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The Cyprus Journal of Medical Sciences (Cyprus J Med Sci) is a peer-reviewed, open access, international publication organ of Cyprus Turkish Medical Association. The Cyprus Journal of Medical Sciences aims to publish manuscripts at the highest clinical and scientific level on all fields of medicine. The journal publishes original papers, review articles, case reports and letters. The journal is printed three times a year in April, August and December. The publication language of the journal is English.

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Original Article

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Video Assisted Thoracic Surgery Outcomes for Primary Spontaneous Pneumothorax, Analysis of 56 Cases, Single University Hospital Experience

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BACKGROUND/AIMS
To evaluate patients with primary spontaneous pneumothorax (PSP) who were treated via the video-assisted thoracic surgery (VATS) procedure by means of clinical features, surgical outcomes, and follow-up results.

MATERIAL and METHODS
We retrospectively analyzed 56 consecutive patients who underwent VATS procedure for PSP between 2012 and 2018. There were 47 male and 9 female patients with a mean age of 26.01±7.4 (18-38) years. VATS was performed under general anesthesia with double lumen intubation. Apical wedge resection and mechanical abrasion or apical pleurectomy was performed in 60% of the patients with uniportal VATS and in 40% of the patients with two portal VATS by the same surgical team.

RESULTS
The operation indications were recurrence in 40 (71.5%) patients, prolonged air leak in 14 (25%), and bilateral pneumothorax in 2 (3.5%). Pleurodesis procedures included upper pleural mechanical abrasion in 44 (78.5%) patients and apical pleurectomy in 12 (22.5%). Bilateral VATS procedure was performed for two patients who had bilateral pneumothorax. The mean operation time, chest tube removal time, and length of hospital stay were 26.04±4.61 (20-45) min, 1.4±0.6 (1-3) days, and 1.7±0.8 (2-4) days, respectively. No significant difference was found between uniportal and biportal VATS or mechanical abrasion and apical pleurectomy groups compared with statistical evaluation with demographic and clinical features and surgical outcomes ($p>0.05$). There was no mortality, and complications occurred in 16 (28.5%) patients. Only 3 (5.3%) recurrence occurred during the mean follow-up period of 48.4±11.4 (9-70) months.

CONCLUSION
Video-assisted thoracic surgery stapled bullectomy for PSP when followed by mechanical pleurodesis is still the gold standard and is a reliable, safe method with a low recurrence rate, complication, length of hospital stay, and quicker recovery time. The formation of new bullae-blebs could be related to continued smoking behavior that can be seen as the main reason for late period recurrences.

Keywords: Pneumothorax, VATS, Recurrence

INTRODUCTION

Primary spontaneous pneumothorax (PSP) is the abnormal accumulation of air into the space between the parietal and the visceral pleura without underlying lung disease; the most commonly suspected reasons are pneumonia and blebs-bullas in the apical lung parenchyma (1, 2). PSP commonly occurs in young, tall, and thin men having high apical pleural negative pressure. The main symptoms are shortness of breath and sudden chest pain. The incidence of PSP is 9/100,000 per year (3). Men are most often affected aged 22 to 26 years old. It is seen <1/5 in females. When detected in a female patient, it should be considered as a rare cause, such as lymphangioleiomyomatosis or catamenial pneumothorax (4). In recent years, the thoracotomy approach is gradually abandoned. The video-assisted thoracic surgery (VATS) method, which is no longer questionable in terms of less pain, treatment success, less length of hospital stay, and less time to return to work, is preferred in all patients.

The aim of the present study was to retrospectively evaluate patients with PSP who were treated via VATS at our clinic between January 2012 and January 2018.

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MATERIAL and METHODS

Fifty-six patients with PSP who were treated and followed up were evaluated retrospectively according to age, gender, smoking, etiology, diagnostic methods, treatment modalities, and recurrence. Patients who had secondary spontaneous pneumothorax and traumatic and iatrogenic pneumothorax; <18 years old; treated conservatively or with awake non-intubated procedures; and with missing data were excluded from our study. VATS was performed under general anesthesia with double lumen intubation. At the beginning and end of the operation, 0.9% isotonic solution was fulfilled to the thorax, and the lung was inflated and carefully inspected for possible air leaks, blebs, and bullae. All patients underwent apical wedge resection and mechanical abrasion or apical pleurectomy with uniportal VATS or two portal VATS (if pleural adhesion was detected) by the same surgical team (Figure 1). Endoscopic staplers with green cartridges (Endo GIA 60 4.8 mm, Covidien Endo GIA Universal Roticulator, Minneapolis, MN, USA) were used for wedge resection, and the upper parietal pleura was mechanically abraded by medical sandpaper or apical pleurectomy (Figure 2). During VATS, pleural adhesions were dissected using electrocautery or blunt dissection, if necessary. All patients were extubated in the operating theater and were followed up in the special care section of our service during the first 16 h. Chest physiotherapy was applied in the early postoperative period. Portable chest X-ray was performed after surgery within hours. Chest tube of the cases with no air leak and fully expanded on chest X-ray was removed. Patients were discharged on the same day or the next day if their expanded lung in PA roentgenogram after the chest tube was removed. All patients were routinely followed up, and the mean follow-up period was 48.4±11.4 (range 9-70) months. Recurrent pneumothorax was defined as a pneumothorax diagnosed by chest X-ray or chest tomography >10 days after the removal of the chest tube. This research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).Written informed consent was obtained from patients who participated in this study.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences program Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM Corp.; Armonk, NY, USA). Data were expressed as mean±SD. Frequencies and percentages were used for categorical variables.

RESULTS

From January 2012 through January 2018, the VATS procedure for PSP was performed in 56 consecutive patients who had a mean age of 26.01±7.4 (18-38) years. There were a total of 9 (16%) female and 47 (84%) male patients. Of the patients, 39 (70%) were treated on the right side, and 17 (30%) were treated on the left side. Among them, 48 (86%) had a history of smoking.

The operation indications were recurrence in 40 (71.5%) patients, prolonged air leak in 14 (25%), and bilateral pneumothorax in 2 (3.5%). The operation procedures included upper pleural mechanical abrasion in 44 (78.5%) patients, apical pleurectomy in 12 (22.5%), and uniportal VATS in 34 (60%) and an additional camera port in 22 (40%). The bilateral VATS procedure was performed in two patients who had bilateral pneumothorax.

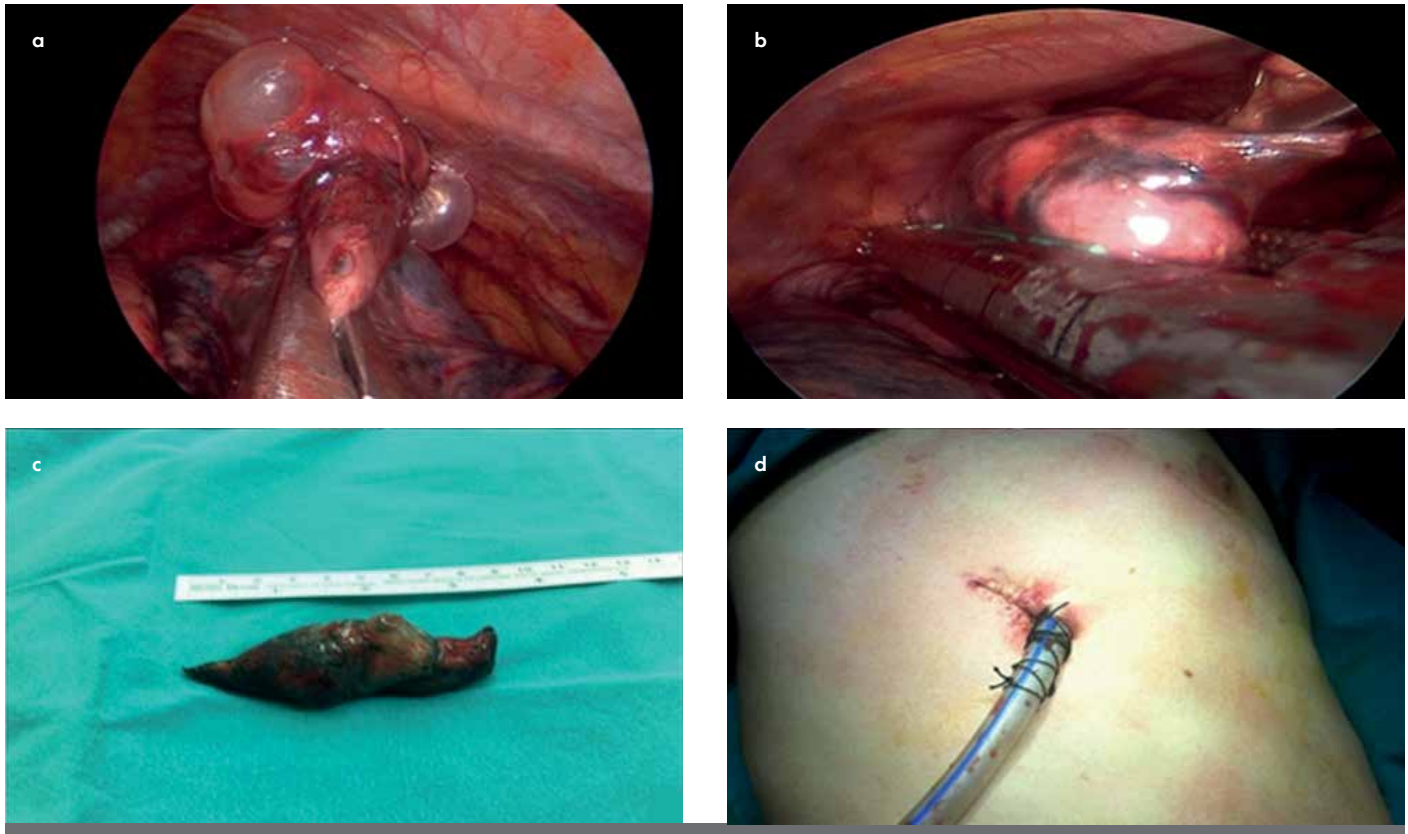

FIGURE 1. a-d. VATS image of bullae in the apical segment of the lung (a). VATS image of performing wedge resection with Endo GIA (b). Macroscopic view of blebs after apical segment wedge resection (c). Incision view of the case performed with uniportal VATS procedure (d)

The mean operation time, chest tube removal time, and length of hospital stay were 26.04±4.61 (20-45) min, 1.4±0.6 (1-3) days, and 1.7±0.8 (2-4) days, respectively. Table I shows the other demographic and clinical data and surgical outcomes. No significant difference was found between uniportal and biportal VATS or mechanical abrasion and apical pleurectomy groups compared with statistical evaluation with demographic and clinical features and surgical outcomes (p>0.05). The mean loss of blood was <100 mL. We found macroscopic blebs or bullae in 50 (89%) patients. The mean of staples used was 2.4±0.6 (1-5). The mean cost of patient's health care system was calculated as US$472.42±56.7.

There were no conversion of VATS to open thoracotomy and intraoperative complications. Subpleural blebs or bullae (emphysema-like changes) were detected as the definitive pathology of all patients.

In 16 (28.5%) patients who developed complication, it was expansion problems in 8 (14.5%), wound infection in 4 (7.5), recurrence in 3 (5.5%), and atelectasis requiring bronchoscopy in 1 (1, 5).

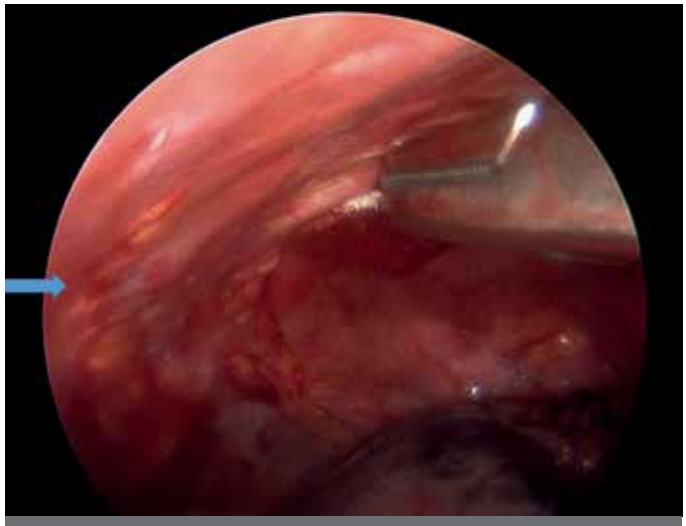

FIGURE 2. Intraoperative VATS view of performing mechanical abrasion of apical pleura with counter sandpaper. Pleural petechiae can be seen, marked with a blue arrow

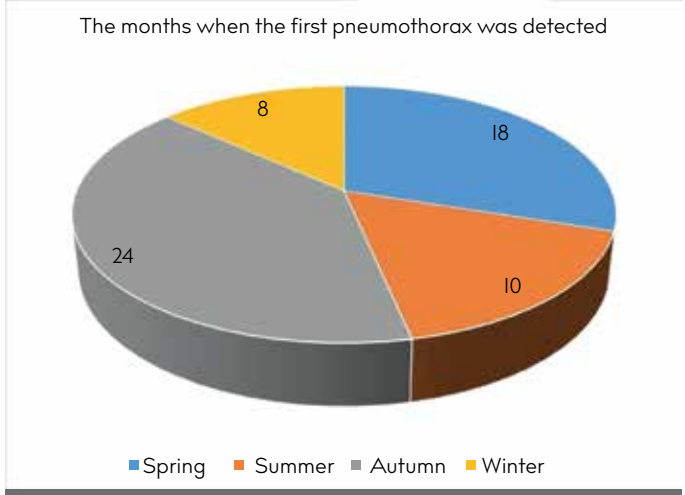

FIGURE 3. Distribution of detected pneumothorax by season

We used an external suction therapy between 20 and 40 cm H_2O in eight patients postoperatively. Air leakage stopped on an average of 3 days. For patients who developed wound infection during admission, intravenous antibiotic was administered. No chronic paresthesia was observed in any patient after >2 months postoperatively.

When patients are classified according to the first pneumothorax attack, 75% of them were in the spring and autumn seasons (Figure 3). The peak time of admission to the hospital was recorded in September (n=10; 17.8%), with the lean time in February (n=2; 3.5%).

