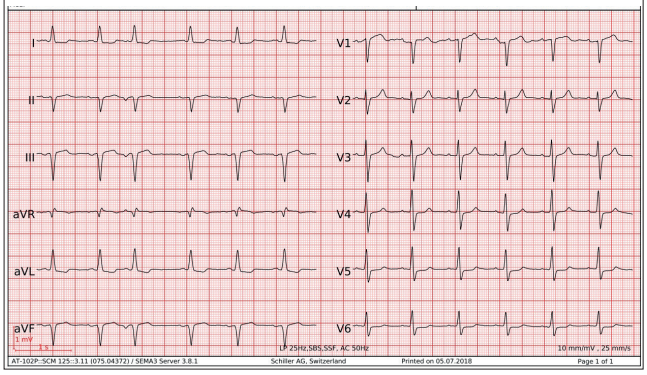

Figure 2. Zoomed view of Figure 1 shows prolonged and biphasic p waves in derivations II (top) and III (bottom)

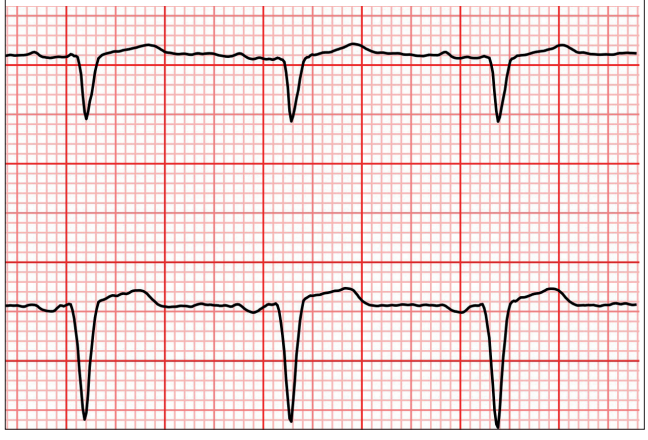

Table 2. Results of the correlation analysis

Variables	IAB Absent	Partial IAB (n=37)	Advanced IAB (n=18)	p
EF (%)	35.99±8.48	33.54±8.65	31.78±11.17	0.194
Age (years)	61.22±14.26	68.11±11.72	70.22±12.51	0.004
LA diameter (mm)	39.56±5.2	41.54±5.93	41±5.73	0.224
LVEDD (mm)	55.34±6.94	58.35±8.37	59.12±9.14	0.135
p–wave duration (ms)	103.87±12.46	130.35±9.77	133±13.14	0.001

EF: ejection fraction; LA: left atrium; LVEDD: left ventricle end–diastolic diameter; IAB: interatrial block

correlation analysis are summarized in Table 2. The etiology of heart failure (ischemic or nonischemic) was not associated with the presence and degree of IAB. Also, gender was not associated with interatrial conduction. The duration of atrial depolarization (electrocardiographic p-wave duration) was not associated with the severity of heart failure (EF) but showed a strong positive correlation with p-wave duration and age (p=0.002). Also, there was a positive correlation between left atrial diameter and p-wave duration (p=0.048). The p-wave duration was not correlated with the etiology of heart failure and gender.

DISCUSSION

Results of this study reveal a significant positive correlation between the presence and degree of IAB and age. Also, a positive correlation between the electrocardiographic p-wave duration and age and left atrial diameter was observed.

Heart failure is a complex clinical syndrome that affects all the systems of the body. In addition to the effects on the other organ systems, reduced systolic function results in a multitude of structural and functional changes to the heart. Increased left ventricular enddiastolic pressure results in increased left atrial pressure, leading to left atrial dilatation. Left atrial dilatation results in derangements in impulse conduction within the atria, there by increasing the p-wave duration seen in the ECG, and atrial fibrillation will develop in advanced cases. Escobar-Robledo et al. (4) demonstrated that in patients with heart failure, advanced IAB was associated with an increased risk of stroke. O'Neal et al. (5) revealed that the incidence rate of ischemic stroke was two-fold higher among patients with advanced IAB compared to those without advanced IAB. Cotter et al. (6) evaluated the incidence of atrial fibrillation among patients who received loop recorder implantation for evaluating unexplained stroke. The authors showed that the frequency of atrial fibrillation was 25.5%, and IAB was significantly more prevalent among patients with atrial fibrillation compared to those without atrial fibrillation. In another study, Cotter et al. (7) evaluated younger patients (<55 years of age) with cryptogenic stroke. They found that young patients with unexplained stroke had longer Pwave durations and a greater prevalence of IAB.

Abdellah and El-Nagary (8) evaluated the prevalence of IAB and its clinical correlations in patients with systolic heart failure (EF <50%) similar to this study. The prevalence of IAB was 57.3% in their study, which was close to the current findings. The authors also noted that patients with IAB had increased rate of hospitalizations and mortality.

The association of IAB with the development of atrial fibrillation after ablation for the atrial flutter was evaluated by Enriquez et al. (9). Patients were followed up after ablation for atrial flutter, and it was found that those with advanced IAB after the ablation had the highest risk of developing atrial fibrillation in the follow-up period.

The most robust association was between age and the presence and degree of IAB. Our results showed that as the population of heart failure ages, the frequency and degree of IAB also increase (p=0.004). Boccanelli et al. (10) evaluated the frequency and predictive value of IAB for atrial fibrillation among elderly patients. They found that the frequency of IAB was 25.5% among the elderly patients (aged 65–84 years). Also, the crude rate of atrial fibrillation incidence was significantly higher among patients with IAB compared to those without IAB (13.1 per 1000 person-years vs. 8.5 per 1000 person-years, p=0.0394). Bernal et al. (11) evaluated elderly patients (≥75 years of age) with acute myocardial infarction. Baseline ECG was evaluated, and after 1 year of follow-up, mortality and the incidence of atrial fibrillation were higher among patients with advanced IAB. Furthermore, the prevalence of frailty was higher among patients with advanced IAB.

As the most important predictor of survival among patients with heart failure, left ventricular EF (LVEF) did not correlate with the presence and degree of IAB. Escobar-Robledo et al. (4) also did not find any interaction between IAB and LVEF among patients with heart failure. These findings suggest that interatrial conduction is not associated with the degree of systolic dysfunction.

CONCLUSION

There is a high prevalence of IAB among patients with heart failure. Also, IAB was strongly associated with aging.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Gaziantep University School of Medicine (no: 348).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The author has no conflicts of interest to declare.

Financial Disclosure: The author declared that this study has received no financial support.

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Original Research

A New Predictor for Patients with Cardiac Implantable Electronic Device in Iatrogenic Pneumothorax: The Clavicle Length Index

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ABSTRACT

Objective: Pneumothorax (PTX) is a complication that occurs while placing cardiac implantable electronic devices (CIED) in the thorax. In the literature, no clear relationship has been identified between the patient's anatomic structure and the occurrence of PTX. We aim to investigate whether there is a relationship between PTX and anatomic structure in patients with CIED.

Methods: We retrospectively included 1602 patients in whom CIED had been placed for any reason between June 2008 and June 2018. The proximal clavicle tip, middle point, distal tip, and angulus mandible were marked and distances between these points were measured. The ratio between body mass index (BMI) and clavicle length was obtained (clavicle length index).

Results: We included 1568 (97.8%) patients without PTX and 34 (2.2%) patients with PTX in our study. The length of the clavicle and the distance between angulus mandible and clavicle middle point, angulus mandible, and clavicle distal tip significantly decreased, while the clavicle length index (CLI) significantly increased in PTX patients. The distance between angulus mandible and clavicle distal tip (OR: 0.811) and CLI (OR: 8.014) were determined to be independent predictors for pneumothorax. When the cut-off value for CLI was taken as 1.67, it was observed that PTX was predicted with 70% sensitivity and 62% specificity.

Conclusion: The operator can predict the PTX in the patient by measuring the length of the clavicle and the BMI.

Keywords: Cardiac device, clavicle, length index, pneumothorax

INTRODUCTION

Recently, cardiac implantable electronic devices (CIED) have been widely used in some cardiac arrhythmic diseases (1, 2). Although the positive effects of these devices on prolonging human life cannot be questioned, to a certain extent they do have some complications and risks (3). Some of these can threaten life unless a timely diagnosis is made. Pneumothorax (PTX) comes first among these complications (4, 5). A rate of 0.2–3.7% for PTX was reported following the placement of CEID in the literature (3-6). PTX can develop according to the patient, operator, or operational procedure (4). A patient being elderly and/or female and an operator having less experience are some risk factors. Besides, venous intervention (axillary, subclavian, or cut-down), ultrasound-guided intervention, or intervention with venography are also identified as risk factors (7).

In pneumothorax, the procedural and operator-related factors can be canceled out almost completely in experienced, high-volume, and full-capacity centers. Patient-related factors are inevitable and must be taken into consideration before the operation. When the related literature was reviewed, it was seen that data on the anatomy of the patient was very limited although the experience of the operator was mentioned as a risk factor for cardiac device implantation complication; pneumothorax (4-7). The clavicular and mandibular bones in the manubrium and neck region are apparent and easy to measure. We thought that clavicle might have an important role in iatrogenic PTX because of its proximity to both the subclavian vein and apex of the lung. Although BMI is defined as a risk factor in many diseases, there are conflicting data about the relationship between BMI and PTX (8, 9). In this study, we aimed to investigate if there was a relationship between the development of PTX in patients with CIED and clavicle and/or BMI.

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METHODS

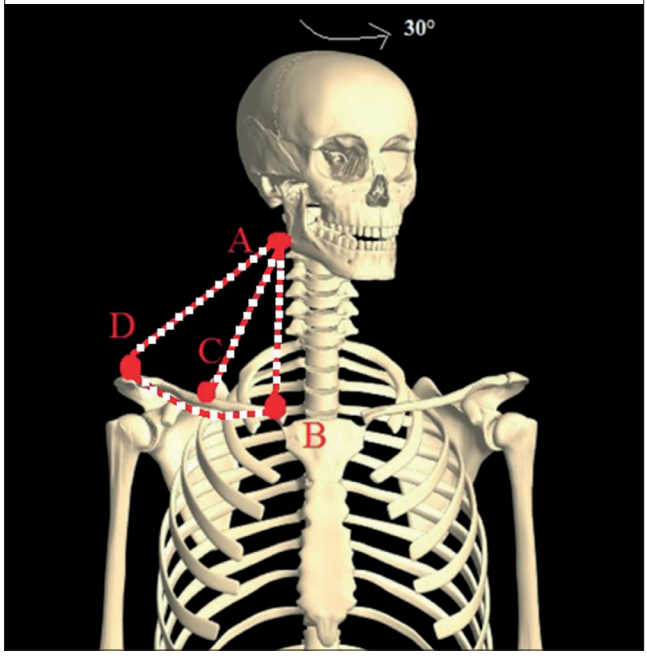
Study Population

We retrospectively included 1602 patients in whom CIED had been placed for any reason between June 2008 and June 2018. We excluded the patients who had chest deformities, had undergone radiotherapy on the chest region or an operation previously. We also excluded the patients in whom a CIED had been placed before or who had an upgraded or revised device due to the possibility of an anatomic change in the subclavian vein. We only included patients with a newly placed CIED. The devices of about 70–80 patients with CIED are controlled in our center every week. Apart from this, the other patients were called and invited to our center. Demographic data of all these patients were recorded. Ethics committee approval was received for this study from the ethics committee of Adana Numune Training and Research Hospital (date: 26.04.2017, no: 59).

Venous Puncture Method

A separate puncture was performed for each lead. Two venous puncture methods, subclavian and axillary, were used by 3 operators with high volume (>100 number/year). A previously described method was used in axillary vein puncture (10). Generally, before forming the device pocket, the skin and subcutaneous tissue were traversed by an 18-gauge needle with an angle of 45° (Cook Medical, Bloomington, IN, USA). The needle was taken forward without going beyond the medial border of the first rib. If the first rib could not be reached, the needle was pulled back close to the first entry point and was redirected with a steeper angle so as to prevent tissue laceration. This procedure was continued under fluoroscopy till it touched the first rib. When the rib was touched, the needle was pulled back slowly by maintaining negative pressure. The injector was pulled back until the venous blood flow was seen through it. If no blood flow was seen, the needle was pulled slightly back and was redirected to an area a few millimeters to the right or left, where upon the same procedure was repeated. When the venous blood flow was seen, the guide wire was advanced forward. The clavicle was divided into 3 imaginary pieces. It was advanced forward from the place where 2/3 of lateral region was intercepted by the first rib under the clavicle with a medial and cranial angle. The sheath was placed by the Seldinger technique. In subclavian venous puncture, the previously described method was used again (11).

Figure 1. Demonstration of anatomical measurement points (A-Angulus mandible, B-Proximal tip of the clavicle, C-Middle point of the clavicle, D-Distal tip of the clavicle)



The Measurement of Anatomical Distances and Pneumothorax Predictor Parameters

Clavicle proximal tip, middle point, and distal tip and angulus mandible were determined. The head was turned to the front with an angle of 90° and to the right with an angle of 30°. Clavicle length (the distance between distal and proximal tip), the distance between the angulus mandible and clavicle proximal tip, and the distances between middle point and distal tip were measured in centimeters (Figure 1). Then, the BMI we had measured before was divided by the clavicle length and a new index was obtained (CLI). All the measurements were recorded by two independent cardiologists.

Evaluation of Pneumothorax Diagnosis

Posterior-anterior (PA) chest radiography was taken routinely after the operation. If aeration deficiency was observed in PA chest radiography, a thorax computed tomography (CT) was performed on the patients. Final PTX diagnosis was established by CT scanning. Then, the patients were sent to the thoracic surgery department for consultation regarding the need for a chest tube. If the PTX area in CT was less than 20%, it was considered to be a small PTX and nasal oxygen therapy was given. Additionally, tube thoracostomy was applied to the symptomatic ones and to those who had more than 20% PTX area.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences for Windows 20.0 (SPSS IBM Corp.; Armonk, NY, USA). Variables were divided into categorical and continuous groups. Categorical variables were expressed as frequencies and percentages and were analyzed using the Chi-square test. The Kolmogorov–Smirnov test was used to determine whether continuous variables had a normal distribution or not. Continuous variables were expressed as mean ± standard deviation. Normally distributed variables were analyzed with independent samples t-test. Non-normal distributed variables were analyzed with the Mann–Whitney U-test. Independent predictors for PTX were determined by the binomial logistic regression analysis using $p<0.05$ variables. Receiver Operating Characteristic (ROC) analysis was used to calculate cut-off, sensitivity, and specificity values of the independent PTX predictors. As mentioned, the SPSS for Windows 20.0 Program was used for statistical analysis. A p-value <0.05 was considered to be statistically significant.

RESULTS

Cohen kappa values were expressed as a percentage that evaluated the inter-observer and intra-observer variability being higher than 95% for all anatomical distances. We included 1568 patients without PTX (average age: 74.4±10.4 years) and 34 patients with PTX (2.2%, average age: 74.4±10.4 years). Only 10 (2.9%) of 34 patients underwent tube thoracotomy. No significant difference was found between the two groups when demographic and procedural data were compared (Table 1). When anatomic distances were compared, it was observed that length of clavicle (p=0.003), distance between angulus mandible and clavicle middle point (p=0.012), and the distance between the angulus mandible and clavicle distal tip (p=0.047) significantly decreased in the patients with PTX, while the CLI of the same patients significantly increased (p<0.001) (Table 2). In the analysis of binomial logistic regression which was done only with the significant variables, it was determined that the distance between angulus mandible and clavicle distal tip (OR: 0.811, CI 95%: 0.692–0.950, p=0.009) and the CLI (OR: 8.014, CI 95%: 2.442–26.302, p<0.001) were the independent predictors for PTX (Table 3). In the analysis of ROC that was performed with the CLI, three cut-off values were defined and the values of sensitivity and specificity were calculated (Figure 2).

Table 1. Comparisons of demographic and procedural findings

	With pneumothorax n=34	Without pneumothorax n=1568	p
Age (years)	73.4±12.1	74.4±10.4	0.637
Male gender, n, %	18 (52.9)	889 (56.7)	0.662
SBP (mmHg)	127.0±11.0	126.2±11.1	0.712
DBP (mmhg)	81.4±6.2	81.5±5.8	0.906
Pulse (beat/minute)	74.2±13.2	75.5±13.1	0.634
BMI (kg/m^2)	25.2±3.2	26.2±2.2	0.078
Smoking, n (%)	6 (17.6)	186 (11.9)	0.304
DM, n (%)	14 (41.2)	658(42.0)	0.927
HT, n (%)	14 (41.2)	165 (38.6)	0.77
HPL, n (%)	2 (5.9)	114 (7.3)	0.757
COPD, n (%)	4 (11.8)	182 (11.6)	0.977
Single lead, n (%)	10 (29.4)	395 (25.2)	0.575
Two leads, n (%)	18 (52.9)	931 (59.4)	0.457
Three leads, n (%)	6 (17.6)	242 (15.4)	0.724
Axiller punction, n (%)	28 (82.4)	1344 (85.7)	0.58
Subclavian punction, n (%)	6 (17.6)	224 (14.3)	0.58
Venography, n (%)	6 (17.6)	180 (11.5)	0.267

COPD: chronic obstructive pulmonary disease, DM: diabetes mellitus, DBP: diastolic blood pressure, HT: hypertension, HPL: hyperlipidemia, SBP: systolic blood pressure

Figure 2. Receiver Operating Characteristic analyses to determine the predictive value of clavicle length index for iatrogenic pneumothorax

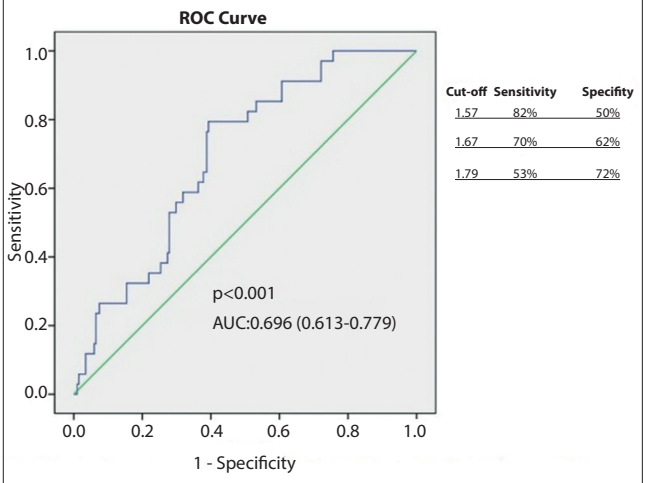


Table 2. Comparison of anatomical distances

	With pneumothorax n=34	Without pneumothorax n=1568	p
Clavicle length (cm)	15.4±1.5	16.4±2.9	0.003
Angulus mandible and clavicula proximal tip (cm)	10.7±1.5	11.2±1.6	0.075
Angulus mandible and clavicle middle point (cm)	5.6±1.0	5.4±0.7	0.012
Angulus mandible and clavicle distal tip (cm)	10.6±2.7	11.6±2.8	0.047
* Clavicle length index (n)	1.83±0.29	1.62±0.32	<0.001

*: body mass index/clavicle length

Table 3. Independent predictors for pneumothorax

	Odds ratio	95% Confidence interval	p
Clavicle length	1.123	0.850–1.484	0.413
Angulus mandible and clavicle middle point	1.457	0.791–2.654	0.227
Angulus mandible and clavicle distal tip	0.811	0.692–0.950	0.009
* Clavicle length index	8.014	2.442–26.302	0.001

*: body mass index/clavicle length

DISCUSSION

Our study is the first to investigate the anatomic quantitative data of patients with PTX. The ratio that is obtained by dividing the BMI by clavicle length is called the CLI (≥1.67), which predicted the occurrence of PTX with 70% sensitivity and 60% specificity. In addition to this, the PTX rate was found to be 2.1%.

The BMI that is accepted all over the world is a predictor for mortality in many diseases (cardiac and non-cardiac). Although the normal range has been defined as 18–25, a change of 1–2 points can be seen in these values across different populations (12).

The clavicle is one of the flat bones of the body. In the intrauterine period, ossification starts in the 5th and 6th weeks and might continue until almost 21 years (13). The subclavian vein which is frequently used for the puncture while placing the cardiac device extends between the first rib and clavicle. Because of its proximity to the subclavian vein and the apex of the lung, the clavicle has a unique role in directing the operator during the procedure. Therefore, it has been thought that a lengthier clavicle is a protector for PTX in patients. Even though the clavicle length is significantly shorter in the patients with PTX in the analysis with one variable, no difference was found in the multivariate analysis. The distance between angulus mandible and clavicle distal tip was determined as an independent predictor for PTX.

The ratio of BMI and clavicle length was also significant in multivariate analysis. We believe that there are two explanations for this relationship. The first one is that the possibility of PTX is lower if the clavicle is long, no matter how overweight the patient is. The second is that extra attention must be paid to the possibility of PTX if the patient's clavicle is short even if the patient's BMI is within the normal range. There are some conflicting results about the relationship between PTX and obesity in previous studies (8, 9). In our study, the BMIs of both groups were found to be similar. It is interesting that obesity, which is an important risk factor in many factors, was not determined as a distinct risk factor for PTX. We believe that clavicle length could be extended in obese patients, which might have protected the patient from PTX. Furthermore, we expected the PTX index that we found to be low in these patients.

In a study by Kotter et al. (14), a large number of patients with CIED were scanned retrospectively. The rate of PTX was reported as 1.7% and it was claimed that the most important predictor was subclavian vein puncture. It was mentioned that PTX was seen significantly less in the use of the axillary vein. In our study, no difference was found in axillary and subclavian punctures in terms of pneumothorax. However, the qualitative value which we described as CLI has a relationship with the clavicle, which is proximate to the subclavian vein. If the operator is experienced, we do not think the vein on which the puncture is made is a significant risk factor for PTX. In our center, no significant difference was found between the subclavian vein and axillary vein puncture by 3 experienced operators, who routinely treat >100 patients/year.