The mean follow-up period was 48.4±11.4 (range 9-70) months. Recurrence was seen in 3 (5.3%) patients who continued smoking postoperatively. In two patients, recurrence occurred 2 and 3 years postoperatively, respectively. We performed reoperation with VATS, and the newly formed bullous areas were resected, and pleurectomy was added. Tube thoracostomy was applied after 6 months from the first operation for those who did not have an operation. Only pleural abrasion had been performed in three patients who developed recurrence. Recurrence-free times for 1 year, 2 years, and 6 years were 98.3%, 96.5%, and 94.7%, respectively. Intraoperative or postoperative mortality was not observed.

TABLE I. Demographic and clinical characteristics and surgical outcomes of 56 cases

Sex, n (%)	56 (100)
-Male	47 (84)
-Female	9 (16)
Age, mean±SD (range, years)	26.01±7.4 (18-38)
Mean operation time, mean±SD (range, min)	26.04±4.61 (20-45) min
Mean tube removal time, mean±SD (range, min)	1.4±0.6 (1-3) days
Mean length of hospital time, mean±SD (range, min)	1.7±0.8 (2-4) days
Access of VATS, n (%)	56 (100)
-Right	39 (70)
-Left	17 (30)
Smoking history, n (%)	56 (100)
-Yes	48 (86)
-No	8 (14)
Operation indications, n (%)	56 (100)
Recurrence	40 (71.5)
Prolonged air leak	14 (25)
Bilateral pneumothorax	2 (3.5)
Complications, n (%)	16 (28.5)
-Expansion problems	8 (14.5)
-Wound infection	4 (7.5)
-Recurrence	3 (5.5)
-Atelectasis requiring bronchoscopy	1 (1.5)

SD: standard deviatio; VATS: video-assisted thoracic surgery

DISCUSSION

Pneumothorax, a disease known since ancient times, has been identified with various clinical approaches and treatment modalities. In addition, PSP is one of the most common problems that a thoracic surgeon encounters in daily practice. The rate of recurrence is 20% after the first, 60% second, and 80% third episodes (5). Cardillo et al. (6) reported that the development rate of PSP in healthy smokers is 12%, whereas it is 0.1% in non-smokers. They reported that recurrence usually develops in the first 2 years, and the recurrence rate is 1.73% after VATS procedure. In our study, 84% of our patients were male, and 86% had a smoking history. The recurrence rate after VATS procedure was 5.3% (3/56), and two of the recurrences were detected after 2 years.

The British Society of Thoracic Surgeons guidelines on the management of PSP recommended surgery after the first recurrence (7). Other operation indications are persistent air leakage (>5-7 days), recurrent ipsilateral pneumothorax, prior contralateral pneumothorax, synchronous bilateral pneumothorax, and occupational risk (aircraft personnel, sportsmen, and scuba divers, etc.). The main goal in surgical management is resection of bullae and blebs and apical pleurodesis to prevent recurrence. Conventional open surgical methods can be used for this, and video-assisted operations are also preferred today. In recent years, VATS is considered as the gold standard surgical technique for the treatment of PSP (8, 9).

Minimally invasive techniques have gradually increased in the last 10 years and also in our own clinic. VATS was considered as the gold standard approach in recurrent PSP. Therefore, in the present study, we wanted to compare our own clinical outcomes with the literature. When VATS is compared with open thoracotomy, the recurrence rates are equal. The superiority of VATS has been proven in many studies in terms of less surgery time, less postoperative pain, shorter hospital stay, less impact of immunity, and shorter time to get started. Therefore, nowadays, it can be said that VATS is associated with better clinical outcomes than thoracotomy for three common thoracic procedures: surgery for pneumothorax, minor resections (wedge and segmental resections), and lobectomy (10).

The recurrence rate after pneumothorax operations with VATS is <5%. This rate is approximately 1% of thoracotomy. Early recurrence (before 1 month) may be due to inadequate pleurodesis or parenchymal leakage. In case of a late recurrent period (after 1 month), newly formed blebs and bullae associated with continuing smoking may be responsible. There are also publications that recommend reoperation with VATS and apical pleurectomy in addition to open thoracotomy in recurrences (2, 11-14). In our study, we detected recurrence in 3 (5.3%) patients who continued smoking after VATS procedure. All of them were during the late period, and pleural abrasion had been performed following apical wedge resection. Two patients were reoperated, and apical wedge resection was applied, and pleurectomy was added with VATS. In one patient, tube thoracostomy was performed for denying reoperation.

The recurrence of pneumothorax after VATS surgery is reported to be higher (2%-14%) than that after open thoracotomy (0%-7%). However, this difference is constantly getting smaller with today's VATS techniques (15). Orki et al. (16) reported their retrospective study of videothoracoscopy bulla ablation using electrocoagulation, and that apical pleurectomy is a safe method for recurrence of PSP with a similar recurrence rate of 4.76%. They concluded that electrocoagulation is cost effective with VATS procedure to avoid the use of expensive stapler devices.

There are many studies comparing the uniportal or multiportal performance of VATS technique for PSP. When the uniportal VATS was compared with the traditional three port VATS for PSP, better cosmetic results, shorter hospital stay, less postoperative pain, short recovery time, and more cost effective were found (17, 18). In our study, 60% of the patients underwent uniportal VATS, and reasonable results were obtained regarding length of hospital stay, restore time, and economic parameters consistent throughout the literature. None of our 56 patients had chronic paresthesia after the procedure.

Akyil et al. (19) evaluated the correlation between meteorological conditions and pneumothorax with a total of 1097 patients with PSP in their study. They reported that the peak time of admission to the hospital is recorded in October (n=131; 12%) and in autumn (n=330; 30%). In our study, we found that 75% of the patients' first pneumothorax attack were in the spring and autumn seasons (September: n=10; 17.8%).

Our study has some limitations. First, it is a retrospective study including consecutive patients and is open to selection bias. Second, we use no direct comparison with conservative treatment or other VATS techniques. However, the strength of our study is that we performed a standard VATS procedure in all patients and evaluated from many perspectives related to PSP.

Primary spontaneous pneumothorax, which has been known since ancient times, is still one of the most frequent diseases that thoracic surgeons encounter. In terms of low major complications, low recurrence, short hospital stay, low postoperative paresthesia, and short recovery time, VATS without regard to uniportal or multiportal is still the gold standard and is a safe method for PSP. Mechanical abrasion or apical pleurectomy can be performed with similar success rates. The formation of new bullae-blebs associated with continued smoking behavior can be seen as the main reason for late period recurrences.

Ethics Committee Approval: The authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

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

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Original Article

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The Relationship between Climacteric Symptoms and Thiol/Disulphide Homeostasis

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BACKGROUND/AIMS
The aim of this study was to examine the relationship between the serum thiol-disulfide balance and climacteric symptoms.

MATERIAL and METHODS
A total of 106 women aged 42 to 78 years (53.18±7.39) participated in the study. The patients were divided into three groups as the perimenopausal period, early postmenopausal period, and late postmenopausal period. The climacteric symptoms of patients were assessed with the Greene scale. The serum thiol/disulfide hemostasis was assessed with a new automatic method. The Mann-Whitney U test, one-way analysis of variance, and post-hoc Tukey tests were used.

RESULTS
Native thiol and total thiol levels start decreasing after menopause. Women in the late postmenopausal period have been observed to have significantly lower levels compared to women in the perimenopausal and early postmenopausal periods. In the late postmenopause, perimenopause, and early post menopause, native thiol was measured as 430.81±45.35, 474.64±47.06, 461.22±47.66 ($p<0.05$), while total thiol was 460.22±49.96, 506.74±51.74, 492.25±57.81 ($p<0.05$), respectively. There was a negative correlation observed between vasomotor symptoms and all thiol components only in the early menopause group.

CONCLUSION
When the duration of the menopause exceeds 5 years, thiol levels reduce. This variation may be considered to be related to increasing age. Especially in the early menopausal period, administering antioxidant agents as support may contribute to reducing the vasomotor symptoms of patients.

Keywords: Climacterium, menopause, thiol/disulfide homeostasis, vasomotor symptoms

INTRODUCTION

Menopause is a natural stage in a woman's life. In addition to physical problems of women in the postmenopausal period, they encounter a variety of physiologic, psychologic, and sociologic problems that disrupt the quality of life (1). One of these problems are vasomotor symptoms. The etiology of vasomotor symptoms is not clearly understood. Many studies have shown that vasomotor symptoms do not only disrupt the quality of life linked to estrogen deficiency but are also early indicators of cardiovascular diseases (2-4). As a result, the presence and severity of vasomotor symptoms are important.

Oxidative stress is a situation formed by the antioxidant systems becoming ineffective against free oxygen radicals due to being insufficient (5). Estrogen acts like a typical antioxidant enzyme and has been shown to neutralize free oxygen radicals (6). Reduced estrogen levels in the menopause, and increased age, negatively affect antioxidant capacity (7). Although there are studies showing that disruption of the balance between oxidative stress-antioxidant capacity may

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be effective in determining the development and severity of climacteric symptoms, the results are not clear (8).

The thiol/disulfide (T/D) balance plays a role in many metabolic pathways. The T/D balance has been shown to be disrupted in situations related to the endothelial damage, such as diabetes and preeclampsia (9-11). Among patients with postmenopausal osteoporosis, T/D homeostasis was shown to be disrupted (12).

In this study, we planned to research the correlation between the severity of climacteric symptoms, led by vasomotor symptoms, in the menopausal transition period and postmenopausal period and the correlation of severity of symptoms with the T/D balance. Previous studies researching the correlation of serum T/D balance with climacteric symptoms only studied the thiol component. In our research, we studied all components of the T/D balance with a new automatic method described by Erel et al. (13).

MATERIAL and METHODS

Planned as a cross-sectional study, the research received the necessary permission from the ethics committee of Atatürk Training and Research Hospital. All women signed the consent form for this research. All patients were questioned in detail about demographics, medical and reproductive history, habits, and medication use. The study included 106 women aged 42 to 78 years. The grouping of patients according to menopausal situation used the STRAW staging criteria (14). The perimenopausal group included patients with 2-11 months of amenorrhea, and the early postmenopausal period group included patients with 1-5 years since last period. The late menopausal group included patients with 6 years or more since last period. Patients who did not volunteer, who did not abide by period descriptions, who used exogenous hormones, who entered the menopause surgically, and with chronic diseases that affect oxidative stress, such as diabetes and hypertension, were not included in the study. Anthropomorphic measurements like height and weight were made.

Biochemical Assessment

Patients had serum samples taken after 8 hours of fasting. Samples were stored at -80°C until study. T/D hemostasis was studied with a newly developed automatic method (Roche, cobas 501, Mannheim, Germany) (13).

Climacteric Symptoms

The Greene climacteric scale was used to assess climacteric symptoms (15). This scale comprises 21 questions separately evaluating vasomotor symptoms, anxiety state, depression, psychological state, somatic symptoms, and sexual symptoms. All questions have a 4-degree answer choice ranging from 0 to 3. If the situation does not apply to the patient, 0 points are given, with 1 given for mild severity, 2 for moderate severity, and 3 for severe symptoms. The Greene scale was used to assess climacteric symptoms with total and subgroup scale points.

Statistical Analysis

The Kolmogorov-Smirnov test was used to assess whether the sample abided by normal distribution. To assess differences between the three groups for variables with normal distribution, the one-way analysis of variance and post-hoc Tukey test were used. The Kruskall-Wallis analysis was performed to assess differences between groups for variables without normal distribution. The Mann-Whitney U test was used to show which groups were different for variables with differences. For correlation between thiol and disulfide values with climacteric symptoms, the Pearson analysis was used for parameters with normal distribution, while the Spearman correlation analysis was used for those without normal distribution. Statistical significance was accepted as $p<0.05$.

TABLE I. Comparison of parameters between groups

	Perimenopause (n=40)	Early Postmenopause (n=30)	Late Postmenopause (n=36)
Age	47.30±3.63	51.97±2.98	60.72 ±6.51*
BMI	27.94±5.15	28.67 ±5.20	29.00±5.31
T.Thiol (SH+SS)(µmol/L)	506.74±51.74	492.25±57.81	460.22±49.96*
N.Thiol (SH)(µmol/L)	474.64±47.06	461.22±47.66	430.81±45.35[a]
Disulfide (SS)(µmol/L)	16.00±8.49	17.09±10.74	14.65±8.82
SS/SH (%)	3.39±1.84	3.67±2.16	3.42±2.16
SS/SS+SH (%)	3.10±1.61	3.36±1.84	3.13±1.86
SH/SS+SH (%)	93.78±3.26	93.98±5.67	93.71±3.74
Greene vasomotor subscale	4.03±1.34[a]	2.27±1.55	2.14±1.60
Greene anxiety subscale	6.64±3.73	8.47±4.24[a]	5.97±3.85
Greene psychology subscale	10.72±6.13	14.50±7.15[a]	10.36±6.27
Greene depression subscale	4.10±3.09	6.03±3.55[a]	4.39±3.06
Greene somatic subscale	5.28±3.96	9.27±3.99[a]	6.58±4.03
Greene sexual subscale	0.92±.83[a]	1.53±1.10	1.56±0.93
Greene total score	20.79±8.52	27.23±10.65*	20.19±9.24

*Between all groups $p<0.05$ (Analysis of variance-Tukey)
[a]a group found to be statistically significant from other two groups ($p<0.05$) (Kruskall-Wallis/Mann-Whitney U)
SS: disulfide; SH: native thiol; BMI: body mass index

TABLE 2. Correlation of age and the BMI with parameters in all groups

N=106	Age		BMI	
	r*	p	r*	p
Native thiol (μmol/L)	-0.427	<0.01	-0.262	<0.01
Disulfide (μmol/L)	-0.143	0.14	-0.031	0.74
Total thiol (μmol/L)	-0.442	<0.01	-0.249	0.01

*Spearman correlation coefficient. BMI: body mass index

TABLE 3. Correlation analysis results for thiol/disulfide balance with vasomotor subscale in the early postmenopausal group

n=30	r*	p
Native thiol	-0.376	0.04
Disulfide	-0.392	0.03
Total thiol	-0.394	0.03

*Spearman correlation coefficient

RESULTS

The mean age of the 106 women participating in our study was 53.18±7.39 years. The mean age of patients was highest in the late postmenopause group (60.72±6.51), and this was significant compared to the other groups. The mean body mass index (BMI) for all groups was 28.51±5.19 with no differences between the groups.

Total thiol and native thiol levels reduced as the menopause progressed. The late postmenopausal group had significantly lower levels compared to the other two groups. Disulfide level was highest in the early postmenopausal group, but there was no significant difference observed between the groups.

On the Greene climacteric scale, only vasomotor symptoms were observed to be significantly high in the perimenopause group compared to the other groups ($p<0.05$). Anxiety, psychologic, depression, and somatic and total Greene scores were significantly higher in the early postmenopause group compared to the other groups ($p<0.05$). Comparison of the perimenopausal period with the other two groups observed the highest vasomotor score and lowest sexual score ($p<0.05$). In the late postmenopause group, the sexual subscale score was observed to be significantly higher compared to the other groups ($p<0.05$). Findings are summarized in Table 1.

An analysis of the correlation between age and BMI with T/D components observed significant negative correlations between increasing age and BMI with native thiol and total thiol levels ($p<0.01$). In our study, a correlation analysis was performed on T/D components, and their indices with the Greene scale subgroups. There was no significant correlation observed between parameters for perimenopausal and late postmenopausal women. In the early postmenopausal period, there were significant negative correlations between all components of the T/D balance with vasomotor subscale scores ($p<0.05$). In this group, the index showing D/T thiol ratios was observed to have a negative correlation with vasomotor subscale ($p<0.05$). Correlation analysis data are summarized in Tables 2 and 3.

DISCUSSION

The menopause is a significant physiological condition characterized by the cessation of the menstrual cycle and loss of ovarian functions. In addition to vasomotor symptoms disrupting the quality of life in the menopausal period, it is known to increase the tendency for osteoporosis, diabetes, hypertension, and cardiovascular diseases in the long term. Oxidative conditions constitute major risk factors for the development of a number of pathologies, such as tumor development, diabetes, and cardiovascular complications (16). An abnormal T/D homeostasis state is involved in the pathogenesis of a variety of diseases (13). The plasma thiol levels assessed in our study are a pool formed of albumin and low molecular weight thiols (like glutathione, cysteine). When oxidative stress dominates the environment, the balance shifts to disulfide due to oxidation of the thiol group proteins (17). The reduction of estrogen in the menopausal period is known to be the main factor in vasomotor symptoms. There are publications proposing an association between reduced estrogen and increased oxidative stress markers (18, 19). The estrogen replacement therapy (ERT) in menopausal women nearly completely resolves vasomotor symptoms (20). However, due to conflicting results about ERT increasing thromboembolic events and malignancies like breast cancer, not all patients use it (21). As a result, developing alternative treatments to reduce vasomotor symptoms becomes important. If oxidative stress can be shown to be an effective mechanism on vasomotor symptoms, the use of antioxidant treatment may be considered.

In all groups, there were negative correlations between the age and BMI with native thiol and total thiol levels. The negative effect of increasing age and obesity on antioxidant systems is in accordance with other studies in the literature (22-24).

A study of 245 patients that was researching the correlation between hot flush symptoms, and serum and urine levels of oxidative stress markers such as 8-iso-prostaglandin F2-alpha (PFG2 alpha), 8-hidroxy-deoxyguanosine (8OHDG), thiol, and paraoxanase-1, showed that none of the markers correlated with the severity of vasomotor symptoms. There was no difference identified for the serum and urine levels of any marker between women with and without symptoms (2). In this study, all patients in the perimenopause and early postmenopause were included in a single group, and assessments were only made for the hot flush complaint. In the T/D balance, only the thiol component was studied. In our study, patients were separated into perimenopause, early postmenopause, and late postmenopause groups, and differences were assessed. Our results found that native thiol and total thiol rates were lowest in the late postmenopause, and this difference was significant. Patients in this period were also the oldest patients and were expected to have lowest estrogen levels. As a result, the low native thiol and total

thiol levels in these patients is an expected outcome. Disulfide levels were highest in the early postmenopause; however, the difference was not significant. A correlation analysis observed a negative correlation between the vasomotor subscale and all thiol components only in the early postmenopause group. In the study mentioned above, there was no correlation between vasomotor symptoms and thiol levels. Our patient numbers, design, and methods are different, which may have led to differences in the study results.

Another study assessed the serum total thiol level and found it was lower in postmenopausal women compared to women in the premenopausal and perimenopausal periods (22). In our study, all components of the T/D balance were studied with a new method, with the native thiol, and total thiol components of the T/D balance significantly lower in the late postmenopause. Highest disulfide levels were measured in the early postmenopausal group; however, no significant correlation was observed between the groups. In the late postmenopausal period, native thiol and linked total thiol levels reduce with age and are associated reduced estrogen levels. This complies with our study results.

A study evaluating the antioxidant enzyme capacities of patients found that superoxide dismutase, catalase, and gluthathione peroxidase levels were significantly lower among women in the postmenopausal period compared to the premenopausal group (1). This decrease was emphasized to be associated with reduced estrogen levels. Similarly, in our study results, it was shown that antioxidant capacity reduced as the menopause duration increased.

A study assessing 50 women physiologically in the menopause evaluated the free oxygen radical test and free oxygen radical defense (FORD) of patients. In this study, only the vasomotor subscale was negatively correlated with FORD levels (25). In our study, a negative correlation between all thiol components and vasomotor subscale was only observed in the early premenopause. Differences may be due to differences in the marker characteristics and patient groups studied.

The highest score on the Greene climacteric scale used in the study was in the early postmenopausal period, and this is considered to accompany physiologic changes in the first 5 years of the process. The highest sexual scale was recorded in the late postmenopausal period. It is known that urogenital symptoms increase with the duration of menopause. These findings are expected changes within the menopausal process.

In this assessment, patients had the highest number of vasomotor symptoms in the perimenopausal period, with disulfide levels highest among late postmenopausal women but low in the early postmenopausal period. There may be limited benefits to administering antioxidant treatment to patients in this period. Native thiol serum levels showing antioxidant activity were lowest in the late postmenopause, and this difference was significant between the groups. As a result, administering antioxidant support in addition to hormone replacement therapy and other medical treatments to patients from the beginning of the menopausal process may be considered. Antioxidants may contribute to an increasing antioxidant capacity, even if they do not support vasomotor symptoms. Among the limitations of our study are the relatively low number of patients, the assessment of oxidative stress only with the T/D balance, and the subjective nature of responses to questions on the Greene scale. According to our research, this is the first study researching the correlation between all components of the T/D balance and climacteric symptoms.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Atatürk Training and Research Hospital. (Approval Date: 13.04.2016, Approval Number: 2637996/145).

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

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Traditional Practices for Mother and Infant Care in North Cyprus: What is Known, and What is Being Applied?

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BACKGROUND/AIMS
We conducted this study to determine traditional methods that women living in the center of Nicosia are aware of and apply in the maternal and infant care in the postpartum period.

MATERIALS AND METHODS
The study had a descriptive design. According to the results of the 2011 census, the universe of research consisted of 11,879 married women from the center of Nicosia. Our study included a total of 372 women. A questionnaire developed by researchers was used. The data were collected between September 1 and December 31, 2015, by the researcher visiting homes and interviewing women personally. A written approval from the Ethics Committee was obtained.

RESULTS
The study showed that 91.94% of the women applied the traditional methods on themselves and 92.2% on their babies in the postpartum period. It was also identified that there was a statistically significant difference ($p<0.05$) between the application of any kind of traditional practices on themselves depending on the age group, their educational status, and health status. The level of significance was set at 0.05.

CONCLUSION
It was determined that the majority of women applied traditional practices in the maternal and infant care in the postpartum period.

Keywords: Postpartum period, traditional practices, nursing

INTRODUCTION

Finding their roots in tradition and being passed on from one generation to another, traditional methods are approaches that are main in almost every part of the world at different frequencies. On the other hand, traditional health practices are the medical practices of the society in relation to that society's beliefs, traditions, values, and culture (1, 2). The prevalence of traditional postpartum practices in all societies is noteworthy (3, 4). Some traditions, customs, and beliefs about birth and reproduction are also seen in the life of the Turks (2, 3, 5, 6).

The impact of traditional practices on health can be positive, whereas it can occasionally also reach negative dimensions, threatening life (7). Malpractice during the postpartum period can prolong the healing process of the mother and the baby, as well as prevent the effective treatment; and they can also result in disability, illness, and even death (4, 8, 9). The application of harmful traditional methods with the belief of *albasması* (a local belief suggesting that the woman can show the symptoms of febrility, somniloquy, and hallucination because of the influence of bad spirits in the postpartum period) may cause a puerperal woman to get worse by delaying the treatment. The traditional method of swaddling the baby may be uncomfortable, lead to restlessness, and leads predispositions to hip dislocation (1, 2).

Reflecting the cultural beliefs and practices of the individuals, nurses should support beneficial practices and include them in their care, and they should be cautious when it comes to preventing adverse health effects of harmful practices (6, 10).

This study was presented at the 1st International and 2nd National Obstetrics and Gynecology and Maternal And Infant Care Congresses. 6-7 October, 2016. İzmir, Turkey.

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Nurses whose role is to improve the health-related behavior of the community should be educated about the cultural factors that improve the health behaviors and reject the wrong practices (10).

The aim of this study was to determine the awareness and application of traditional methods among women and infants during the postpartum period in the center of Nicosia. We investigated the knowledge of traditional methods in the postpartum period that will improve the awareness and enhance health services for the families and public.

Study Questions
Women living in the center of Nicosia

1. What is the knowledge level about the traditional methods with regard to maternal and infant care in the postpartum period?
2. Is there any difference between descriptive characteristics and knowledge of the traditional methods?

MATERIALS AND METHODS

Study Design
The study has a descriptive design.

Sample Selection
According to the results of the 2011 census, there was a total of 11,879 residing married women in the center of Nicosia. Our study included 372 women. Twenty-three neighborhoods were stratified in order to be able to represent the married women living in the center of Nicosia in the study and to ensure a homogeneous distribution. According to the influent layer weight, a minimum of 1 and maximum of 79 people were sampled in this area. Then, the women included in the sample according to the stratum size from neighborhoods were selected by the random sampling method. Samples were taken from women, who were married, have at least one child and knew Turkish. There were no refusals to participate in the study.

Study Tools
A questionnaire was developed by the researchers based on the literature, and it was used as a data collection tool in this study (1, 7, 10). The questionnaire consisted of two parts. In the first part, questions were prepared to determine the socio-demographic and descriptive characteristics of women, and in the second part, the aim was to identify the traditional practices of women regarding the maternal and infant care.

Statistical Analysis
The questionnaire was collected between September 1 and December 31, 2015, by the researcher who visited homes and interviewed the women personally. A statistical analysis of the obtained data was performed using the Statistical Package for Social Sciences version 21.0 (IBM Corp.; Armonk, NY, USA) program, and the number and percentage distributions were used in addition to the chi-squared tests.

Pilot Study
A pilot study was performed on 37 women in a neighborhood outside the center of Nicosia. After the pilot study, a revision was not necessary. However, the women who participated in the pilot study were not included in the main sample.

Ethical Considerations
Ethical approval was obtained from the Research Ethics Committee of the Near East University, and before the data collection, a written informed consent was also obtained, and the researchers explained the study aims. An additional written permission was obtained from the Nicosia Local Government.

RESULTS
A total of 37.63% of the survey participants were in the age group between 40 and 49 years, 43.5% were high school graduates, 60.75% had a job, and 98.92% had a nuclear-type family. Most of the participants responded that they perceived their economic situation level as moderate (91.4%). Majority of respondents had health insurance (81.8%). In the postpartum period, 91.94% of the women reported that they applied at least one traditional practice on themselves and 92.2% on their babies.

TABLE 1. The data of women who apply a traditional method on themselves, according to descriptive characteristics (n:372)

	Applied		Not Applied			
	n	%	n	%	X^2	p
Age Group						
29 and below	61	91.04	6	8.96	14.46	0.00*
Between 30 and 39	81	97.59	2	2.41		
Between 40 and 49	120	85.71	20	14.29		
50 and above	80	97.56	2	2.44		
Education						
Elementary school (Not literate/Elementary)	63	76.83	19	23.17	34.05	0.00*
Secondary school (Secondary/High school)	178	97.80	4	2.20		
Higher education (Undergraduate/Graduate)	101	93.52	7	6.48		
Health Insurance						
Yes	273	90.40	29	9.60	5.12	0.02*
No	69	98.57	1	1.43		

The level of significance was set at $p<0.05$.

TABLE 2. The statistics of women who apply a traditional method on their babies, according to some descriptive characteristics (n:372)

	Applied		Not Applied			
	n	%	n	%	X^2	p
Age Group						
29 and below	64	95.52	3	4.48	18.48	0.00*
Between 30 and 39	83	100.0	0	0.00		
Between 40 and 49	119	85.00	21	15.00		
50 and above	77	93.90	5	6.10		
Education						
Elementary school (Not literate/Elementary)	61	74.39	21	25.61	46.65	0.00*
Secondary school (Secondary/High school)	178	97.80	4	2.20		
Higher education (Undergraduate/Graduate)	104	96.30	4	3.70		
Health Insurance						
Yes	274	90.73	28	9.27	4.86	0.03*
No	69	98.57	1	1.43		

The level of significance was set at p<0.05.

TABLE 3. The statistics of women who knew at least one traditional method to apply for the care of the puerperal women (n:372)

	Statistics of Knowing	
Practices	**Number (n)**	**Percentile (%)**
For the puerpera	372	100
Postpartum hemorrhage	194	52
Increasing lactation of the puerpera	372	100
Decreased lactation of the puerpera	253	68
Preventing *albasması*	356	96
Healing *albasması*	286	77

According to the demographic characteristics of the women, the results of applying traditional practices in the postpartum period are presented in Table 1, and the results for infants are presented in Table 2. A statistically significant difference was found between the age groups of women, their educational status, their health status, and the practice of traditional method in the postpartum period (p<0.05). No statistically significant difference was found between the application of traditional practices and respondents' economic situation (p>0.05). The frequency of traditional method practices in women who were in the age group between 40 and 49 years with the primary school education level and who had health insurance was lower than that of women who were either above 50 or under 40 years of age, completed secondary school or higher education, and had no health insurance.

Table 3 represents the situations where women knew at least one traditional practice for maternity care. It was found that all women knew at least one traditional practice for maternity care and increasing lactation. Regarding traditional practices for postpartum hemorrhage (52%), decreased lactation (68%), prevention of *albasması* (a local belief suggesting that the woman can show the symptoms of febrility, somniloquy, and hallucination because of the influence of bad spirits in the postpartum period) (96%) and healing of *albasması* (77%).