It was reported in two previous studies where a large number of patients were scanned, that there are many risk factors for PTX (4, 5). These are; the female gender, patient age of 80 years or above, chronic obstructive pulmonary disease, inexperienced center, extended operation time, and subclavian vein puncture. It was claimed that the experience of the operator was not a risk factor. Although many of these risk factors were checked in our study, no significant difference was revealed. In this study, multiple data were obtained about the patient, operation procedure, and the experience of the operator. It is important to scan a sufficiently large number of patients. We believe that significant difference in the rate of PTX would have been found if experienced and inexperienced operators had been compared separately as the effect of the experience of the operator on the development of PTX is unquestionable. It is interesting to have found that the experience of the operator is not a risk factor in the conclusion even though such a separation had not been made. We believe that many risk factors listed above can become unimportant in experienced centers.

In a meta-analysis of patients with cardiac implantable devices, it was reported that intervention technique and the place of puncture was not a risk factor for PTX in some selected studies and PTX was seen relatively more in the patients who underwent thoracotomy (6). It can be said that the results of this meta-analysis and our study match each other.

We also concluded in our study that the place of intervention is not a risk factor in experienced hands. It was presented in a studyon patients with CIED that PTX was seen less in the patients in whom a single chamber pacemaker had been placed (15). In our study, no significant relationship was found between the number of leads that were placed and PTX occurrence. Multiple punctures might increase the possibility of PTX but this might be reduced by experienced hands. In a study conducted on patients who received a revised and upgraded CIED, PTX was seen most in cardiac resynchronization therapy-defibrillators and pace upgrade patients. The general rate of occurrence was reported as 0.8% (3). Upgraded patients were not included in our study. A high rate is expected in upgraded patients due to disrupted anatomy. We think that the PTX rate was low as revised patients were also included in this study.

There are some limitations to our study. Since our rates and findings belong to a single high volume center, they might not be instructive in centers with low volume and in inexperienced centers. As the clavicle length is manually measured from the outside, it could be difficult to measure in obese patients. Further multi-center studies are needed to apply the CLI to all the patients in whom a CIED has been placed.

CONCLUSION

CLI is an easy and useful method to predict PTX. Before the CIED is placed, prior information about the risk of pneumothorax can be given to the operator, who can then be guided to be more careful.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Adana Numune Training and Research Hospital (date: 26.04.2017, no: 59).

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.O.D., Y.K.İ., E.D., İ.E.Ö., H.K., F.K., M.K.; Design – A.O.D., Y.K.İ., E.D., İ.E.Ö., H.K., F.K., M.K.; Supervision - A.O.D., Y.K.İ., E.D., İ.E.Ö., H.K., F.K., M.K.; Resources – A.O.D.; Materials – Y.K.İ.; Data Collection and/or Processing – H.K., F.K.; Analysis and/or Interpretation – M.K.; Literature Search – M.K., A.O.D.; Writing Manuscript – A.O.D., Y.K.İ.; Critical Review – M.K.

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Original Research

Significantly Increased Liver Stiffness Detected by ElastPQ Ultrasound Shear Wave Elastography in Patients with Chronic Liver Disease of Over 75 Years of Age: A Cross-Sectional Study

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ABSTRACT

Objective: Aging is associated with worsening of disease severity and poor prognosis in patients with non-alcoholic fatty liver disease (NAFLD), chronic hepatitis B/C (HBV/HCV), alcoholic liver disease, and liver transplantation. The aim of this study was to determine the frequency of liver fibrosis (LF) and its related parameters by calculating the liver stiffness (LS) value in patients having NAFLD and HBV/HCV who were over 75 years of age.

Methods: A total of 120 individuals over 75 years of age were included in our study, according to their liver disease status as having normal liver function (NLF), NAFLD, or HBV/HCV. The LS measurement was performed with the elastography point quantification (ElastPQ) technique. If a patient had an LS value of >7.0 kPa, he or she was was accepted as having LF.

Results: The LS values of patients over 75 years of age with NLF, NAFLD, and HBV/HCV were 4.75±2.34 kPa, 6.45±3.12 kPa, and 8.68±2.76 kPa, respectively. LF was found to be 25%, 40%, and 70% in the NLF, NAFLD, and HBV/HCV groups, respectively. Creatinine and AST levels were independently associated with the LS value. Creatinine, AST values, and liver size were independently determined to be associated with LF; creatinine (0.1 increase), AST (1 increase), and liver size (1 cm decrease) levels were found to increase the LF by 18.4%, 14.6%, and 42.9% respectively.

Conclusion: Patients with NAFLD and HBV/HCV who were over 75 years old had their level of LS determined by liver elastography, which was increased as compared to those with NLF. Patients older than 75 years of age with NAFLD and HBV/HCV also showed significant decrease in LF as compared to NLF patients.

Keywords: Aged, chronic hepatitis B and C, non-alcoholic fatty liver disease

INTRODUCTION

Worldwide socioeconomic developments with advancing medical care and increasing life expectancy have become more prevalent in recent years. This is why the elderly population is increasing globally, especially in developed countries (1). Aging is associated with worsening of disease severity and poor prognosis in patients with non-alcoholic fatty liver disease (NAFLD), chronic viral hepatitis B/C (HBV/HCV), alcoholic liver disease, and liver transplantation (2). The treatment of liver disease in elderly patients is difficult and long-lasting, but more so in patients over 75 years of age, with respect to whom there are problems with data incompetence, existing co-morbid diseases, and involvement in the study. NAFLD and HBV/HCV are associated with impaired liver function and increased liver fibrosis (LF) in such patients (3-5).

Elastography is a newly developed ultrasonography (USG) technique that can measure tissue stiffness and fibrosis development noninvasively and quantitatively. Liver stiffness (LS) measurements have also been made using liver elastography (LE) in patients with NAFLD and HBV/HCV and it has been shown that LF was increased in these patients as compared to the control groups (3-6). To our knowledge, there is no information regarding the changes in LS or LF in patients with NAFLD and HBV/HCV who are over 75 years of age in the current literature. In addition, LS normal range is not even known in individuals who are over 75 years of age and who have a normal liver function (NLF).

The aim of this study was to determine the LF frequency using the LS value in patients over 75 years of age with NAFLD and HBV/HCV, and describe the LF-related parameters in the same

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patients. In addition, we aimed to obtain a normal range of LS values in patients with NLF who were over 75 years of age, in addition to the NAFLD and HBV/HCV patients.

METHODS

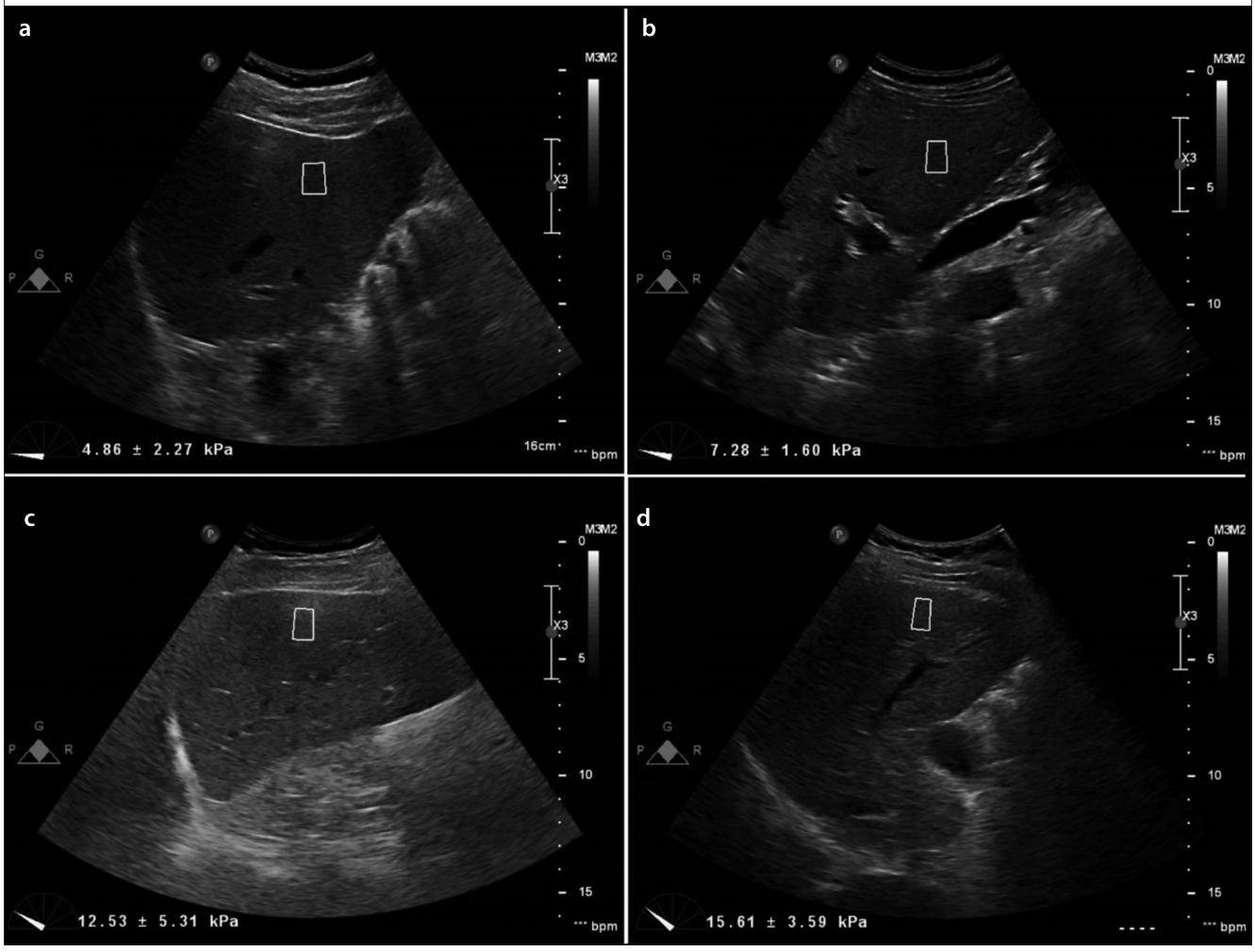
A total of 165 individuals with three different liver disease conditions were screened for this study. Patients were classified and grouped according to the AASLD guidelines for the diagnosis of chronic liver disease (CLD) (7). Patients with known regular alcohol use (>20 gr/day), <18 years of age, hepatocellular carcinoma, cirrhotic status, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≥3 times more than normal, very severe ascites, serious heart valve disease, right or left heart failure, pulmonary or portal hypertension (HT), active thyroid disease, cancer, morbid obesity and/or pregnancy, and HBV or HCV patients who were continuing with their treatment were excluded from the study. Forty-five patients were excluded based on the set criteria and the remaining 120 patients were included in the study. The study included individuals with Group 1: NLF; Group 2: patients with NAFLD, and Group 3: those with a new diagnosis or active HBV/HCV.

Our study subjects were included based on the recommendations of the Biennial Research Helsinki Declaration of Human Subjects and the protocol was approved by the ethics committee of Çukurova University (date: 06.07.2018; no: 2018–79-59). Voluntary consent forms were explained in detail and the patients were included in the study only after the written consent was obtained.

Detailed anamnesis and physical examination were performed and the presence of hypertension (HT), diabetes mellitus, active smoking, hyperlipidemia was assessed, followed by age- and gender-related questioning in all the groups. The systolic blood pressure and diastolic blood pressure were recorded. The body mass index (BMI) was calculated by measuring the patients'weight and height. Fasting blood glucose, blood urea nitrogen, creatinine, AST, ALT, total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and triglyceride levels were measured (Abbott, Aeroset, USA and commercial kits).

Figure 1. a-d. In NLF subjects: normal LS in 4.86±2.27 kPa (a); In NAFLD patients: increased LS in 7.28±1.60 kPa (b); In HBV patients: severely increased LS in 12.53±5.31 kPa (c); In HCV patients: severely increased LS in 15.61±3.59 kPa (d)

NLF: normal liver function; LS: liver stiffness; NAFLD: non-alcoholic fatty liver disease; HBV: hepatitis B virüs; HCV: hepatitis C virüs



All patients underwent liver USG screening using a high-resolution USG device (Philips EPIQ 7, Philips Health Care, Bothell, WA, USA) with a 1–5 MHz high-resolution convex probe (Philips Health Care, Bothell, WA, USA). The liver ultrasound (US) was performed after a minimum initial fasting period of 8 hours with B-mode US on gray-scale, which was used to assess the liver dimensions. LS measurements were performed using the elastography point quantification (ElastPQ) technique, which is a point shear wave elastography (SWE) assessment, with the patient being in the lateral decubitus position. During the procedure, the subjects were asked to pause breathing for a few seconds to minimize the hepatic movement occurring with respiration. All measurements were made at the end of the inspiration period. After traditional hepatic US images were obtained, the target area was determined and the measurements were performed after positioning the range of imaging (ROI) on the target (Figure 1a-d). The ROI was positioned perpendicular to an area containing no vascular structures or space-occupying lesions. The maximum ROI target distance was 8 cm in our study, with a constant ROI box dimension of 0.5–1 cm. The compression during the imaging was maintained as low as possible to avoid mechanical pressure on the liver. In each subject, 10 valid measurements from different hepatic parenchymal segments were obtained and their average was calculated and the results were expressed in terms of kilopascal (kPa). When the reliability of the measurement was low, the image had a kPa value of 0.00. Based on the value of LS, the subjects were stratified into two groups; as those with or without LF. Using the cut-off values reported in two important recent studies, the LS threshold for the presence of LF was adopted as ≥7 kPa (3, 5). Subjects were evaluated by a single well-experienced radiology specialist for conventional, Doppler, and SWE examinations. The specialist had more than 5 years of experience in SWE studies and had performed at least 500 SWE procedures in a year.

Table 1. Study findings according to liver disease groups

	NLF (n=40)	NAFLD (n=40)	HBV/HCV (n=40)	p
Age (year)	79.1±3.8	78.9±3.2	78.5±3.5	0.732
Sex (male/female)	19/21	12/28	15/25	0.362
Hypertension, n (%)	30 (75%)	24 (0%)	25 (63%)	0.242
Diabetes mellitus, n (%)	10 (25%)	17 (43%)	15 (38%)	0.245
Current smoker, n (%)	4 (10%)	5 (13%)	13 (32%)	0.010
Hyperlipidemia, n (%)	12 (21%)	13 (24%)	17 (31%)	0.277
Systolic blood pressure (mmHg)	130±17	131±17	131±10	0.904
Diastolic blood pressure (mmHg)	77±12	77±8.4	78±5.8	0.854
Body mass index (kg/m^2)	27.6±2.5	27.5±3.5	25.9±3.3	0.030
Fasting plasma glucose (mg/dL)	125±34	142±63	145±48	0.178
Total cholesterol (mg/dL)	184±53	207±60	202±63	0.169
LDL cholesterol (mg/dL)	118±39 β	143±48	133±50	0.041
HDL cholesterol (mg/dL)	47±19	46±13	44±11	0.590
Triglycerides (mg/dL)	141±42	176±90	161±82	0.125
Aspartate aminotransferase (u/L)	22.3±5.8 α, β	26.9±8.4*	33.6±10.6	<0.001
Alanine aminotransferase (u/L)	19.8±5.1 α, β	23.2±7.9*	28.8±9.7	<0.001
Blood urea nitrogen (mg/dL)	40.4±19.7	36.5±15.6	40.8±14.9	0.254
Creatinine (mg/dL)	0.89±0.30	0.98±0.39	0.88±0.30	0.352
Liver size (cm)	13.8±2.1	14.3±1.1*	13.2±1.6	0.013
Liver stiffness (mean±SD) (kPa)	4.75±2.34 α, β	6.45±3.12*	8.68±2.76	
Liver stiffness (median, min– max) (kPa)	5.02 (1.25–9.75)	6.22 (2.20–11.78)	8.39 (4.06–15.62)	<0.001
Liver stiffness >7kPa, n (%)	10 (25%)	16 (40%)	28 (70%)	<0.001

NLF: normal liver function; NAFLD: non-alcoholic fatty liver disease; LDL: low density lipoprotein; HDL: high density lipoprotein; hs-CRP: high sensitive C reactive protein; ACR: albumin creatinine ratio; HBV: hepatitis B virus; HCV: hepatitis C virus

α: the significant association between the NLF group and HBV/HCV group (p<0.05)

β: the significant association between the NLF group and NAFLD group (p<0.05)

*: the significant association between the NAFLD group and HBV/HCV group (p<0.05)

Statistical Analysis

For all analyses, the Statistical Package for the Social Sciences 20.0 statistical software pack (SPSS IBM Corp.; Armonk, NY, USA) was used. The variables were divided into groups: categorical and continuous. Continuous variables were expressed as mean ± standard deviation, while categorical variables were expressed as numbers and percentages. Continuous variables that showed normal distribution were compared using the Student's t-test and the ANOVA, whereas the Mann-Whitney U test and the Kruskal-Wallis test were used for samples without normal distribution. For the comparison of categorical variables, the Chi-square test was used. In univariate analyses, a logistic regression analysis was performed to determine the differences between the independent markers among patients with LF. Parameters associated with LS were determined with univariate Pearson's and Spearman's correlation analyses. Statistically significant parameters were included in a linear regression analysis, and the parameters having the closest association with the LS were identified. A p-level of < 0.05 was considered statistically significant.

RESULTS

LS was successfully measured in 96% of all patients over 75 years of age who were screened for LS measurement in the study, out of the total 120 individuals who were evaluated. The study data were compared among 3 groups, classified according to liver function status as NLF, NAFLD, and HBV/HCV.

Table 2. Independent parameters for occurrence of liver fibrosis

	Odds Ratio	95% Confidence Interval	p
Aspartate aminotransferase (each–1 u/L)	1.146	1.079–1.216	<0.001
Liver size (each–1 cm)	0.571	0.404–0.808	0.002
Creatinine (each–0.1 mg/dL)	1.184	1.009–1.389	0.039

Table 3. The parameters associated with liver stiffness measurements

	Univariate analysis		Multivariate analysis	
	p	r	p	β
Blood urea nitrogen (mg/dL)	0.010	0.235	0.619	0.046
Creatinine (mg/dL)	<0.001	0.365	0.003	0.187
Aspartate aminotransferase (u/L)	<0.001	0.743	<0.001	0.695
Alanine aminotransferase (u/L)	<0.001	0.625	0.444	0.071
Liver size (cm)	0.022	–0.257	0.459	–0.069

$R^2_{Adjusted}$ = 0.571 in multivariate analysis

Table 4. Normal limiting values in studies with different measurement methods and evaluation of liver stiffness according to age and sex

	Our study	Ling et al. (10)	Huang et al. (12)	Sırlı et al. (14)	Popescu et al. (15)	Kim et al. (16)
Total number of subjects (n)	40	175	502	82	76	69
Mean age	79.1±3.8	35±10.5	37.9±15.5	26 (18–76)	34.5±14.3	38.9±11.9
Maximum age groups	≥75 years	>50 years	≥60 years	≥60 years	≥71 years	≥50 years
Patents in older (n)	40	16	62	5	5	16
LS value (mean or median)	4.75±2.34 kPa	3.60±0.5 kPa	5.10±1.02 kPa	6.0±1.3 kPa	1.15±0.21 m/s	4.6±0.5 kPa
LS value in older patient	4.75±2.34 kPa	4.3±1.3 kPa	5.35±0.89 kPa	–	1.21±0.21 m/s	4.8±0.7 kPa
LS value in men	5.0±2.37 kPa	3.8±0.7 kPa	5.45±1.02 kPaα	6.6±1.5 kPaα	1.16±0.21 m/s	4.6±0.5 kPa
LS value in women	4.15±2.24 kPa	3.5±0.4 kPa	4.89±0.96 kPa	5.7±1.3 kPa	1.14±0.22 m/s	4.5±0.5 kPa
LE technique	ElastPQ	ElastPQ	SWE	ARFI	ARFI	TE
Failed measurement rate	4%	0%	1.4%	10.9%	7.4%	2.7%
Study time (year)	2018	2013	2014	2013	2011	2009

LS: liver stiffness; LE: liver elastography; SWE: shear wave elastography; ARFI: acoustic radiation force impulse; TE: transient elastography
α: a significant association between the men and women group (p<0.05)

The HBV/HCV group had a higher smoking rate and a lower BMI value than the other 2 groups (Table 1). The LDL cholesterol level was the highest in the NAFLD group and was significantly different between this group and the NLF group. Serum levels of AST and ALT were different among the 3 groups, and it was found that the lowest level was in the NLF group and the highest in the HBV/HCV group. It was found that there was a statistically significant difference between all the groups (Table 1). LS values were 4.75±2.34 kPa, 6.45±3.12 kPa, and 8.68±2.76 kPa in the NLF, NAFLD, and HBV/HCV groups, respectively (Table 1, Figure 2). Median and IQR values of NLF were 4.75±2.34 kPa and 5.02 kPa (1.25–9.75 kPa), respectively. In the NLF, NAFLD and HBV/HCV groups included in the study, LF was found to be 25%, 40% and 70%, respectively (LS ≥7 kPa) (Table 1). LS value was found to be the highest and lowest in the HBV/HCV groups and NFL, and statistically significant between only these two groups (Table 1).

Figure 2. Liver stiffness values of the study groups according to liver disease status.