TABLE 4. Distribution of traditional practices applied by women for maternal care (n:372)

Practices	**n**	**%**
Blessing the fortieth day of the puerpera	295	79.30
No sexual intercourse for 40 days for the puerpera	250	67.20
Not letting women who are having their period get near the puerpera	165	44.35
For woman with postpartum hemorrhage		
Raising puerpera's feet	71	36.60
Suppressing puerpera's abdomen	62	31.96
For increasing the lactation		
Making puerpera consume plenty of fluids	320	86.02
Making puerpera eat sweet	271	72.85
Making puerpera eat onion	223	59.95
In case of decreased lactation		
Letting the mother eat whatever she craves for	192	75.89
Applying steam to breasts	69	27.27
For preventing the albasması of the puerpera		
Placing Quran in the room where the puerpera rests	240	67.426
Not leaving the puerpera alone in the house	235	6.01
For healing the albasması of the puerpera		
Praying	81	28.322
Having the puerpera take a bath for blessing on the fortieth day	71	4.83

More than one answer was given. Percentages were taken over the number of women who knew at least one traditional practice for the puerperal woman.

The traditional practices for women during the postpartum period are shown in Table 4. Among these practices, the blessing of the fortieth day of the postpartum period (79.3%), not having sexual intercourse for 40 days (67.2%), and not letting women who are having their period to get near the puerperal women (44.35%) were the practices in general. When asked what they

would do with the puerperal woman who has postpartum hemorrhage, 36.6% said that they would raise her feet, and 31.96% stated that they would suppress her abdomen. While 86.02% of the women would make sure that the mother consumed plenty of fluids, 72.85% of them suggested that the mother should have sweet foods, and 59.95% of them would advise mothers to eat onions to increase the lactation; 75.89% claimed that the mothers should eat whatever they crave for, and 27.27% said that they would apply steam to the breasts if the lactation would decrease. Placing Quran in the room where the puerperal woman rests (67.42%) and not leaving her alone in the house (66.01%) were among the traditional practices to prevent the *albasması*. However, to heal the *albasması*, it was reported that 28.32% of the women would pray, and 24.83% of them suggested that the mother should have a bath for blessing on the fortieth day of the postpartum period.

The results of women who knew at least one traditional practice for the newborn or infant care is reported in Table 5. It was found that all women knew at least one traditional practice for newborns and babies. The practices of protecting the baby from the evil eye (100%), preventing jaundice (99%), the first baby bath (94%), and the first feeding of the baby (93%) were the top ones among the practices that women expressed they knew.

Table 6 shows the traditional practices that women apply to newborns and babies in the postpartum period. A total of 77.69% of the women celebrated the fortieth day, and 40.32% of them swaddled their babies. For the first feeding of the newborns, 46.82% of the women gave the newborn sugar water as the first nutrient. 48.29% said that they bathed the newborn after the baby's umbilical cord fell off, 43.36% of them used olive oil for the baby's umbilical cord to make it fall off quicker, and 26.58% of them buried the baby's umbilical cord in the school

TABLE 5. The statistics of women who knew at least one traditional practice to apply in the newborn and infant care (n:372)

	Statistics of Knowing	
Practices	**Number (n)**	**Percentile (%)**
For the newborn and baby	372	100
First feeding	346	93
First bath	350	94
For the umbilical cord to fall off quicker	286	77
After the umbilical cord falls off	301	81
Not to develop jaundice	368	99
In case of jaundice	324	79
Protecting from the evil eye	372	100
When touched by the evil eye	338	91
For the baby to be beautiful	275	74
In case of candidiasis	246	60
In case of neonatal dermatitis	324	87
In case of rash	353	95
In case of gas pain/bloating	372	100
In case of diarrhea	352	95
In case of fever	372	100

TABLE 6. Distribution of traditional practices applied by women in the newborn and infant care (n:372)

Practices	**n**	**%**
Blessing the fortieth day	289	77.69
Swaddling	150	40.32
For the first feeding of newborn		
Giving the newborn sugar water as the first nutrient	162	46.82
Giving the newborn formula food as the first nutrient	51	14.74
For the first bath of newborn		
After the newborn's umbilical cord falls off	169	48.29
Before the newborn's umbilical cord falls off	163	46.57
For the newborn's umbilical cord to fall off quicker		
Applying olive oil on the belly	124	43.36
Wiping with alcohol	106	37.06
After the newborn's umbilical cord falls off		
Burying it in the school garden	80	26.582
Burying it in the house garden	75	4.92
For the newborn not to develop jaundice		
Breastfeeding/Feeding	278	75.54
Tying yellow cloth or gauze	261	70.92
Having the newborn sunbathe for 40 days	146	39.67
For the newborn in case of jaundice		
Breastfeeding/Feeding	245	75.62
Having the newborn sunbathe	208	64.20
Tying yellow cloth or gauze	141	43.52
To protect the baby from evil eye		
Pinning an amulet (blue bead) on clothes	346	93.01
Praying	286	76.88
For the baby when touched by the evil eye		
Pouring lead	152	44.972
Having an elderly person or a Muslim preacher to pray	90	6.63
For the baby to be beautiful		
Pinching nose	122	44.36
Applying pressure to cheeks and the jaw	74	26.91
For the newborn in case of candidiasis		
Wiping mouth with dry cloth	81	32.932
Applying baking soda in the mouth	59	3.98
For the newborn in case of neonatal seborrheic dermatitis		
Applying olive oil on the head	221	68.21
Combing baby's hair with a thin brush	177	54.63
For the newborn in case of rash		
Applying cream	312	88.39
Applying powder	196	55.52
For the newborn in case of gas pain		
Massaging belly with olive oil	328	88.17
Feeding with anise tea	288	77.42
For the newborn in case of diarrhea		
Giving plenty of water	247	70.17
Feeding with rice and yogurt	200	56.82
For the newborn in case of fever		
Taking off the baby's clothes	350	94.09
Warm bath/warm application	355	95.43
Wiping with vinegar diluted with water	246	66.13

More than one answer was given. Percentages were taken over the number of women who knew at least one traditional practice for the newborn and infant care.

garden. Regarding preventing the newborn baby from developing jaundice, women stated that they tied yellow cloth, 75.54% of them while breastfeeding and 70.92% of them directly to the bed. In case of jaundice, 75.62% of the women breastfed, and 64.2% of them let the newborn sunbathe. To protect the baby from evil spirits, 93.01% of the women were wearing blue beads, and 76.88% were praying; and if it was believed that the baby was touched by the evil eye, 44.97% poured lead (a ritual of pouring molten lead from one pot to another pot held above a baby's head to keep the evil eye away), and 26.63% requested an elderly person or a Muslim preacher to pray. 44.36% of the women expressed that they pinched the baby's nose to make the baby beautiful, 32.39% of them wiped the mouth of the newborn with a dry piece of cloth if the baby had candidiasis, and 68.21% said that if the baby had honeycomb disease, they rubbed some olive oil onto the head of the newborn. In case of rash, 88.39% of the women chose to rub the rash with a cream, in case of gas pains (bloating), 88.17% of them rubbed the newborn's stomach with olive oil, and in case of diarrhea, 70.17% of them gave plenty of water to the babies. In case of fever, giving a warm bath (95.43%) and taking the clothes off (94.09%) were among the most frequent practices that the women applied.

DISCUSSION

It was observed that most of the women in the study knew and applied traditional practices for the maternal and infant care in the postpartum period. These included practices that might be both useful and harmful to the mother or the baby.

The practice of "not allowing sexual intercourse for 40 days" is one of the useful practices. This method is also applied in Turkey. A review of the literature showed that this method was also being applied in different cities of Turkey (3, 7). In fact, this practice of "not allowing sexual intercourse for 40 days" can be considered as a beneficial practice because it is supported by modern medicine in the sense that the puerperal woman who is sensitive to the infections in this period due to lacerations or episiotomy that occur during labor feels pain during sex (7).

Hemorrhage that occurs in the postpartum period is one of the leading causes of maternal deaths in Turkey (11). Any kind of traditional practice during bleeding can put women's health and life under risk. Studies in the literature showed that there were many traditional applications for the postpartum period (7, 12). In our study, it was determined that women applied the methods of "raising the puerpera's feet" and "suppressing the puerpera's abdomen" in cases of postpartum hemorrhage. Suppressing the puerpera's abdomen is an application that can save lives when done correctly. However, only educated health care staff can do this most accurately and can provide a medical follow-up. Women should be informed about reporting to a health institution in case of bleeding, as soon as possible before resorting to any traditional practice.

"The puerpera's consuming plenty of fluids" is a useful practice for increasing the lactation. In case of decreased lactation, "letting the puerperal woman eat whatever she craves" may be considered harmful in case of an excessive calorie intake. In the study by Lafçı and Erdem (12), it was found that the most commonly used method for increasing lactation was to eat molasses or halva with 68%, and in the study by Gölbaşı and Eğri (7), it was found that it was preferred for puerperal woman to consume watery foods with a maximum of 71.3%. In the first 6 months, mothers should only breastfeed their babies, and the most important reason for the early start of additional meals is inadequate lactation. For adequate milk production, it can be said that these practices are beneficial, given that the puerperal woman should consume at least 3 liters of fluid per day, and 500 calories per day should be added to her diet. However, an excessive consumption of sweet foods or caloric intake can lead women to gain weight (7, 13).

For preventing the *albasması*, practices such as "not leaving the puerperal woman alone in the house" and "placing Quran in the room where the puerperal woman rests"; and for healing the *albasması*, practices such as "having puerperal woman take a bath on the fortieth day" and "praying" are the practices that can be considered beneficial since they relieve the mother psychologically. It draws attention that in order to prevent the *albasması*, the most used method in Gölbaşı and Eğri's (7) work was "placing things in the room where the puerperal woman rests" (bread, scissors, broom, Quran) with 89.4%, and in Lafçı and Erdem's (12) work, the same practice was also on top with 48%.

Koyun et al. (14) found that the practice of "placing a cutting, drilling tool under the cushion of the puerpera" was 22%, while Işık et al. (13) stated that "not letting the puerperal woman out of the house for 40 days" was the top practice regarding the *albasması* belief in their study. When the survey results were evaluated, in our district and in various regions of Turkey, we saw that these practices were still being widely applied. These practices have no harm to the mother and are considered useful psychologically. However, there is a health problem at the root of the situation that is believed to be *albasması* colloquially. It can be maternal sadness, postpartum depression, infection, or dehydration (7, 15). Applying traditional methods with the belief of *albasması* may cause the health condition of the puerperal woman to get worse by delaying the treatment.

In the postpartum period, breastfeeding is found to be one of the beneficial traditional practices applied for the newborn not to develop jaundice. "Yellow cover or tying gauze" method can also be considered as a psychologically beneficial practice without direct harm to the baby. However, in case of jaundice, this may be harmful since it may delay diagnosis and treatment. Covering the newborn's face with yellow gauze was the most used practice with 55.3% in Yalçın's (16) work, which he conducted in Karaman, and with 84% in Lafçı and Erdem's (12) work. In the study by Arısoy et al. (6), it was determined that the most frequently used method for keeping the newborn from developing jaundice was frequent feeding, at 78.5%. Traditional practices for the prevention of jaundice in newborn babies have generally no adverse effects on baby's health (1, 13). Feeding with breast milk have great importance in preventing jaundice. For this reason, breastfeeding the newborn is effective in avoiding jaundice. Nurses should train parents to breastfeed after birth and should make them aware of the effect of this behavior on physiological jaundice.

"Applying olive oil on newborn's head" in case of neonatal seborrheic dermatitis, "rubbing the newborn's belly with olive oil" in

case of gas pains (bloating) are beneficial practices supported by modern medicine, whereas "applying olive oil on the belly" for baby's umbilical cord to fall off quicker is a harmful practice. In both the studies conducted by Çınar et al. (17) and Çalışkan and Bayat (18), women also stated that they used olive oil for neonatal seborrheic dermatitis. Çınar et al. (17) identified that in order to relieve the gas pain, the methods such as massaging (50.8%) and making newborn drink some olive oil (9.2%) were used. In Uğurlu et al.'s (19) study, making newborn drink herbal tea was found in 21.3% of cases. Because of the gas problem, abdominal pain is a common condition in infants. Modern medicine supports the application of olive oil, and massage is an effective application to alleviate the gas problem and symptoms. But since olive oil is not sterile, it is inconvenient and harmful to apply olive oil on the belly for baby's umbilical cord to fall off quicker. Non-sterile or dirty items placed on the umbilicus may cause tetanus or infections leading to infant's sepsis deaths (6, 7, 13).

Furthermore, it was found that the women included in the study made the newborn drink plenty of water in case of diarrhea. In the study by Bölükbaş et al. (10), the percentage of "giving the newborn plenty of water to drink" was found to be 26.6%. In the study by Çınar et al. (17), we saw breastfeeding at 14.3%, and "giving the newborn plenty of water to drink" at 13.2%. Other study results are similar to our results. Decreased body fluids with diarrhea can cause dehydration of the baby, resulting in many complications or even death (20). In case of diarrhea, it is a pleasing situation that the mothers do not restrict the fluid, and on the contrary, the fact that they increase the amount of fluid is a useful application.

In this study, among the traditional methods applied in the newborn and baby in the postpartum period, "blessing the fortieth day" and the practices applied after the newborn's umbilical cord fell off were not harmful to baby's health and were found to be psychologically relaxing for the family.

There are no direct injuries to newborns or babies when it comes to the practices aiming to protect from the evil eye or the ones done when the newborn or baby is believed to be touched by the evil eye. However, the interpretation of the actual disease symptoms as an evil eye and resorting to various traditional practices instead of reporting to a health institution may have negative consequences for the health of the baby. The study results are parallel to our study (1, 12).

The practices of "swaddling" and "giving sweetened water" as the first food to newborn are the unhealthy traditions which stand out in our work. The tradition of swaddling is a common practice in Turkish society. The swaddled baby will be uncomfortable, restless, and prone to hip dislocation (1, 2). For this reason, we can say that swaddling affects the health of the baby adversely. In the literature, it can be found that it is possible to prevent newborn complications by breastfeeding and early breastfeeding within the first 30 minutes after birth (21, 22). So, raising mothers' awareness about baby care may be effective in reducing harmful traditional practices.