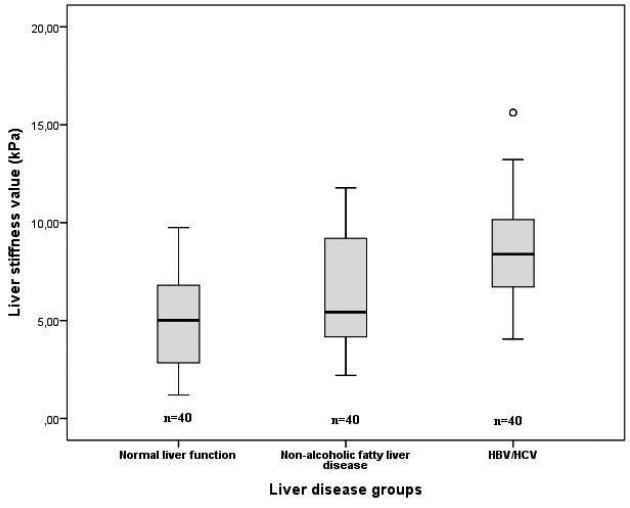
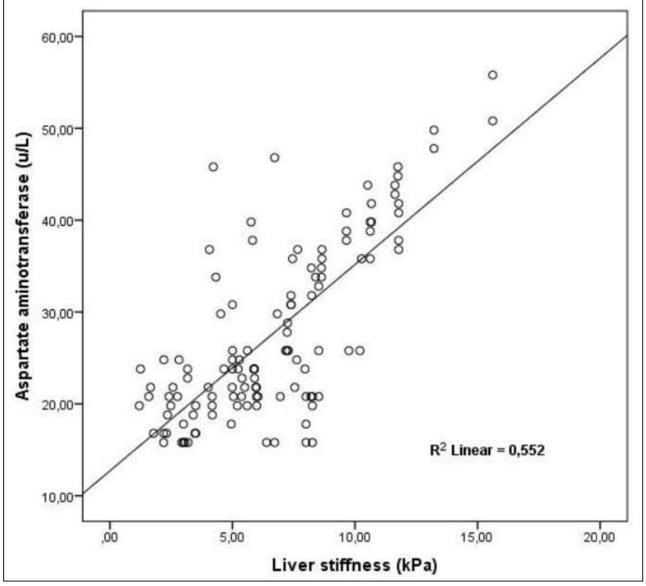


Figure 3. There is a significant correlation between liver stiffness and AST levels.

AST: Aspartate aminotransferase



The 3 parameters associated with LF in univariate analysis were evaluated by multivariate logistic regression analysis. Creatinine, AST, and liver size values were independently determined to be indicative for LF (Table 2). According to this analysis, it was found that creatinine (0.1 increase), AST (1 increase), and liver size (1 cm decrease) increased LF by 18.4%, 14.6%, and 42.9%, respectively (Table 2).

The laboratory and USG parameters associated with LS in the univariate analysis are summarized in Table 3. Linear regression analysis was performed with these LS-related parameters (Table 3). Creatinine and AST levels were found to be independently associated with LS (Table 3, Figure 3).

DISCUSSION

The main finding of this study is that the LS value obtained with the ElastPQ technique was significantly higher in patients with CLD (≥75 years old) with NAFLD and HBV/HCV than in those with NLF. We found that LS values and incidence of LF were increased in patients over 75 years of age as compared to patients under 75 years of age. In patients over 75 years of age, LE was performed using ElastPQ technique, and successful LS measurement was performed in 96% of all patients. Another important finding was that the development of LF increased the serum creatinine, whereas the AST levels and decreased liver size values are independently associated in patients over 75 years of age.

While aging reduces the blood flow to the liver, volume of the liver, and albumin production, it increases the levels of LDL, HDL, and total cholesterol (2). The aging process also decreases the mitochondrial function at the cellular level and increases oxidative stress and inflammation, all of which enhance the susceptibility of hepatocyte injuries (8). In older people with CLD, LF is higher and age is an important risk factor for fibrosis in elderly patients with HCV (9). However, this issue is still a matter of research, and there is no clear and objective data present as yet about LS and LF in patients over 75 years of age. In our study, we tried to find the answer to this question. We objectively found an increase in LS and associated LF in patients over 75 years of age who had CLD, but did not perform invasive and cellular evaluation.

To assess the liver fattiness and fibrosis levels, biochemical markers such as AST and ALT or liver USG could be used. Regardless, liver biopsy remains the gold standard for this purpose. However, liver biopsy is an invasive procedure and complications can occur, so it is rarely used. Liver USG is a non-invasive, inexpensive, and easily accessible assay that can be used in detecting fatty liver and fibrosis. For the last 10 years, the LF assessment with LE method has had critical importance and is known to provide clearer and more objective information. LS values detected in LE studies have been shown to be closely related to biopsy-detected fibrosis (4-6). Our study used a high resolution USG device and the ElastPQ technique (one of the point SWE reviews) us-

ing state-of-the-art technology. The most important feature of the ElastPQ technique, along with the different LE measurement methods, is its ease of use, high accuracy of measurement, and high power to predict any liver pathology (6, 10-12).

In a recently published review, it was reported that the most common non-invasive method used in LF evaluation is LS measurement by transient elastography (13). However, non-invasive serum fibrosis markers have also been shown to be associated with LF. It was shown that SWE examination was superior to these studies due to both instantaneous changes in laboratory parameters and technical limitations of transient elastography (13). In the literature, it was not possible to obtain information on the evaluation of the group of patients ≥75 years in these ElastPQ trials that were conducted on a limited number of LF patients. In our study, the LS value obtained with the ElastPQ technique was found to be significantly higher in the elderly (≥75 years) patient group with or without liver disease. LS normal values are known to range from 3.2–5.10 kPa in healthy controls with NLF (10-16). Although these normal values have been shown to increase with age with no statistical significance, there is no information on normal values in patients of ≥75 years. In our study, the LS value obtained with the ElastPQ technique was found to be 4.75±2.34 kPa in patients of ≥75 years of age with NLF for the first time. We were informed about the results obtained from previous studies and the increase in the LS of NLF in patients of over 75 years of age, since these patients have no comparable data for LS in the literature.

In a recent study by Petta et al. (17), NAFLD fibrosis score and Fibrosis-4 (FIB-4) were closely associated with LF in the non-invasive evaluation of LS. LS was reported to be of the highest sensitivity and the highest negative predictive value. In our study, except LS and histological evaluation, other non-invasive fibrosis parameters were not evaluated. The most important reason for this was the fact that LS evaluation was superior to other non-invasive parameters in previous studies.

The age and gender groups and LS values obtained by our study and those obtained with different measurement methods in previous literature are shown in Table 4. Ling et al. (10) used the ElastPQ technique, which is the same method as our study, to investigate the LS change with age and sex in 175 healthy individuals. It was reported that LS value was higher (4.3±1.3 kPa) in the elderly patient group, but this finding was not statistically significant because of the relatively few numbers of patients (only 16 patients were over 50 years of age). Patients with an older age group who were included in the study (≥75 years of age) using the same method showed an LS value that was 0.5 kPa higher than the previous study.

NAFLD and HBV/HCV are the most common causes of CLD that are associated with impaired liver function and elevated LF (4-6). NAFLD is the most important cause of liver disease worldwide and NAFLD is present in 1 of 4 patients on average (18). Other important causes of liver disease are HBV and HCV diseases. Chronic viral hepatitis is also affected by increasing age. It has been shown that LF is greater in HCV patients who are ≥40 years of age (9). The most important parameter in the progression of both diseases is the presence and degree of LF, as the case in all liver diseases. Many studies on NAFLD have reported that 7.0 kPa can be used as a limit value in LF evaluation (F stage≥2), although different methods have been used (18). Wong et al. (19) found that ≥7.0, ≥8.7, and ≥10.3 kPa could be used as limiting values for fibrosis grade at the F2 stage, F3 stage, and F4 stage, respectively. Similarly, in HBV/HCV patients, cut-off values of approximately 7.0 kPa have been reported to be associated with LS and LF (5, 6). Only in patients with chronic viral hepatitis, a study with ElastPQ technique reported a lower LS value than the TE, with 5.7 kPa and 6.9 kPa, respectively (11). Very recently, a study by Mare et al. (5) that evaluated HBV/HCV patients with the ElastPQ technique reported that the value of 7.2 kPa independently predicted the presence of LF. The mean value of LS in this study is much higher than our study because cirrhotic patients were also included in the study. For this reason, it cannot be compared with our study. In 2018, Ferraioli et al. (3) used the ElastPQ technique for LS measurement in a study that used a similar patient group as our study; with 664 CLD patients in 4 centers (HBV/HCV patient ratio: 74.6% and NAFLD ratio: 5%). The mean age of the patients in this study was 54.8±13.5 years. The results obtained with the kPa and ElastPQ technique were reported to be 7.53 kPa (5.8–17.8 kPa) for median and IQR values, respectively. In our study, patients had a mean LS value of 7.57±3.16 kPa, 6.45±3.12 kPa and 8.68±2.76 kPa in all patients, in HBV/HCV patients, and NAFLD patients, respectively. In the CLD cases, the median and IQR were found to be 7.58 kPa (2.20–15.62 kPa), respectively. This value is very similar to the previous study. It should be noted that the present study was conducted with an equal number of NAFL and HBV/HCV patients; to avoid obtaining ≥8.0 kPa values, which would have occurred if our study would have been conducted with the patient rates from the study of Ferraioli et al. (3). In another recent study published in 2018, Conti et al. (4) performed LS measurements using the ElastPQ technique, which included a 361 CLD patients (NAFLD and HBV/HCV included). The mean age of the patients in this study was 51±17 years and the obtained values were lower than previous studies. The median LS value obtained with ElastPQ was 5.0 kPa, and the measurement of the failure rate was 1%. Also, for the first time in the present study, the limit value for LF was used as 6.2 kPa, and the LF ratio was reported to be 18.8%.

The most important limitation of our study is that our study data have not been confirmed with liver biopsy because it was an invasive procedure. Further, magnetic resonance imaging was not used in our study because it was expensive. If these tests had been done, we would have obtained more objective results. Our study would have been more meaningful if patients of ≥75 years of age were compared with a different group of patients who were <75 years of age, or if LS measurements were performed within a 5–10-year follow-up period. Recent studies have indicated that patients with pre-diabetes had significantly higher LS as compared to normal glucose metabolism subjects (20). We did not evaluate the presence of pre-diabetes in the patients included in our study. In 2016, 9 noninvasive fibrosis tests including LS values that were obtained with transient elastography were compared (BARD, which was the sum of three variables; BMI

≥28=1 point, AST/ALT ratio≥0.8=2 points, diabetes=1 point; the NAFLD fibrosis score; Fibrometer NAFLD; AST/platelet ratio index (APRI); FIB-4; FibroTest; Hepascore; FibroMeterV2G; and LS) (21). LS was reported to be the most accurate noninvasive fibrosis assessment to detect LF (21). Therefore, we used only LS examination in our study.

CONCLUSION

Our study is the first study to evaluate LS value in patients with and without liver disease over 75 years of age. As in patients aged <75 years, LF is exacerbated with increasing age and LS should be planned following the develpoment of LF in these patients. LE is an inexpensive, noninvasive, reproducible USG, which is measurable in a short amount of time, as less as <5 minutes in most centers. This test can, therefore, be used in the evaluation of LS and associated LF in patients of ≥75 years of age. People with LS of ≥7 kPa should be closely followed-up and treated.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Çukurova University (date: 06.07.2018; no: 2018–79-59).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – D.D.; Design – D.D.; Supervision – D.D.; Resources – D.D.; Materials – D.D., H.E.S.; Data Collection and/or Processing – D.D., H.E.S.; Analysis and/or Interpretation – D.D., H.E.S.; Literature Search – D.D., H.E.S.; Writing Manuscript – D.D.; Critical Review – D.D.

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

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Case Report

Features of Monostotic Fibrous Dysplasia in Maxilla using Cone Beam Computed Tomography

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ABSTRACT

Fibrous dysplasia (FD) is a benign nonneoplastic bone disorder in which fibrous tissue replaces normal bone. It is a genetic non-inherited condition caused by a mutation in the GNAS1 gene and is characterized by abnormal proliferation of fibrous tissue interspersed with normal or immature bone. FD causes esthetic disfigurement and loss of function when the maxillo-mandibular region is affected. A dental practitioner can be the first to detect such conditions. We reported a case of a 28-year-old male, with a history of swelling of the left side of the maxilla for 20 years. The present report highlights the clinical, radiographic, and histopathologic features of this condition along with a review of past literature.

Keywords: Cone-beam computed tomography, fibrous dysplasia, maxilla

INTRODUCTION

Fibro-osseous lesions are a diverse group of diseases that are characterized by the replacement of normal bone by fibrous connective tissue. These lesions result from the abnormal development of bone-forming mesenchyme (1). Fibrous dysplasia (FD) is a benign fibro-osseous lesion of unknown etiology, uncertain pathogenesis, and diverse histopathology. It comprises of 2-5% of all bone pathologies. It can be classified as monostotic and polyostotic FD (2). The most common form is the monostotic FD that comprises 70-80% of the lesions (3). The femur, tibia, ribs and facial bones are the most commonly involved structures. The craniofacial bones are involved in 40-60% of the cases (4). We hereby report a case of FD presenting as a swelling of the left maxilla.

CASE PRESENTATION

The patient provided consent for the case report. A 28-year-old male reported to the outpatient department with a chief complaint of swelling in the upper left back region of the face for 20 years. He had noticed the swelling 20 years ago, which was smaller in size at the time but gradually progressed to the present size with associated facial asymmetry. He reported that there was no history of trauma to the region and no history of pain or any associated discharge. The patient had consulted a local doctor for the same but records of the previous visit were unavailable. The medical and dental history was noncontributory.

On extra-oral examination, mild facial asymmetry was detected on the left middle one-third of the face with an ill-defined swelling anteroposteriorly extending from the left ala of the nose to the tragus, and 1 cm below from the left lower eyelid to the ala-tragus line superoinferiorly. The swelling was approximately 4x4 cm in size and was non-tender and bony hard on palpation. No abnormality was associated with the overlying skin (Figure 1a). Intra-oral examination revealed a diffuse swelling in the left maxilla region, extending from the distal aspect of maxillary left lateral incisor to the maxillary tuberosity anteroposteriorly. Expansion of the alveolus and obliteration of the buccal vestibule was noted. The maxillary left first premolar was decayed (Figure 1b, c).

Based on the history and clinical findings, a provisional diagnosis of FD was considered with a differential diagnosis of ossifying fibroma. Intra-oral periapical radiograph revealed loss of lamina dura, narrowing of the periodontal ligament space, altered trabecular pattern with ground glass appearance in the region of maxillary left first premolar to the second molar. Radiolucencies involving the enamel, dentin, and pulp were also noticed concerning maxillary left first premolar, with the bulbous appearance of the apical one-third of the root and an ill-defined periapical radiolucency suggestive of a periapical abscess (Figure 2a). Expansion of the buccal cortical plate was appreciated

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in a lateral occlusal radiograph (Figure 2b). A panoramic radiograph revealed altered trabecular pattern with ground glass appearance from maxillary left lateral incisor to maxillary left third molar region, with obliteration of the floor of the maxillary sinus (Figure 3). CBCT was done to evaluate the extent of the lesion and showed the presence of a homogeneous radiopacity in the left maxilla extending from the midline till the left zygoma with the involvement of the maxillary sinus and expansion of the alveolar process (Figure 4a-c).

The patient's serum alkaline phosphatase level was within normal limits (130 IU/L). The histopathological examination revealed the formation of numerous immature woven bone cells showing a trabecular and curvilinear pattern, with fibro-cellular connective tissue seen interspersed between them (Figure 5). These features were compatible with the clinical diagnosis of FD. The patient was referred to the oral and maxillofacial surgeon for surgical recontouring of the left maxillary alveolus. Root canal therapy was advised for the maxillary left first premolar.

Figure 1. a-c. Clinical photograph of the patient. (a) Extra-oral photograph of the patient showing swelling of the middle one-third of the face, (b) Intra-oral photograph of the patient showing diffused swelling in the left maxillary region, (c) Intra-oral photograph of the patient showing diffused swelling in the left maxillary region (palatal view)

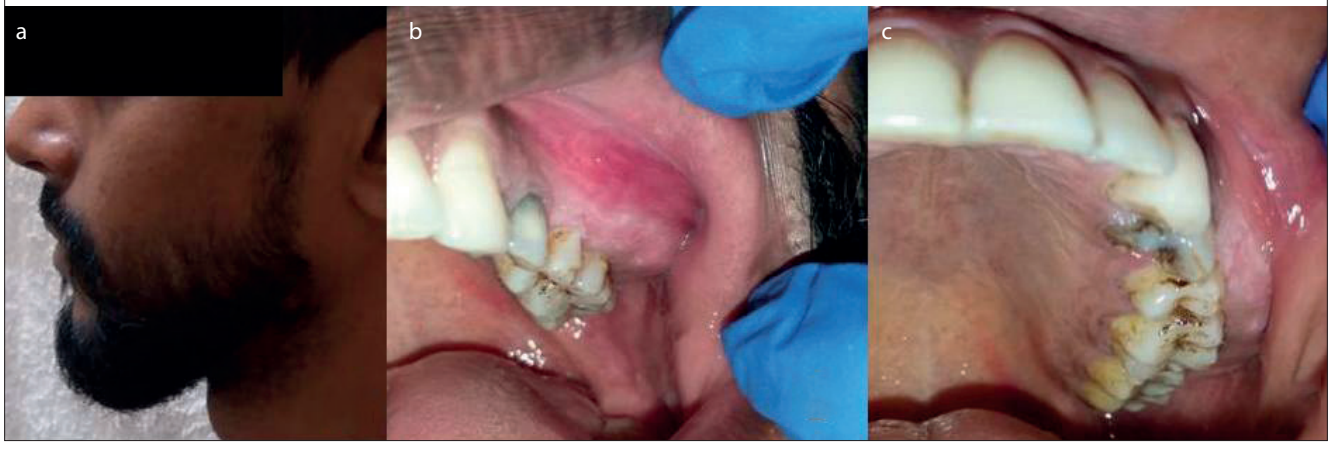
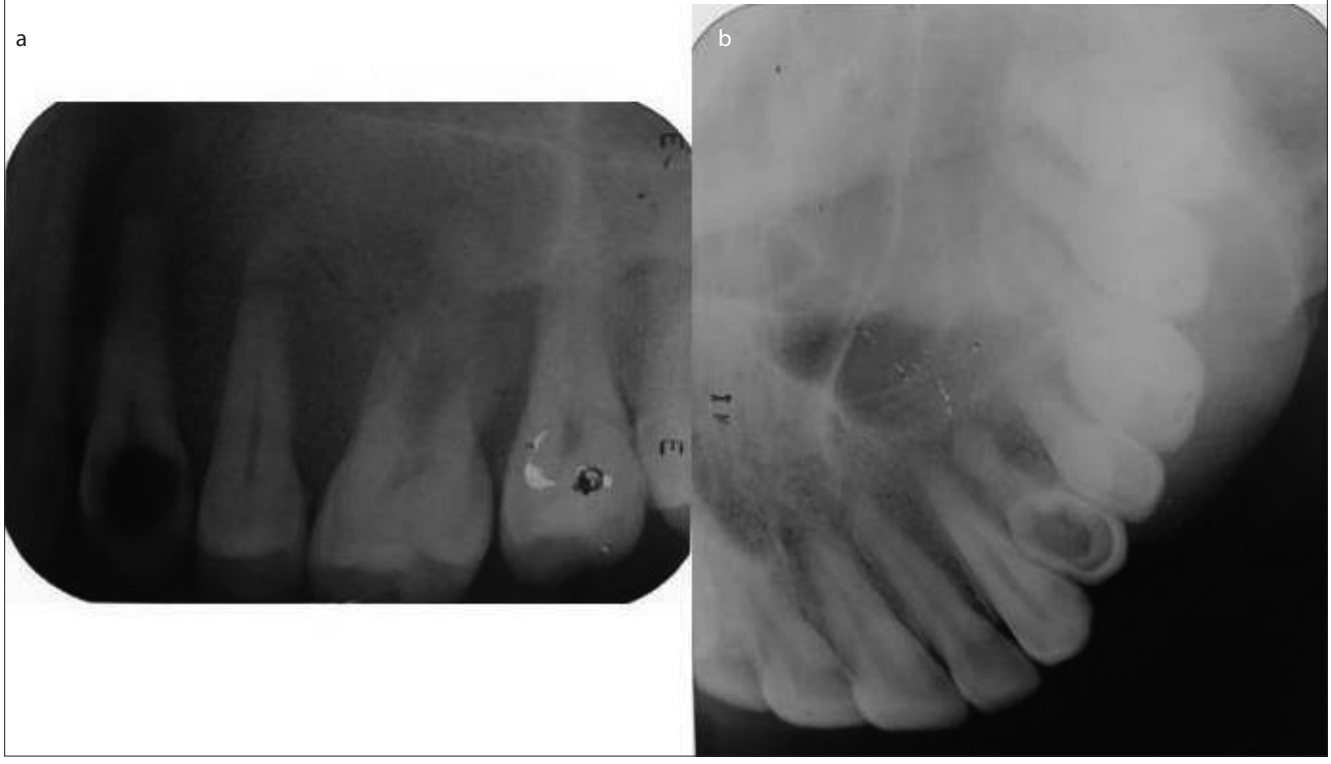


Figure 2. a, b. Intra-oral periapical radiograph (IOPA) and left lateral maxillary occlusal radiograph. (a) IOPA showing an altered trabecular pattern with ground glass appearance along with caries and periapical pathology for maxillary left first premolar, (b) Left lateral occlusal radiograph showing expansion of the buccal cortical plate



DISCUSSION

Fibrous dysplasia is a nonneoplastic condition caused by mutations of the GNAS-1 gene that results in the inhibition of differentiation and proliferation of bone-forming cells. This leads to the replacement of normal bone by fibrous tissue and woven bone (5). The incidence varies from 1:4000 to 1:10,000 (6). It was initially called "osteitis fibrosa generalisata" by Van Recklinghausen in 1891 and was renamed "fibrous dysplasia" by Lichenstein in 1938 (7). The disease is classified into three forms: monostotic, polyostotic, and craniofacial.

The monostotic form comprises about 80% of these lesions, mostly seen in the second and third decade of life. Involvement of facial bones is seen in 10-27% of cases of monostotic FD (6). It is a self-limiting condition in most cases and reaches a state of dormancy by adolescence. Monostotic FD has a predilection for males and affects the maxilla more frequently than the mandible. It manifests clinically as a slow-growing painless mass, leading to facial asymmetry, as seen in the present case. Headache is one of the common symptoms associated with FD when it involves the maxilla, the orbit, and the sinus (5). The patient can develop other symptoms due to the growth of the mass and the compression of the adjacent structures. Hypertelorism, visual impairment, and blindness are seen in association with orbital involvement. Symptoms of neuralgia and sinusitis may also be present (8).