The discussion part has been done with a limited number of studies from the literature because, to the best of our knowledge, there are no studies previously conducted in Cyprus covering this topic.

Finally, in the direction of our findings, it was determined that there were traditional methods known or applied by the women living in the center of Nicosia for maternal and infant care in the postpartum period. As the traditional methods applied in the postpartum period are being evaluated by nurses, cultural differences should be taken into consideration, the situations should not be handled by judgmental behaviors, maternal education about the harmful practices should be provided, and harmless or beneficial traditional practices should be supported.

Ethics Committee Approval: Ethics committee approval was received for this study from Near East University (Approval Date: 17.19.2015, Approval Number: YDÜ/2015/32-222).

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

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Original Article

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Stress Analysis of Direct Restoration Techniques for Endodontically Treated Maxillary Premolars

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BACKGROUND/AIMS
Direct restoration of root-filled premolars with cusp fractures is controversial. The aim of the present study was to compare two different direct restoration techniques with and without cuspal coverage for the restoration of root-filled two-rooted maxillary premolar without palatal cusp using three-dimensional (3D) finite element method (FEM).

MATERIAL and METHODS
Three-dimensional FEM mathematical models were used to evaluate how different restorative options changed stress distribution of the remaining dental tissues. These models were: (1) intact maxillary first premolar (control group), (2) coronal-radicular build-up restoration (CRBR) with buccal cusp coverage (BCC), (3) CRBR without BCC, (4) post-retained direct restoration (PDR) with BCC, and (5) PDR without BCC. A 100 N occlusal load was applied to calculate stress distributions. The Algor Fempro program was used for FEM analysis. von Mises stress distributions and values on the remaining enamel, dentin, and restorative materials were evaluated.

RESULTS
Regarding stresses that occurred in the enamel, models with BCC transferred lower stress than models without BCC. The lowest stress value in the enamel was observed in the control group with 24.86 MPa. The stress values of the control group, PDR, and CRBR in the dentin were 9.93, 9.68, and 9.32 MPa, respectively.

CONCLUSION
The present study found out that direct cuspal coverage with resin composites appeared to be a reliable method in restoring maxillary first premolar with missing palatal cusp. Reinforcing the restoration with either post- or intraradicular extensions was both protective in the case of dentin.

Keywords: Finite element analysis, premolar, composite resins

INTRODUCTION

The quality of post-endodontic restorations is as important as endodontic therapy for the prognosis of endodontically treated teeth (ETT) (1). In modern dentistry, the approaches related with the least invasive and the most tissue-preserving techniques are recommended to be followed for the long-term survival of ETT. In this context, composite resins with improvements on the physical and mechanical properties become suitable materials for the restoration of these teeth with extensive cavities (2). With the development of fiber-reinforced composite (FRC) technology, practitioners found a new perspective to solve problems with unique and modern solutions (1). When the fiber-reinforced post systems developed, they were offered as good esthetic alternatives to metal posts with the elastic modulus close to that of dentin, resulting in lower stress transmission to the root and decreasing the risk of root fracture (1, 3). Then, the short FRC (everX Posterior; GC, Tokyo, Japan) has been developed to mimic the stress-absorbing properties of dentin and dentin-enamel junction and to be used in high stress-bearing areas (2).

Restorative treatment options of ETT that is more brittle than vital teeth should be carefully considered (4). Traditionally, these teeth could be reinforced with pins, cast restorations, and post placement and full-crown coverage. However, these materials and methods weaken the remaining tooth tissue and led to fracture of the root and/or crown (5). Extracoronal

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(4) and intracoronal methods with adhesive technology have been suggested for the reinforcement of weak posterior ETT (5).

Finite element analysis is a method that has its own advantages, such as repeatability, high accuracy, and efficiency. It also allows measurement of stress values and distributions that cannot be measured due to the actual size of the teeth at any desired point and interface. It provides reference data in determining the durability of the restorations planned to be performed (6).

There have been many finite element studies about restoration of ETT with direct methods (1, 2, 7, 8). This three-dimensional (3D) finite element study aimed to compare stress distributions of two different direct restoration designs with support from root canals with and without cuspal coverage for a maxillary first premolar tooth without functional cusp.

MATERIAL and METHODS

The Rhinoceros 4.0 (McNeel North America, Seattle, WA, USA) 3D modeling software, VRMesh Studio (VirtualGrid Inc., Bellevue, WA, USA) meshing software, and Algor Fempro (ALGOR Inc., Pittsburgh, PA, USA) analysis program conducted the 3D finite element study. A plaster model was scanned using SmartOptics (smart optics Sensortechnik GmbH, Bochum, Germany) to obtain a 3D finite element premolar model. The morphology of the two-rooted maxillary first premolar was generated using data from Wheeler's atlas (9). The surrounding structures were modeled as cortical bone (1.5 mm), trabecular bone (rest of the bone model), periodontal ligament (0.2 mm), and lamina dura (0.2 mm). Intact two-rooted maxillary first premolar was modeled as the control group. Four finite element mathematical models were created with mesial-occlusal-distal-palatal (MODP) cavity with a 2 mm intact tooth structure above the cement-enamel junction in two designs with and without a 2 mm buccal cusp reduction. One model was used for each group in the present study. Figure 1 shows the image of intact tooth and MODP cavity design with and without buccal cusp coverage (BCC). Each cavity design was restored by either coronal-radicular build-up restoration (CRBR) or post-retained direct restoration (PDR). The restoration models were as follows: (1) CRBR with BCC, (2) CRBR without BCC, (3) PDR with BCC, and (4) PDR without BCC.

TABLE 1. Elastic moduli, Poisson's ratios, and references of the dental tissues and materials (1, 2, 7, 10-13)

	Young's modulus (MPa)	Poisson's ratio (υ)	References
Enamel	84,100	0.33	(10)
Dentin	18,600	0.32	(7)
Cortical bone	10,700	0.30	(2)
Trabecular bone	1370	0.30	(1)
Periodontal ligament	68.9	0.45	(12)
Pulp	0.98	0.45	(13)
G-aenial Posterior	8200	0.24	(2)
everX Posterior	12,300	0.24	(2)
Post	40,000	0.26	(1)
Gutta-percha	0.69	0.45	(13)

TABLE 2. Number of elements and nodes of models

Models	Elements	Nodes
Intact tooth	281,394	52,732
CRBR with BCC	299,768	55,977
CRBR without BCC	323,881	59,608
PDR with BCC	317,411	60,112
PDR without BCC	315,834	59,625

CRBR: coronal-radicular build-up restoration; BCC: buccal cusp coverage; PDR: post-retained direct restoration.

In CRBR, intraradicular support was provided by 3 mm extensions into both canals, and everX Posterior was used for intraradicular extensions and dentin replacement, whereas G-aenial Posterior (GC Europe, Leuven, Belgium) was used for enamel replacement. In PDR, a glass fiber-reinforced post was inserted in the palatinal canal with a 5 mm apical gutta-percha, and everX Posterior and G-aenial Posterior were used as dentin and enamel replacements, respectively. A 10 μm adhesive thickness was modeled for bonding, whereas a 50 μm cement was modeled for luting procedure (10). All oral structures and materials were assumed to be linearly elastic, homogeneous, and isotropic. The corresponding mechanical properties are determined and shown in Table 1 according to literature data (1, 2, 7, 10-13).

For the generation of the models, bricks and tetrahedral solid elements were prepared whereby 281,394 elements and 52,732 nodes for intact tooth were used in the present study. Table 2 shows the number of elements and nodes of each model.

A 100 N occlusal load was applied to simulate foodstuff. Results were presented by considering maximum von Mises (VM) stress values in megapascals (MPa). The calculated numerical values were transformed into color graphics to better visualize mechanical stresses in the models. The remaining enamel, dentin, and restorative materials were separated from the rest of each model for the analysis of stress distributions. Stress values differing by <5% were considered to be similar.

RESULTS

Intact tooth had minimum VM stress values in the enamel (24.86 MPa). Models of restorations without BCC accumulated maximum VM stresses in the enamel followed by CRBR with BCC. PDR with BCC showed 31.23 MPa VM stress accumulation in the enamel (Figure 2a). Figure 2b shows the stress distribution patterns of the enamel. The cervical region is the most common area for all of the models where intense stress accumulation occurred.

In the case of dentin, intact tooth, models of CRBR, and models of PDR had VM stress values as 9.94 MPa, 9.32 MPa, and 9.68 MPa respectively. There had been no difference between the stress values of models of CRBR and PDR with and without BCC. Stress distribution patterns showed that the most intense VM stress accumulation occurred at the palatal side of the buccal apical root (Figure 3).

Restorative materials were evaluated into two parts. In the case of materials used as enamel replacement, there had been no

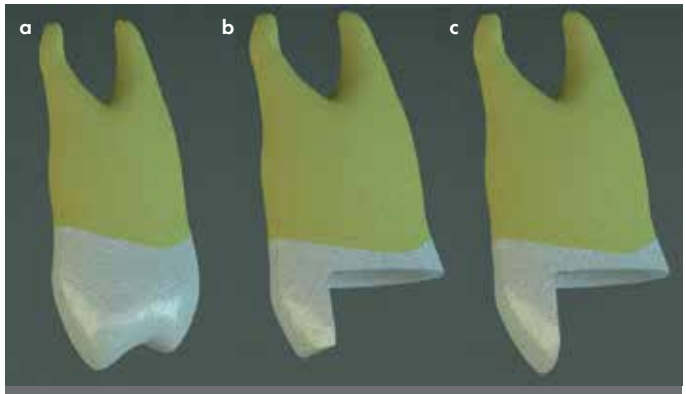
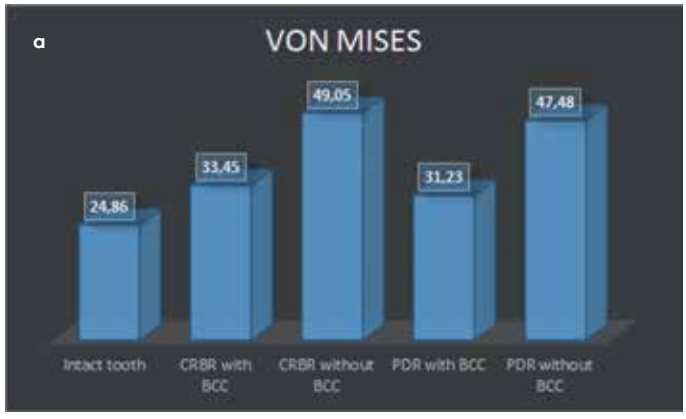


FIGURE 1. a, b. Images of intact tooth (a) and MODP cavity design (b) with and without buccal cusp reduction (c)
MODP: mesial-occlusal-distal-palatal.



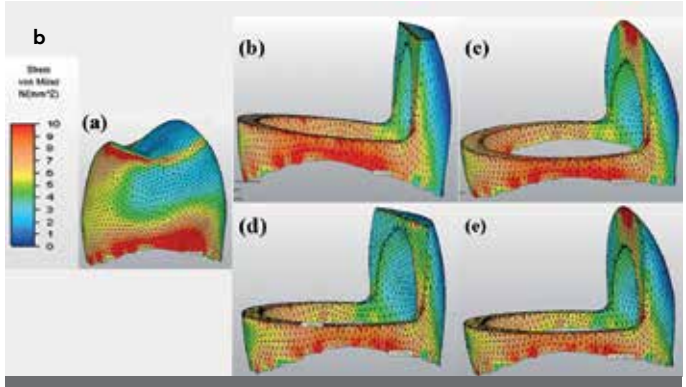


FIGURE 2. a, b. Stress values of models that occurred in the enamel (a). CRBR: coronal-radicular build-up restoration; BCC: buccal cusp coverage; PDR: post-retained direct restoration. Stress distribution patterns of the enamel (b). Intact tooth (a), CRBR with BCC (b), CRBR without BCC (c), PDR with BCC (d), and PDR without BCC (e).

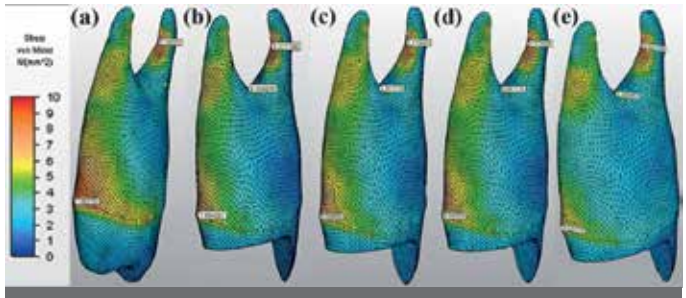
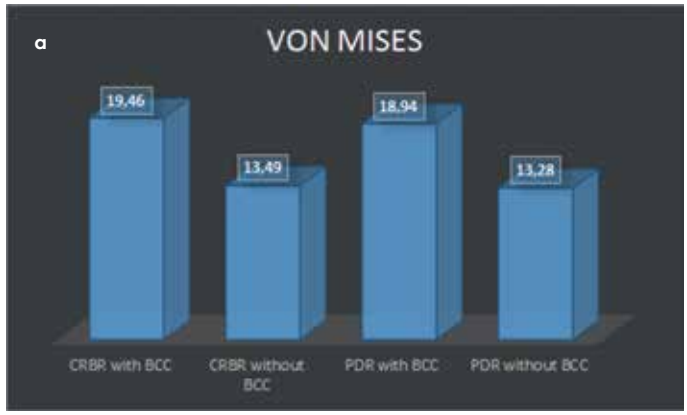


FIGURE 3. a-e. Stress distribution patterns that occurred in the dentin. Intact tooth (a), CRBR with BCC (b), CRBR without BCC (c), PDR with BCC (d), and PDR without BCC (e).



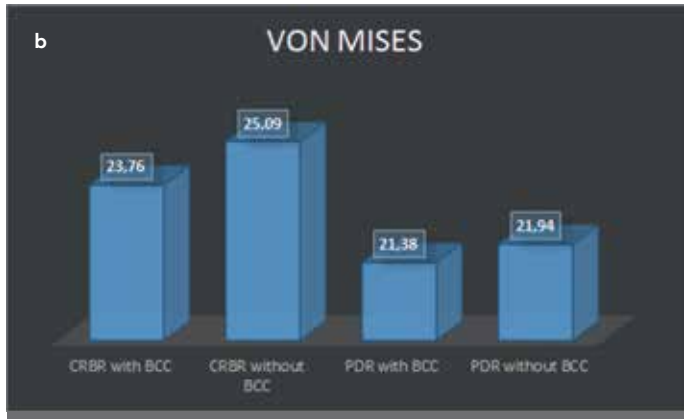


FIGURE 4. a, b. Stress values of restorative materials used as enamel replacement (a). Stress values of restorative materials used as core and substructure (b)
CRBR: coronal-radicular build-up restoration; BCC: buccal cusp coverage; PDR: post-retained direct restoration.

significant difference between models with BCC and without BCC (Figure 4a). The most intense stresses were accumulated on the occlusal surfaces where loading occurs. everX Posterior, used as a substructure material, showed more stress acumulation than G-aenial Posterior. CRBR without BCC accumulated more stress than CRBR with BCC; however, similar stress values were observed between the models of PDR (Figure 4b).