Malocclusion and facial disfigurement is a common feature associated with FD. Other associated dental disorders are enamel hypoplasia, dentin dysplasia, taurodontic pulp, odontoma, tooth displacement, and high caries index (9). In our patient, decay involving pulp and the associated periapical abscess was noticed for the maxillary left first premolar.

Fibrous dysplasia shows a vast variety of radiographic appearances, which depends on the stage of diagnosis of the lesion. The most common manifestations include ground glass appearance, chalky pattern, and cystic pattern (10). The present case showed

Figure 3. Panoramic radiograph showing an altered trabecular pattern with ground glass appearance from maxillary left lateral incisor to maxillary left third molar region, with obliteration of the floor of the maxillary sinus

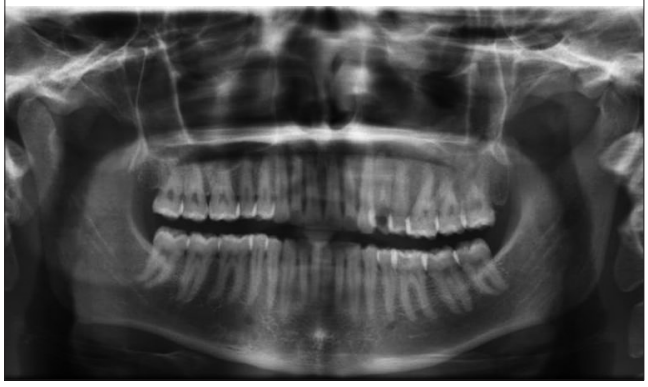


Figure 5. Histopathological picture showing the formation of numerous immature woven bone cells in a trabecular and curvilinear pattern

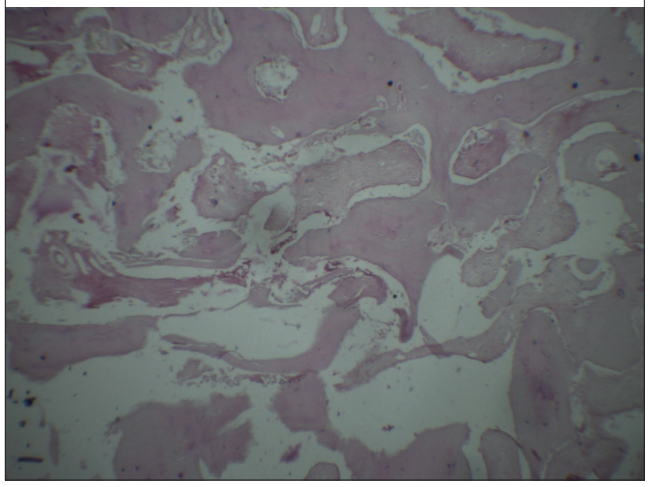
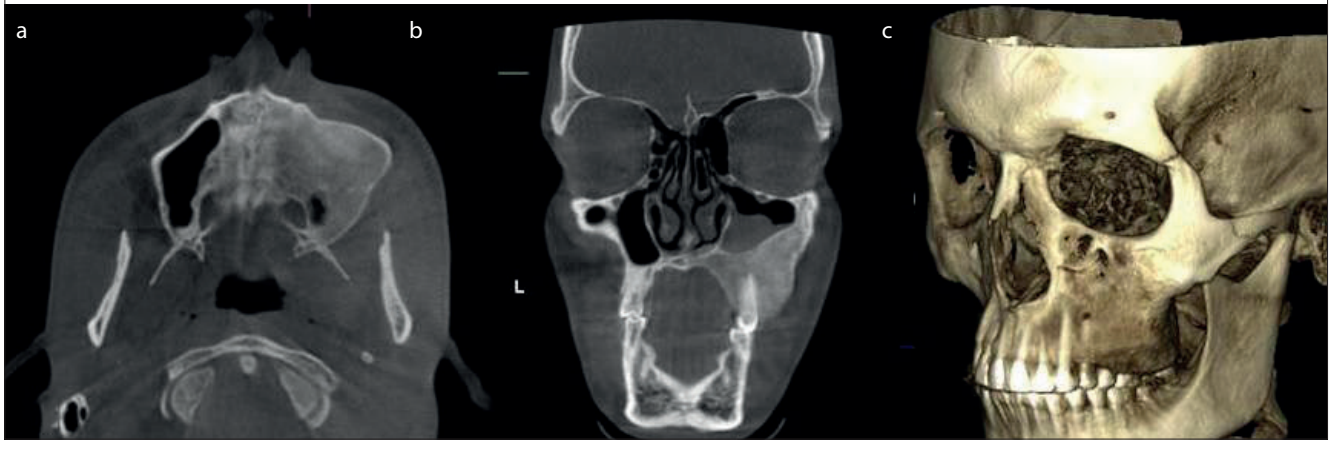


Figure 4. a-c. Cone beam computed tomography (a: axial section, b: coronal section, c: 3D reconstruction) showing the presence of a homogeneous radiopacity in the left maxilla extending from the midline anteriorly till the left zygoma posteriorly with the involvement of the maxillary sinus superiorly and expansion of the alveolar process



the presence of ill-defined radiopacity with the characteristic ground glass appearance in conventional imaging. CBCT helps to evaluate the extent of the lesions. The radiographic features of FD are not pathognomic (9). Histopathological examination is considered as the gold standard, which shows the presence of low to moderate cellular fibrous stroma surrounding irregular trabeculae of woven bone, commonly referred to Chinese letter characters. Osteoblastic rimming is characteristically absent (11).

Laboratory investigations include the estimation of serum calcium and alkaline phosphatase levels which can be elevated in certain cases (8). The present case showed normal serum alkaline phosphatase level.

Management of patients with FD involving maxilla and mandible who require dental extractions, dental implants, root canal therapy, and orthodontic therapy is challenging for the dentist, but it is possible to carry out routine dental care in FD patients. However, research and evidence are needed to address issues such as healing after tooth extraction, aggravation of FD lesion after surgical treatment, and successful orthodontic therapy due to poor quality of bone. Further research in patients with FD involving maxilla and mandible regarding the above-mentioned issues can help in better understanding of treatment outcomes (9).

Treatment modalities of FD vary according to the area of involvement of the craniofacial skeleton, function, and esthetics. Surgical approaches for skeletal deformities include two types: conservative and radical. Conservative method includes osseous contouring, which has to be performed periodically until the lesion achieves a static phase. Radical therapy includes the complete excision of the lesion with reconstruction (12). Medical management with the help of bisphosphonate therapy and calcitonin have also been mentioned in the literature (13, 14). The surgical management of FD has a high recurrence rate of 15-20% (15), hence, patients have to be kept on a long-term follow-up schedule.

CONCLUSION

Fibrous dysplasia is a benign lesion that causes esthetic disfigurement and loss of function when the maxillo-mandibular region is affected. A dental practitioner can be the first to detect such conditions. Thorough knowledge and careful clinical and radiographic examinations are required for proper diagnosis and management. Further management of other dental problems in the same region as the FD poses a challenge to dentists. The present report highlights the clinical, radiographic, and histopathologic features of this condition along with a literature review.

Informed Consent: Verbal informed consent was obtained from patient who participated in this case.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.H., D.S.P.; Design – S.R., S.B.; Supervision – S.B., V.A.; Data Collection and/or Processing – S.H., D.S.P.; Analysis and/or Interpretation – V.A., D.S.P.; Literature Search – S.H., S.R.; Writing Manuscript – S.H, D.S.P.; Critical Review – V.A., S.B.; Other – S.R.

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

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Case Report

Munchausen Syndrome: An Adolescent Injuring Her Mother and Herself

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ABSTRACT

Munchausen syndrome is characterized by physical symptoms that are produced by the individual to present as an ill person. Patients in this group may present with various symptoms, such as neurological, hematological, and gastrointestinal problems; this is one of the reasons that make it difficult to diagnose. We report a case of a 16-year-old female patient who was admitted to the Pediatric Surgery Clinic after appendectomy due to abdominal pain, bleeding from the umbilicus, and bulging on the operation zone; laboratory tests performed were found to be in the normal range. On continuation of hemorrhage and doubt that it may be the center of bleeding, the wound area was explored in operating room conditions, but no bleeding center was found. On laboratory examination of the blood sample in the umbilical area, it was determined that the blood was incompatible with the patient, and that she obtained the blood from her mother by an injector. The patient was referred to our Child and Adolescent Psychiatry Clinic. It was learned that the patient had been taking care of her mother and also of housework. The child was getting away from difficult life conditions for a time during hospitalization, and her workload was diminishing. These individuals may apply with an acute disease scenario, which are particularly caused by self-injurious behavior, for which reason they may be exposed to invasive diagnostic procedures. Munchausen syndrome is considered when there is absence of underlying organic pathology.

Keywords: Adolescent health, Munchausen syndrome, psychiatry, psychology

INTRODUCTION

Munchausen syndrome is one of the rare psychiatric disorders that was described by Richard Asher in 1951 and also called "hospital addiction syndrome" (1, 2). This syndrome can also be defined as "artificial disorder" so that the terms "Munchausen syndrome" and "artificial disorder" can be used interchangeably (3). The prevalence of Munchausen syndrome is reported to be 0.3%–0.8%, which is more common in women than in men (4).

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria, artificial disorder is divided into two subgroups: the type of imposed oneself, the individual presents himself/herself to others as ill, impaired, or injured and the other type of imposed on another, the individual presents another individual (victim) to others as ill or injured (5).

This syndrome is characterized by physical and physiological symptoms that are wrongfully produced by the individual to present as an ill person (1, 3). Patients in this group may present with various symptoms, such as neurological, hematological, and gastrointestinal problems; this is one of the reasons that make it difficult to diagnose Munchausen syndrome (6).

We present a case of a 16-year-old adolescent patient with Munchausen syndrome who was referred to our clinic after laparoscopic appendectomy with swelling in the appendectomy zone, abdominal pain, and recurrent umbilical bleeding.

CASE PRESENTATION

A 16-year-old adolescent patient was admitted to the Emergency Service in November 2016 with complaints of abdominal pain, nausea, and vomiting. She was referred to the Pediatric Surgery Department by the Emergency Service. On physical examination and laboratory tests, she was diagnosed with acute appendicitis and hospitalized. She underwent laparoscopic appendectomy on the same day.

On postoperative day 2, there was bleeding from the operation zone. There were no abnormalities in the hemogram, prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR) levels, or other biochemical tests. In addition, the operation area was explored in operating room conditions, and no bleeding center was found. Complaint of bleeding occurred again on day 4 of hospitalization, this time from the umbilical zone. There was no hemor-

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rhage focus as two days previously, and in addition to routine investigations, Factor XIII, Factor VIII, von Willebrand factor, PT, aPTT, and INR levels were within normal limits. The patient was consigned to the Otorhinolaryngology Clinic because of complaints of bleeding from the ear during hospitalization. There was no related pathology.

She was accompanied by her mother who had had a diagnosis of chronic kidney failure for 5 years. During hospitalization at the Pediatric Surgery Clinic, hospital staff noticed that the patient was secretly taking an injector from the hospital inventory. In addition, when the mother's hemodialysis catheter cover was found open with blood leaking to the mother's clothes, hospital staff checked in the patient's room and saw an injector with blood in it under the patient's bed. Laboratory results showed that the blood sample obtained from the patient's abdominal region and the blood found in the injector was not compatible with the patient's blood; it was concluded that the patient was drawing blood from her mother. Thus, the patient was referred to the Child and Adolescent Psychiatry Department. It was learned from the patient that she was staying as the only child at home after her sister married, and that she was taken out of school involuntarily because of her mother's chronic kidney failure; she was taking care of her mother and doing most of the housework. The child was getting away from difficult life conditions for a time during her hospitalization, and her workload was diminishing.

On psychiatric evaluation, the patient met the DSM-5 criteria for major depressive disorder, and sertraline was started at 50 mg/day. Risperidone 1 mg/day was also initiated because of impulsive tendencies, such as self-harming behavior. On follow-up examinations in the Department of Child and Adolescent Psychiatry, the patient was inconsistent in her explanations about the occurrences during her hospitalization and denied the situation. After she was discharged from the Pediatric Surgery Department, she applied repeatedly to the Emergency Department with complaints of umbilical bleeding, swelling, and redness in the operating area, yet there were no abnormalities found in biochemical tests and radiological examinations.

It was noticed that the patient did not use her medication in control examinations performed in the Child and Adolescent Psychiatry Clinic and also obtained secondary benefits due to her illness, especially from her family. In the course of clinical interviews, the patient was not able to regularly visit our clinic's controls, similar to her other referrals in other departments, and discontinued follow-up. Written informed consent was obtained from the patient and her parents.

DISCUSSION

Our patient repeatedly applied to the Emergency Service and Pediatric Surgery clinics with complaints of postoperative bleeding and swelling in the operation area. All organic pathologies that may have caused bleeding including diathesis, postoperative complications, and other causes that may have lead to the patient's complaints were investigated, but no cause was found. In contrast to the other Munchausen cases in the literature, it has been determined in our case that the patient caused harm both to herself and to her mother because of her artificial disorder.

Patients with Munchausen syndrome try to project themselves as a patient by recurrent neurological, hematological, and gastrointestinal symptoms (6). In addition, these individuals may apply with a number of wounds or an acute disease scenario, which are particularly caused by self-injurious behavior, for which reason they may be exposed to invasive diagnostic procedures and treatments (7). Our patient had a similar condition and was exposed to invasive repetitive procedures.

Munchausen syndrome is considered when there is absence of underlying organic pathology, history of many hospitalizations, abnormal shaped lesions, delayed wound healing, presence of recurrent hemorrhage, infections including postoperative period, and unexplained or incoherent disease (4). However, patients generally do not accept psychiatric support because they deny the symptoms of this disorder (8). Similarly, in our case, Munchausen syndrome was considered, and the case was consulted to us. The patient visited the clinic for check-ups at the beginning but did not continue the treatment afterwards.

In Munchausen syndrome, a multidisciplinary approach is important, and the main element in the management of the syndrome should be excluding the organic pathologies and treating it with an empathic approach (2). In the treatment process, treatment approaches directed toward the motivations underlying the individuals' illnesses and those that cause them to do self-harm should take precedence (8). At the same time, the aim of psychotherapy should be to reduce the secondary gains of the disease, to increase the social acceptability of the patient, and to gain socially appropriate behavioral skills (2). However, antidepressant therapy and low-dose antipsychotic therapy can be used in addition to psychotherapy to increase the patient's motivation and decrease self-injurious behavior (9).

CONCLUSION

As a result, Munchausen syndrome is considered when there is absence of underlying organic pathology. Multidisciplinary approach is important, and the main element in the management of the syndrome should be excluding the organic pathologies and treating it with an empathic approach.

Informed Consent: Written informed consent was obtained from the patient and her parents.

Peer-review: Externally peer-reviewed

Author Contributions: Concept – C.G., N.G., M.K., B.H.Ö.; Design – C.G., N.G., M.K., B.H.Ö.; Supervision – C.G., N.G., M.K., B.H.Ö.; Materials – B.H.Ö.; Data Collection and/or Processing – N.G.; Analysis and/or Interpretation – C.G., N.G., M.K., B.H.Ö.; Literature Search – C.G., N.G., M.K., B.H.Ö.; Writing Manuscript – N.G.; Critical Review – C.G.

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Case Report

Congenital Extrahepatic Portosystemic Shunt: Abernethy Malformation Type 2

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ABSTRACT

Abernethy malformation is a vascular congenital anomaly in which extrahepatic portocaval shunts develop. The patient was admitted to the gastroenterology department with complaints of abdominal pain and nausea. Ammonia and bilirubin levels were increased in the laboratory values and other liver function values were normal. The shunt was detected between the inferior vena cava and portal vein by ultrasonography and computed tomography, and the portal vein was hypoplastic. In this case report, we present a male patient diagnosed with Abernethy malformation type 2.

Keywords: Abdominal pain, abernethy malformation, congenital anomaly

INTRODUCTION

Abernethy malformation (AM) with congenital anomaly was defined by John Abernethy in 1973. This malformation is characterized by shunting between the portal vein (PV) and systemic circulation (1, 2). AM is frequently associated with other rare congenital anomalies, including the extrahepatic portocaval shunt, heterotaxy, biliary atresia, and liver nodules (3, 4). AM has been classified into two types on the basis of the pattern of anastomosis between the systemic circulation and PV and the presence of intrahepatic portal venous supply. AM type 1 portosystemic shunt is characterized by complete shunting and absence of a PV. AM type 2 is characterized by partial shunting with a small grade of PV flow to the liver (5). Assessment of the vascular anatomy and liver using new abdominal imaging modalities aids in treatment planning so that patients with AM can receive appropriate treatment. An alternative treatment mode is non-surgical endovascular treatment; if this treatment fails, liver transplant may be considered (5). In this study, we present the case of a male patient who was incidentally diagnosed with AM type 2.

CASE PRESENTATION

A 68-year-old male patient presented to the gastroenterology department with the complaints of abdominal pain and nausea. The patient had no significant personal or family medical history. No pathology except the right upper quadrant sensitivity was found on physical examination. The patient had undergone total gastrectomy for gastric adenocarcinoma 3 months ago. The laboratory test findings were as follows: hemoglobin, 13 g/dL; direct bilirubin, 1.24 µmol/L; indirect bilirubin, 3.70 µmol/L; lactate dehydrogenase, 322 U/L; alanine aminotransferase, 21 U/L; aspartate aminotransferase, 40 U/L; gamma-glutamyl transpeptidase, 32 U/L; alkaline phosphatase, 116 U/L; and prothrombin time, 39.0 s. Serologic test results for hepatitis B and C viruses were negative. Abdominal ultrasonography (USG) showed the presence of an anechoic tubular structure approximately 13 mm in diameter in the liver with no current Doppler signal. Computed tomography (CT) axial sections showed superior contrast enhancement in the right lobe of the liver, suggesting a hemangioma 5 mm in diameter. PV diameter was measured as 5 mm. PV superior mesenteric vein (SMV) and splenic vein junction left renal vein portocaval shunt (Figure 1). Given these radiological findings, a hypoplastic PV with a portocaval shunt (AM type 2) was suspected. Conservative treatment was continued for the patient, and after 1 month, abdominal pain and nausea became mild. At 3-month follow-up, no change was observed on USG. First, the alternative treatment option of non-surgical endovascular treatment should be considered for the patient. If this treatment fails, liver transplant may be considered. Informed consent was taken from the patient before writing this report.

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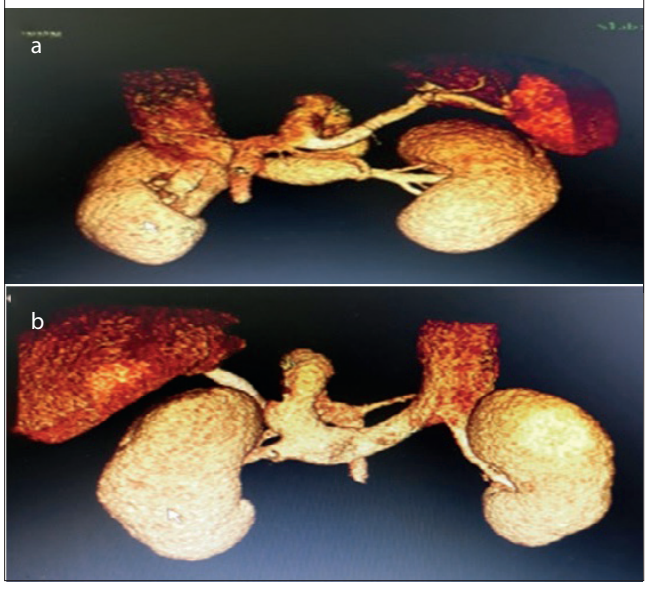
Figure 1. a, b. CT axial sections showed SMV and the splenic vein merging into the left renal vein. PV is thin-walled and hypoplastic

CT: computed tomography; SMV: superior mesenteric vein; PV: portal vein



DISCUSSION

Congenital anomalies and vascular shunt diseases have been reported to occur together (6). AM can be anatomically classified using radiological imaging modalities. AM type 2 portosystemic shunt is characterized by the presence of a patent intrahepatic portal venous supply and a partial shunt (7). Type 1 can be further subclassified into type 1a and type 1b. Type Ia is characterized by separate drainage of SMV and the splenic vein into systemic veins; in type 1b, SMV and the splenic vein join to form a short extrahepatic PV, which drains into a systemic vein. This patient had AM type 2 with a side-to-side portocaval shunt between the left renal vein and the splenic vein. Congenital vascular malformations are frequently associated with congenital anomalies. Other anomalies have also been reported in patients with AM; these include chromosomal anomalies such as Down syndrome and structural anomalies of the cardiac defects, biliary atresia, polysplenia, and situs inversus (8-10). Hepatic shunt can also frequently present with hypoglycemia. This is attributable to the effect of defective glucose uptake and defective insulin secretion due to reduced hepatic degradation of the normal quantity of the secreted insulin (11, 12). AM can now be diagnosed using noninvasive abdominal imaging modalities such as USG, CT, and magnetic resonance imaging (MRI) (13). The imaging findings in patients with AM with hepatocellular carcinoma do not appear to be typical, that is, hypervascularity on the arterial-phase images with washout on delayed phase (14). Patients who do not exhibit typical findings of a benign lesion, i.e., lack of arterial enhancement or arterial enhancement without washout, should be closely followed up. Two groups according to the type of shunt those should be offered shunt closure either interventional embolization or surgical whereas those with type 1 shunts should be liver transplanted (15, 16).

CONCLUSION

Abernethy malformation is a rare congenital vascular malformation that can be diagnosed using abdominal imaging modalities (USG, CT, and MRI). We presented the case of a male who was incidentally diagnosed with AM type 2. Endovascular treatment should be the first-line treatment for this type of AM; if it is not successful, liver transplant should be considered.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

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