DISCUSSION

The unfavorable morphology and portions of maxillary premolars cause them to be named as the most susceptible posterior teeth to be fractured (7, 14, 15). The cusps of premolars are subjected to a set of forces that is formed by axial and shear loads that could be harmful, whereas the buccal and palatal cusps tend to seperate due to occlusal forces (5, 14, 16). In clinical practice, palatal cusp fractures are observed more than buccal cusp fractures (17). In the present study, the maxillary premolar tooth with MODP cavity design was modeled to simulate the worst case scenario for direct restoration methods.

The materials used for restorations of ETT have been amalgams, composite resins, and indirect materials. The materials should be able to replace loss of tooth tissues to ensure mechanical and functional properties, esthetics, and coronal seal (16). Since maxillary premolars are close to the anterior esthetic region, tooth-colored materials are preferable (14). Composite resins and ceramics are the most frequently used materials due to their esthetical requirements. Ceramic materials exhibit

superior esthetic appearance, wear resistance, biocompatibility, stability in the oral cavity, high compression resistance, and a coefficient of thermal expansion similar to that of dental structure in comparison with those of composite resins. However, both materials favor reinforcement of the weakened tooth when combined with adhesive technology (15). Today, composite resins that are more affordable for patients are preferred for the restoration of large cavities including cusp replacement (2). The results of this finite element study showed that intraradicularly supported restoration of endodontically treated maxillary first premolar with composite resins was a safe option for dentin, while it may not be the best choice for enamel.

Restoration of ETT has been a challenging procedure for many years (13). Modern clinical approaches are based on the principles of minimally invasive dentistry that aims to protect sound tooth tissue (13, 16). In spite of using "aggresive macroretentive techniques", the new approaches accomplish adhesive technology. In the case of premolars, a post placement is recommended in order to protect the remaining dental structures (16). Furuya et al. (18) reported that restoring endodontically treated multiple root premolars with very little remaining tooth tissue with fiber posts is the most suitable option. However, the unsatisfying adhesion of fiber posts to luting cements or core materials led to criticism (3). Another method for restoring multiple root teeth is based on the technique by Nayyar et al. (19) with an amalgam dowel core. In this technique, gutta-percha is removed from root canals to a depth of 2-4 mm, and root canals are restored with amalgam (19). In our study, a 3 mm depth gutta-percha was removed from root canals, and a short FRC was used to fill the root canals and to form the core structure. According to the results of the comparison of the restoration models, it appeared that stress values on the enamel were similar except for the restorations having BCC, and stress values on the dentin were similar for all models. These findings are consistent with the study by Forster et al. (20) that fracture resistance of glass fiber-reinforced group and short FRC applied as substructure with a 2 mm depth in the root canal group were found to be similar. This result allows us to hypothesize that the selection of restoration type had an importance on the enamel when BCC was performed.

Cuspal coverage that conduces to less cuspal deflection and better protection of the remaining tooth tissue is recommended for the reinforcement of the tooth (15). An early finite element study reported that a minimum of 1.5 mm reduction is recommended for the significant decrease of stress values (17). A 2 mm reduction for cuspal coverage was found as a safe option for the restoration of ETT (21). The results of the present study pointed out that restoration models with BCC transferred less stress to the enamel than models without BCC, and a 2 mm cuspal coverage option significantly reinforced the remaining enamel tissue, whereas it has no effect on the remaining dentin.

EverX Posterior has been used for onlays, core build-up with posts, only core build-up, and direct layered posts (5, 21). In the present study, it was used as core material in PDR models and as substructure material in CRBR models. Garoushi et al. (22) reported that there is a linear direct relationship between the load-bearing capacity of the combination and the thickness of FRC when short random FRC is used under particulate filler composite as substructure. Thus, in the present study, the minimum thickness of G-aenial Posterior was modeled around FRC in order to allow the maximum amount of FRC placement.

Since the functional and parafunctional forces occurring within the mouth result in extremely complex structural responses by the oral tissues, rehabilitation of the oral environment is difficult. Finite element analysis is an appropriate theoretical tool for the evaluation of the resulting stresses (12). On the other hand, finite element analysis is dependent on theoretical assumptions and simplifications, such as material properties, geometry, and boundary conditions (23). Thus, finite element analysis ranks as a powerful tool if all assumptions and material properties coincide with the real situation (23).

In the present study, a 100 N occlusal load was used in order to stimulate foodstuff. Since the models were assumed to be linear, stress values for higher loads can be predictable. On the other hand, Erarslan et al. (1) emphasized that when standardization is ensured between the conditions, it is not precisely necessary to match the reality exactly.

In the literature, there were some studies (24, 25) that accepted luting cement thickness as a part of the dental tissues, and stresses were not evaluated for cement because it was too thin to adequately model in finite element simulation. Furthermore, in a study, no statistical differences in stresses were found between cement thickness varying from 50 to 150 μm on the remaining enamel and dentin for ceramic systems (26). For this reason, in the present study, the thin luting cement and adhesive layer thickness were neglected.

In order to eliminate the disadvantages of assumptions and ignorants and differences in values of parameters and obtain a better insight into the biomechanical aspects and estimation risk of the endodontically treated maxillary two-rooted first premolar, the behavior of different direct restoration designs and materials in the treatment of cuspal fracture of maxillary first premolars should be evaluated with laboratory experiments and long-term clinical trials.

Within the limitations of the present study, it can be concluded that direct cuspal coverage with resin composites transfers less stress to the enamel than restorations without cuspal reduction and appears to be a reliable extracoronal reinforcement method in restoring maxillary first premolar with missing palatal cusp. Reinforcing the restoration with either post or intraradicular extensions was both protective in the case of dentin. Intraradicularly supported direct restoration of endodontically treated maxillary first premolar with resin composites appears to be a safe option for dentin, while it may not be the best choice for enamel.

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Original Article

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Skin Findings in Cystic Fibrosis Cases

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BACKGROUND/AIMS
Clinical trials investigating skin findings of cystic fibrosis are limited. The aim of the present study was to evaluate the dermatological findings of patients with cystic fibrosis.

MATERIAL and METHODS
Twenty-six patients diagnosed with cystic fibrosis by the Department of Pediatric Chest Diseases were included in the study. In the pediatric chest diseases outpatient clinic, full blood, vitamin D, vitamin E, albumin, and IgE tests were recorded. In addition to the routine dermatological examination required from the pediatric chest diseases polyclinic, a diagnosis of aquagenic wrinkling was made. The cases were contacted with water at at 39°-40° C in 27°C room temperature conditions, and the water-related wrinkle was assessed after 3 and 5 min of contact.

RESULTS
There were 12 male and 14 female cases. The average age of the patients was 78.80 (8-192) months, and the mean disease duration was 52.53 (2-180) months. In the dermatological examination of the cases, xerosis cutis (18 cases, 69.2%) was most frequently found. Aquagenic palmar wrinkles were observed in 20 (76.9%) cases, and palmar wrinkles were >30% at 5 min. In 5 (25%) cases, delta F508 mutation was present. In 7 (26.9%) cases, pili annulati was observed by light microcopy.

CONCLUSION
The most common skin finding in cystic fibrosis cases is xerosis. The percentage of aquagenic wrinkling is 76.9%. To our knowledge, the association of cystic fibrosis with pili annulation is a previously unreported finding and was reported for the first time in our study.

Keywords: Cystic fibrosis, dermatologic findings, pili annulati, aquagenic palmar wrinkle

INTRODUCTION

Cystic fibrosis is an autosomal recessive disorder. There is a defect in the gene region that encodes the chlorine ion transmembrane regulatory channel located in the long arm of chromosome 7. Globally, the delta F508 mutation has been identified to be responsible for the formation of 85% of defective genes (1). Abnormal ion transport is responsible for the clinical presentation. Chronic bacterial infection of airways and sinuses, fat malabsorption, infertility in men, increase chlorine in sweat, and exocrine pancreatic insufficiency are the clinical findings. Skin findings of cystic fibrosis are important findings of the disease. Increased incidence of atopy, increased drug hypersensitivity reactions, premature skin wrinkles caused by water, and vasculitis are the skin findings, especially in vitamin deficiencies (zinc, protein, and essential fatty acids). Early skin wrinkle that is formed with water is a rare condition, and its cause is unknown. Early skin wrinkle formed with water is also reported to be seen with atypical cystic fibrosis and classical cystic fibrosis. Skin findings can be associated with the disease as primary or secondary (2). Pili annulati is a rare hair shaft abnormality with a characteristic shiny appearance due to alternating light and dark bands of the hair shaft, and there is no study about the relationship between cystic fibrosis and pili annulati in the literature (3). Clinical trials investigating cystic fibrosis skin findings are limited. The skin findings are sometimes the first findings in this disease. The aim of the present study was to evaluate the dermatological findings of patients with cystic fibrosis.

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MATERIAL and METHODS

Ethical approval was obtained from the ethics committee of Necmettin Erbakan University Meram School of Medicine. Inclusion criteria were cystic fibrosis cases diagnosed by the department of pediatric pulmonary disease clinic and referred for dermatological evaluation and cases admitted to the dermatology department. The diagnosis was based on the current criteria, including symptoms consistent with cystic fibrosis and the presence of two disease-causing cystic fibrosis transmembrane conductance regulator (CFTR) mutations or sweat chloride levels >60 mm (4). The study was conducted from January to July 2016. The exclusion criteria for aquagenic wrinkling were used, and these are hyperhidrosis of the palms and soles and usage of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, and selective cyclooxygenase-2 inhibitors. Age, gender, disease duration, history of dermatological disease, which present at birth without a diagnosis in the early period, atopic predisposition, and history of previous or active dermatological disease were determined, and dermatological examination was performed. The hands of the cases were contacted with 39°-40° water; water-dependent wrinkle was assessed after 3 min of contact.

FIGURE I. Palmar wrinkles >30% at 5 min

FIGURE 2. Pili annulati

In the palmar area, a wrinkle >30% was evaluated as positive (4). The hairs collected from the cases were evaluated by a light microscopy. Drugs used and laboratory findings were recorded. The pediatric chest diseases clinic performed routine complete blood count, zinc, vitamin D, vitamin E, and IgE tests in these cases. The hair, skin, and nail examinations of the cases were completed, and the appropriate dermatosis treatment was planned. Verbal informed consent was obtained from the patients and parents for the publication of the study.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences version 22.0 (IBM Corp.; Armonk, NY, USA). The normal distribution suitability of the variables was tested by the one-sample Kolmogorov-Smirnov test. Variables with normal distribution were expressed as mean and standard error averages (mean±SHO). Chi-square and Student's t independent tests were used for statistical analysis. A $p<0.05$ was accepted as statistically significant.

RESULTS

Twenty-six patients diagnosed with cystic fibrosis by the Department of Pediatric Chest Diseases were included in the study. There were 12 male and 14 female cases diagnosed. The average age of the cases was 78.80 (8-192) months. The median disease duration of the cases was 52.53 (2-180) months. Owing to atopic dermatitis, diaper dermatitis, urticaria and dyshidrotic eczema, xerosis, and ichthyosis vulgaris, 5 (19.2%) cases were referred to the dermatology polyclinic. Two (7.69%) cases had a persistent diaper dermatitis story. The most common dermatological examination of the cases was xerosis cutis (18 cases, 69.2%) and other dermatoses (30.7%). Xerosis cutis was accompanied by cafe au lait macules (4 cases, 22.2%), nevus (4 cases, 22.2%), and seborrheic dermatitis (3 cases, 16.6%). Drumstick fingernails were observed in 7 (26.9%) cases. All of the cases had normal tooth development. Aquagenic wrinkling of the palms was observed in the cases. The hands of the cases were held in 39°-40° water. Twenty (76.9%) cases had palmar wrinkles >30% at 5 min (Figure 1). In 5 (25%) cases, delta F508 mutation was present. The hairs of the cases were evaluated by light microscopy, and 7 (26.9%) cases had pili annulati (Figure 2). The median scores of vitamin A, vitamin D, and vitamin E were 0.90 (0.40-12.20), 21.50 (7.00-38.0), and 14.55 (0.35-55.00), respectively. The median score of zinc in 20 cases was 13.75 (1.00-40.08). Of the cases, 69.2% vitamin A, 46.2% vitamin D, 42.3% vitamin E, and 19.2% zinc levels (23.1% in female and 15.4% in male) are decreased. Among them, 15.4% had anemia. The normal ranges of vitamin A (1.05-2.45 µmol/L), vitamin D (winter: 10-60 ng/mL and summer 20-120 ng/mL), vitamin E (11.6-46.4 µm/L), and zinc (men: 11.1-19.5 µmol/L and women: 10.7-17.5 µmol/L) were assessed in our laboratory.

DISCUSSION

Cystic fibrosis with dermatitis is known only in 24 cases (5), and presumably metabolic abnormalities and deficiencies of protein, zinc, and essential fatty acids are responsible for the formation of this dermatitis (1, 6-8). In the cases, widespread desquamative skin eruption starting from periorificial, perineum, and extremities and peeling paint rash accompanied by hypoproteinemia, anemia, increased liver enzyme, and malabsorption findings with widespread eruption can be seen. Generally,

the hair and nails are not affected (9). These rashes resemble acrodermatitis enteropathica (1). Pekcan et al. (10) reported a case of a 4-month-old boy who was admitted for having diffuse eruption in the perianal region, legs, trunk, hands, and face with failure to thrive, edema, hypoalbuminemia, and anemia. They thought he had acrodermatitis enteropathica-like eruption due to malabsorption. Cystic fibrosis associated with malabsorption and insufficient nutrition will lead to hypoproteinemia, zinc deficiency, and fatty acid deficiency, which may cause skin eruptions similar to acrodermatitis enteropathica. The eruption completely resolved with enzyme supplement, proper nutrition, and skin care (10). Vesicle, bullae, and pustule formation can also be seen. Eczematous skin can be infected secondary to *Candida albicans* and/or bacteria. Eruptions typically begin in the diaper area and may range in the perioral area, extremities, and entire body. A previous study reporting cheilitis was found (11). This rash is resistant to topical steroids, imidazoles, and antibiotics. Zinc replacement alone is not enough. The rash is stretching by intense nutritional support with pancreatic enzyme replacement within 2 weeks. A widespread rash with protein energy malnutrition in cystic fibrosis cases, an indication that prognosis is worse in these cases, was seen (1). Although antibiotics used for the treatment of lung infections in cystic fibrosis are thought to have an increased incidence of atopy as a secondary, in a study of 100 patients with cystic fibrosis, 16% (12) were found with urticaria, which is not different from the incidence of urticaria in the normal population (15%-25%) (12-13). In addition, atopic conditions do not cause urticaria development. It was found that urticaria was seen more frequently in atopic individuals, and that the cause was often food. It is also seen in non-atopic cases as chronic urticaria and often idiopathic (12). One of our cases had anamnesis of urticaria.

The atopy rates are higher in cystic fibrosis cases than in normal populations. The rates of atopy vary from 46% to 76% (14-15), but this ratio is found to be 40% in the normal population (16). In our case, 5 (19.2%) patients were referred to the dermatology polyclinics due to atopic dermatitis, diaper dermatitis, urticaria and dyshidrotic eczema, xerosis, and ichthyosis vulgaris. There were stubborn diaper dermatitis stories in 2 (7.69%) cases. The most common dermatological examination of the cases was xerosis cutis (18 cases, 69.2%) and other dermatoses (30.7%). Xerosis cutis was associated with cafe au lait macules (22.2% in 4 cases), nevus (22.2% in 4 cases), and seborrheic dermatitis (16.6% in 3 cases). None of the cases described a common skin eruption at the time of diagnosis. None of the case has acrodermatitis enteropathica-like eruption or its history. One of our cases had atopic dermatitis story in the past. The most common skin lesion detected is xerosis cutis (69.2%). Of the cases, 18 can be interpreted as favoring atopy because it is in the minor criteria of atopic dermatitis, but it may not be directly related to atopic dermatitis. In addition, vitamin A deficiency causes skin dryness (17). Vitamins A and D were decreased in our study. In our cases, the mean zinc level was found within the normal range. Therefore, the presence of both cystic fibrosis and vitamin deficiency in our cases can be seen as atopic predisposition used to describe skin dryness.

In cases with cystic fibrosis, premature skin rupture on the hands and feet is seen after exposure to water (9, 18). The skin crust typically begins to form in the second minute of exposure to the water (19) and describes that when they have jobs associated with water, they have wrinkled hands (20-21). This finding is usually transient and remains within a few hours of contact with water (20). Findings, such as itching, tingling, and hyperhidrosis, may be accompanied (20-21). This condition is not related to the degree of malnutrition. The aquagenic palmar wrinkle is called transient reactive papulotranslucent acrokeratoderma. When seen without cystic fibrosis, it is called aquagenic keratoderma, aquagenic syringeal acrokeratoderma, aquagenic palmoplantar acrokeratoderma, and transient reactive papulotranslucent acrokeratoderma. The mechanism of formation, increased sweat chloride content, increases the binding of keratin to water, the mutated CFTR gene changes the regulation of the water membrane channels, aquaporins, resulting in abnormal fluid regulation throughout the epidermis. Eccrine channel dysfunction is also responsible for aquagenic palmar wrinkling (9). Early palmar wrinkles associated with water were found to be related to the homozygous gene delta F508, which is frequently detected for cystic fibrosis (20). In a study in which 44 cases and 26 healthy cases were included, the cases were evaluated for aquagenic palmar wrinkles by standing in water at 39°-40° C in 27°C room temperature conditions for 3 min. The aquagenic palmar wrinkle score was statistically significantly higher in cases with cystic fibrosis than in the control group. These cases were found to be homozygous positive for delta F508 (18). In another study, 21 patients with cystic fibrosis, 13 carriers, and 15 control patients were found to be positive in 25% and 80% of patients with aquagenic wrinkling, respectively, but not in the control group and statistically significant (2). In the study by Tolland et al. (22), 105 cases of cystic fibrosis questioned for aquagenic palmar wrinkling and 41% were positive. Since these cases are preliminary about the gastrointestinal system and chest diseases, they suggest that they do not care about it as much as they should, and they do not report to the doctor. Again in a study of 37 cases, this rare condition was found to be positive in 19 cases (18). In the study by Arkin et al. (4) involving 51 cystic fibrosis cases and 25 controls, the hand was immersed for 5 min in 39°-40° water. The detection of an aquagenic wrinkling at ≥30% of the hand surface was considered positive. Transepidermal water loss of the palms was also seen. Aquagenic palmar wrinkles were detected in 43 (84%) cases, but not in the control group. In addition, it has been found that transepidermal water loss is higher in cases with cystic fibrosis, which is an aquagenic palmar wrinkling, than in cases without aquagenic palmar wrinkling with cystic fibrosis (4). In our study, 20 (76.9%) cases had palmar wrinkles in >30% at 5 min. In 5 (25%) cases, delta F508 mutation was present.

The nail and hair are not affected in cystic fibrosis (9). In our study, fingernails were clubbed in 7 (26.9%) cases. It was thought that the appearance of this drumstick finger, which had no significant nail finding, developed due to pulmonary involvement of the present disease. All of the cases had normal tooth development. In contrast to acrodermatitis enteropathica, the mucous membranes and nails are not retained (2). In our study, there were no description of mucosal involvement and no mucosal involvement at the time of examination.

Alopecia has been reported at various grades, and hypoalbuminemia and hypoproteinemia are usually present in these

cases (23). Congenital generalized follicular hamartoma associated with hair loss was reported in three relatives with cystic fibrosis (24). Case reports with hair depigmentation and dermatitis were present (25). Dalgıç et al. (26) reported an acrodermatitis-like rash on an 11-month-old cystic fibrosis and a gray hair onset at 3 months. With enzyme replacement, the complaints at the case have declined, and gray hair is defined as associated with cystic fibrosis. Pili annulati is a rare hair shaft abnormality with a characteristic shiny appearance due to alternating light and dark bands of the hair shaft. The light bands seen by the unaided eye correspond to the dark bands seen by light microscopy. They are due to air-filled cavities within the cortex of the hair shaft, which has been confirmed by scanning and transmission electron microscopy (27). Pili annulati is considered to be an autosomal dominant disorder, but sporadic cases have also been described (3). Pili annulati diagnosis and clinical manifestations, as well as in light microscopy, are made based on the presence of dark bands (28). On differential diagnosis, the pseudo-pili annulati that shows similar banding in the main body of the hair is located. The banded appearance of the pseudo-pili annulati is due to the superficial optical effect caused by the characteristic bending and elliptical shape of the hair. Although the pseudo-pili annulati shows similar microscopic findings, this condition is not inherited and is not associated with any hair cortex anomaly. Both hair diseases are mainly seen in light hair, and there is no coexistence with hair fragility. With transverse illumination, the pili annulati light is banded whichever way it comes from, whereas the pseudo-pili annulati is seen only when the hair is turned to certain positions. In addition, the pseudo-pili annulati has no abnormality in the scanner and transparent electron microscope examination of the hair cortex and cuticle (29). In the literature, there were no studies about the relationship between cystic fibrosis and pili annulati. Pili annulati is found to be a locus of chromosome 12q24.32-24.33 (28, 30). Cystic fibrosis chromosome is 7. Although there is a connection for the F508 mutation in the chromosome, inheritance patterns are not similar. Pili annulati is an autosomal dominant disorder, and cystic fibrosis is an inherited autosomal recessive disorder. The hairs of the cases were analyzed under light microscopy, and 7 (26.9%) cases had pili annulati. In our case with cystic fibrosis, this finding is striking considering the frequency of occurrence in both diseases. The main limitation of this study were the limited number of cases.

The most common skin lesion is xerosis cutis. Transient aquagenic palmar wrinkling is a rare condition associated with the occurrence of cystic fibrosis and may be a clue to early diagnosis. In our study, the percentage of this symptom is 76.9%. When there are skin drying and transient aquagenic wrinkling of the palms in the cases, cystic fibrosis should also be considered and investigated by the pediatricians. Pili annulati was an interesting finding, and we thought that these two conditions can be often seen together. Previously, children with cystic fibrosis have not been reported in the literature. Therefore, this finding is needed to assess cystic fibrosis in children for pili annulati more carefully. In the cystic fibrosis investigated cases, in addition to other findings, aquagenic skin wrinkling should also be questioned, which sometimes makes it easier to make the diagnosis and maybe look for hair for pili annulati.

Ethics Committee Approval: Ethics committee approval was received for this study from Necmettin Erbakan University Meram School of Medicine (Approval Date: 01.06.2018, Approval Number: 2018/1392).

Informed Consent: Verbal informed consent was obtained from the patients and parents of the patients for publication.

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Original Article

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Using Quick Test, California Mastitis Test, and Somatic Cell Count for Diagnosis of Subclinical Mastitis Related with Human Health Risk

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BACKGROUND/AIMS
The aim of the present study was to compare Quick Test (QT) in the diagnosis of subclinical mastitis related with human health risk with California Mastitis Test (CMT) and to determine the compatibility of QT with Somatic Cell Count (SCC) using reference data from Fossomatic.

MATERIAL and METHODS
The study was performed using milk samples collected from 160 individual udder quarters of 40 Holstein cows at three different farms. Milk samples were initially checked by CMT and QT. Then, the samples were sent for SCC analyses.

RESULTS
The SCC results (0-100,000 cell/mL) of 101 (101/160) samples belonging to ≤100 standards of QT category were found to be compatible in the ratio of 60.39%. When QT standards of ≤100 and 250 were compared with the SCC results, the negative subclinical mastitis values (0-250,000 cell/mL) were compatible in the ratio of 84%. When CMT was compared with SCC, the negative subclinical mastitis values of CMT were found to be compatible with the SCC results (0-250,000 cell/mL) in the ratio of 85.9%. For the determination of all cases with subclinical mastitis, SCC data were found to be compatible with QT and CMT in the ratios of 97.6% and 63.4%, respectively. When QT and SCC were compared with each other, the specificity, sensitivity, and false ratio of QT were detected as 84.0%, 97.5%, and 16.7%, respectively.

CONCLUSION
Quick Test is a supporting method to other tests or alternative method to CMT in the diagnosis of subclinical mastitis related with human health risk.

Keywords: California mastitis test, quick test, somatic cell count, subclinical mastitis

INTRODUCTION

Generally, mastitis is the inflammation of the mammary glands with no involvement of the skin tissue (1). The use of bulk milk Somatic Cell Count (SCC) as an indicator of farm hygiene has been related to the potential human health risk. Viable pathogens and their toxins can be transferred from the milk of infected quarters directly to humans. A large and diverse group of human pathogens reside in the cow's environment, such as *Salmonella dublin*, *Campylobacter jejuni*, and *Listeria monocytogenes*. These bacteria are often pathogens or normal flora of dairy cows. Evidence has shown that *Mycobacterium avium* subsp. *paratuberculosis*, associated with Johne's disease in cattle and isolated from human patients with Crohn's disease, may survive some accepted milk pasteurization procedures. Although the possible association between shedding of *M. avium* subsp. *paratuberculosis* in milk and subsequent survival after pasteurization is compelling, the rate of shedding is low in infected cows and not related to an increase in SCC. Evidence suggests that contamination of milk with most of these pathogens occurs during or after harvest of milk and is not due to intramammary infections. However, herds with high bulk milk SCC are more likely to have these pathogens infecting cows and are present in elevated populations in the farm environment. The tempting inference is that farms ineffective in implementing hygiene practices to reduce bulk milk SCC are also ineffective in other farm hygiene measures aimed at reducing exposure of milk to human pathogens via routes other than intramammary infections (2, 3). Mastitis is a

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disease that causes important economic losses (4-6). In cows, it is generally accepted as the most complicated and high-cost disease, causing the highest economic losses to the milk producer (7-9). Subclinical mastitis is an overemphasized form of mastitis in economic terms due to its deleterious effect on both milk production and quality (10). It is a kind of mastitis in which factors causing infection are found in the mammary glands; however, there is no visible disturbance on the mammary or in milk. Among the mastitis originated losses, 70% of the loss is related to subclinical mastitis (11). The development of subclinical mastitis increases during the early lactation period, and a great percentage of intramammary infections appear in the postpartum period (12-14). There have been many studies that aim to develop treatments for clinical mastitis and to obtain high milk by controlling subclinical mastitis (15, 16). An increase in SCC is observed following inflammation of the mammary glands (17). The SCC value of milk from healthy mammaries is <200,000 cell/mL, involving epithelial cells and leukocytes (18). Direct and indirect methods are required for SCC. Electronic devices are used in the laboratory for the direct determination of SCC (19). The SCC values of milk samples are the indicator of inflammation level of the mammaries and form the basis of various indirect tests for mastitis. High values of SCC are generally an indicator for inflammation in the mammaries (17). In 1957, the California Mastitis Test (CMT), which is a quick and reliable method, was developed to identify unhealthy milk (20). It is a cheap, fast and easy test and is one of the indirect methods used in the determination of SCC in milk (19, 21). Under field conditions, although microbiological analysis from each mammary lobe and analysis of active substance are the most confidential methods in the diagnosis of mastitis, they are time-consuming and expensive. Therefore, CMT and SCC provide economic, quick, and reliable results in the diagnosis of infected mammary lobes (22).

MATERIAL and METHODS

Milk samples were collected from 160 individual udder quarters of 40 Holstein cows at three different farms. Foremilk was obtained from cows without mastitis, udder lobes and cow numbers were recorded, and samples were placed in tubes. First, CMT analysis was performed on all samples at the farm, followed by SCC and QT. Finally, all samples were sent to the Cyprus-Turkish Dairy Industry Institution, Quality Control Laboratory for the determination of the SCC values.

The tests were evaluated as follows:

California Mastitis Test (CMT): CMT was performed according to the Schalm and Noorlander principles (20). For this purpose, the CMT solution was obtained from DeLaval (Cardiff, UK). In test chambers, milk samples were evaluated in accordance with the structure and color change of the reaction after the addition of the CMT solution. The condition without any reaction was evaluated as negative (-); whereas positive reactions were categorized as weak positive (+), positive (++), and strong positive (+++).

Quick Test (QT): The PortaSCC Quick Test (PortaCheck, Moorestown, USA) was used for the practical determination of the SCC. QT standards were categorized as ≤100, 250, 500, 750, 1500, and ≥3000. The results were evaluated based on color change according to different shades of blue.

Somatic Cell Count (SCC): The SCC was performed in milk samples by using the Fossomatic™ FC 5000 (Foss, Hillerod, Denmark) device, and the results were evaluated as SCC.

In the present study, ranges including ≤100: 0 to ≤100×10^3 cell/mL, 250: 101-250×10^3 cell/mL, 500: 251-500×10^3 cell/mL, 750: 501-750×10^3 cell/mL, 1500: 751-1500×10^3 cell/mL, and ≥3000: 1501 to ≥3000×10^3 cell/mL were selected as the baseline for the QT standards, and the results were compared with those from the CMT and SCC analyses.

According to the –, +, ++, and +++ classification of CMT, SCC was determined as –: 0-250×10^3, +: 251-500×10^3, ++: 501-1500×10^3, and +++: 1501 to ≥3000×10^3 cell/mL, respectively.

The SCC values were accepted as the reference comparison values during laboratory evaluations.

Statistical Analysis

The method by Roelofs et al. (23) was modified for the calculation of sensitivity, specificity, and false ratio and applied as follows:

Diagnosis	QT or CMT	SCC
Mastitis +	a	b
Mastitis -	c	d

CMT: California Mastitis Test; QT: Quick Test; SCC: Somatic Cell Count.

In the diagnosis of mastitis, the sensitivity (efficiency, detection rate, and treatment ratio), specificity (negative diagnosis), and false ratio were calculated according to the formulas: (a/(a+c)×100), (d/(b+d)×100), and (b/(a+b)×100), respectively (23). Sensitivity calculates the positive diagnosis and the detection reliability of mastitis. Specificity calculates the negative diagnosis and the detection reliability of mastitis. False ratio calculates the mistakes in the deviations. Descriptive tests were performed in the calculation of mean values and standard deviations. The PASW Statistics (IBM, SPSS Corp.; Armonk, NY, USA) version 18.0 software for Windows was used for all statistical analyses. The aim of the study was to determine the use of QT in comparison with CMT and SCC in the diagnosis of subclinical mastitis.

The present study was laboratory based and did not use any human materials. Therefore, ethical approval and informed consent are not necessary. The study was performed in accordance with the principles of the Declaration of Helsinki.

RESULTS

Among 160 samples, 101 had a standard value ≤100 with QT. When the SCC results (0-100,000 cell/mL) of 101 samples were compared, the results were found to be compatible in the ratio of 60.4% (n=61). Of 101 samples with ≤100 standard value, 28.7% (n=29) were evaluated as negative in terms of subclinical mastitis according to the SCC (100-250,000 cell/mL) interval. When QT ≤100 standards were compared with the SCC results that were accepted as negative subclinical mastitis (0-250,000 cell/mL), the results were found to be

TABLE 1. The compatibility ratios between QT and SCC

QT/SCC		SCC (×1000/cell/mL)					
		0-100	101-250	251-500	501-750	751-1500	1501-3000 ↑
QT	≤100	61 60.39%	29 28.71%	8 7.92%	-	2 1.98%	1 0.99%
	250	1 5.55%	9 50%	3 16.66%	4 22.22%	1 5.55%	-
	500	-	1 7.14%	2 14.28%	4 28.57%	5 35.71%	2 14.28%
	750	-	-	1 16.66%	3 50%	1 16.66%	1 16.66%
	1500	-	-	-	-	4 44.44%	5 55.55%
	3000	-	-	-	-	-	12 100%

QT: Quick Test; SCC: Somatic Cell Count

TABLE 2. The compatibility ratios between CMT and SCC

CMT/SCC		SCC (×1000/cell/mL)					
		0-100	101-250	251-500	501-750	751-1500	1501-3000 ↑
QT	Negative (0-250)	53 67.94%	14 17.94%	7 8.97%	2 2.56%	1 1.28%	1 1.28%
	+ (251-500)	7 16.67%	15 35.72%	10 23.81%	3 7.14%	6 14.28%	1 2.38%
	++ (501-1500)	2 9.09%	6 27.27%	3 13.63%	3 13.63%	4 18.18%	4 18.18%
	+++ (1501-≥3000)	-	-	-	1 5.55%	3 16.66%	14 77.77%

QT: Quick Test; SCC: Somatic Cell Count

TABLE 3. The compatibility ratios between CMT and QT

CMT/SCC		SCC (×1000/cell/mL)					
		0-100	101-250	251-500	501-750	751-1500	1501-3000 ↑
CMT	Negative (0-250)	67 84.81%	6 7.59%	6 7.59%	-	-	-
	+ (251-500)	25 60.97%	10 24.39%	2 4.87%	1 2.43%	3 7.31%	-
	++ (501-1500)	7 31.81%	2 9.09%	5 22.72%	4 18.18%	3 13.63%	1 4.54%
	+++ (1501-≥3000)	2 11.11%	1 5.55%	1 5.55%	1 5.55%	3 16.66%	10 55.55%

CMT: California Mastitis Test; QT: Quick Test

TABLE 4. The manifestation of specificity, sensitivity, and false ratio results in comparison with half-quantitative test number (QT and CMT) with SCC

Parameters	Comparisons		
	QT/SCC	CMT/SCC	CMT/QT
Subclinical mastitis negative 0-250(×1000/cell/mL) (specificity)	84.0% (100/119)	85.9% (67/78)	92.40% (73/79)
Subclinical mastitis positive ≥250 (×1000/cell/mL) (sensitivity)	97.5% (40/41)	63.4% (52/82)	41.97% (34/81)
False ratio	16.7% (20/120)	27.5% (44/160)	39.1% (47/120)

CMT: California Mastitis Test; QT: Quick Test; SCC: Somatic Cell Count

highly compatible with ratios of 89.1% and 10.9%, respectively. When the results of QT ≤100 and 250 standards were compared with SCC, the negative subclinical mastitis values (0-250,000 cell/mL) were found to have a compatibility ratio of 84.0% (Table 1).

When CMT was compared with SCC, the negative subclinical mastitis values (0-250,000 cell/mL) of CMT were found to be compatible in the ratio of 85.9% (Table 2).

When the results of QT and CMT were compared, the negative subclinical mastitis values (0-250,000 cell/mL) of CMT were found to be compatible in the ratio of 93.3% (Table 3).

Proportional compatibility was determined between QT and SCC and CMT and SCC with the ratios of 97.57% and 63.42%, respectively, in all positive subclinical mastitis cases ($p<0.001$).

When QT was compared with the SCC results, the specificity, sensitivity, and false ratio of QT were 84.0% (negative), 97.5% (positive), and 16.7%, respectively. In other CMT/SCC and CMT/QT comparisons, the specificity ratios of CMT were determined as 85.9% and 92.4%, respectively (Table 4).

DISCUSSION

In cows, mastitis has been generally accepted as the most complicated and costly disease, resulting in the highest economic losses in the milk industry (8-10, 24, 25). Subclinical mastitis is the overemphasized form of mastitis in terms of economical aspect due to its effects on milk production and milk quality. The losses caused by mastitis involve deteriorating milk quality, lack of quality premium milk for buyers, treatment expenses for clinical mastitis, risks of antibiotic residuals, slaughtering, and death (10). Most of the farmers considered the losses for clinical cas-

es, animals that had to be killed, veterinary services, and drug costs (24, 25). The high losses of milk production are unclear or non-relevant reasons of subclinical mastitis cases (25).

Dohoo and Meek (26) evaluated the SCC limit of subclinical infected mammary lobes and mixed milk as 300,000 cell/mL and 250,000 cell/mL, respectively. Direct (e.g., Fossomatic) and indirect (CMT) methods are used for the determination of SCC in subclinical mastitis. PortaSCC® QT is an important indirect and simple test, showing the categories of <100,000 cell/mL and 250,000 cell/mL, separately. Our study was performed to show the compatibility levels and practicability of QT with CMT and SCC (Fossomatic Test). Sanforda et al. (27) have stated that CMT is the gold standard and has wide ranges. In the present study, the SCC results were considered as the standard value, and the accuracy of both tests (QT and CMT) was emphasized in accordance with the SCC results.

When healthy values below subclinical mastitis levels (<250,000 cell/mL) were considered, the compatibility ratios between QT and SCC and CMT and SCC were found as 81% and 85.9% (CMT negative values), respectively. Casura et al. (28) stated that CMT does not provide an adequate safety level in comparison with SCC for the diagnosis of subclinical mastitis, and that SCC is more reliable than CMT. The relationship between CMT and bacteriological results was between 70% and 86% (27, 29), and these results are supported by the CMT results obtained in the present study. The same result ratios were obtained from QT and SCC in this value category. The comparison ratio of 93.3% between CMT and QT revealed that both tests were reliable in the diagnosis of negative subclinical mastitis (0-250,000 cell/mL).

For the determination of all positive cases of subclinical mastitis, SCC data were found to be compatible with QT and CMT with ratios of 97.57% and 63.42%, respectively. The results of + subclinical mastitis were found to be compatible with SCC (0-250,000 cell/mL) in the ratio of 92.4%, particularly for CMT controls. There were statistically significant differences between both tests in terms of determination ratios of positive results ($p<0.001$). The sensitivity (63.4%) and specificity (85.9%) ratios between CMT and SCC demonstrated the possibility of mistakes in positive values using CMT. In studies comparing CMT with bacteriological results according to all CMT factors, Baştan et al. (29) detected a compatibility ratio of 85% between CMT and bacteriological results, whereas Varatanovic et al. (30) found a ratio of 55.7%. Obviously, compatibility ratios are dependent on bacterial types. In the present study, the SCC results were similar to those of Varatanovic et al. (30) although their comparison was performed using bacteriological results. Data obtained from SCC showed that CMT tests were less compatible than QT in cases of positive mastitis results with SCC. Studies were also performed on sheep and goat (31-33). The CMT control results showed that negative scores were more sensitive than positive scores. In the present study, the same result was also found in cows.

Sensitivity shows the true positive ratio (34). The higher sensitivity ratio of QT obtained by SCC revealed a more reliable determination of positive cases with QT in comparison with CMT. Specificity is the determination of true negative cases (34). The close and high specificity ratios in CMT and QT suggested that negative cases had the same reliability in both tests. Mastitis was not detected when CMT and QT results were compared, and the compatibility ratio of 93.33% (0-250,000 mL/milk) between both tests supports these findings.

Most studies indicate that decreasing the limits of SCC will positively influence acceptability and suitability of milk as measured by improved safety, milk quality, and value-added products. The relationship of high SCC milk with poor farm hygiene, antibiotic residues, and presence of pathogenic organisms and toxins offers an insight into the potential increase in safety risk factors to consumers when high SCC milk is marketed. However, consuming milk with high SCC does not appear to pose direct, specific health risks to humans. In conclusion, scientific studies have not shown that the ingestion of large numbers of bovine leukocytes is harmful to humans (35).

When comparing QT and CMT with both SCC and between themselves (CMT/QT), the specificity ratios were calculated as 84.0% and 92.4%, respectively. This result revealed the high sensitivity ratio of both tests in the determination of healthy cases (negative mastitis). When this result was compared with SCC, the sensitivity of QT was found as 97.5%. It is concluded that QT can be used easily in the field, and the ratios of "mastitis is present" and "mastitis is absent" are detected in higher ratios with QT in the diagnosis of subclinical mastitis related with human health risk.

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Determination of Antimicrobial Activity of *Corchorus olitorius* Leaf Extracts

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BACKGROUND/AIMS
The aim of this study was to determine the antimicrobial (antibacterial and antifungal) activity of the *Corchorus olitorius* (*C. olitorius*) leaf extracts, obtained from different regions of the Turkish Republic of Northern Cyprus.

MATERIAL and METHODS
A total of seven samples of seven different brands of the dried plant material (*Corchorus olitorius* leaves) were collected from Lefkosa, Kyrenia, Guzelyurt, Lefke, Iskele, and Gazimagusa. The leaf extracts were extracted with the methanol, ethanol, chloroform, and hexane solvent (1:10 [weight/volume]) at room temperature for 3 days under shaking conditions. After evaporation, the samples were suspended in methanol, ethanol, chloroform, and hexane at the final concentration of 100 mg/mL. The antimicrobial activity was evaluated using the disc diffusion method. The negative control included pure ethanol, methanol, chloroform, and hexane for each respective sample (methanol, ethanol, chloroform, and hexane extracts). The positive control included tetracycline for *S. aureus, S. epidermidis*, and *B. subtilis*; ciprofloxacin for *E. coli, Klebsiella* spp., and *E. cloacae*; nystatin for *C. albicans*; and teicoplanin for *E. faecalis*.

RESULTS
Antimicrobial activity was only displayed by hexane leaf extracts toward *B. subtilis* and *S. aureus*.

CONCLUSION
At the end of this study, it was observed that the methanol, ethanol, and chloroform extracts of the *C. olitorius* leaf displayed no antibacterial activity. Only one of the extracts, the hexane extract, showed the antimicrobial activity against both *B. subtilis* and *S. aureus*. Therefore, the leaf of *C. olitorius* can be used to treat people having infections caused by *S. aureus* and *B. subtilis*.

Keywords: Antimicrobial activity, *Corchorus olitorius* leaf, medicinal plant

INTRODUCTION

Corchorus olitorius (*C. olitorius*) is known as both a medical and a fiber plant from the family Tiliaceae. Commonly referred to as jute plant, it is known as *molehiya* in North Cyprus, Turkey, and Philippines, *moroheiya* in Japan (1), *Jew's mallow* in Hebrew, and *bush okra* in Nigeria and other West African countries (2). According to the authors, this species is native to India or the Indian sub-continent (Sri Lanka, Burma, etc.), but due to the presence of a variety of wild relatives in Africa and the fact that it has always been the leading leafy vegetable for the people of Nigeria, Sudan, Ivory Coast, Benin, Cameroon, etc., some authors now believe that the origin of *C. olitorius* is in fact Africa (3).

Corchorus olitorius leaves are known to be rich in nutrients such as iron, phosphorus, calcium, potassium, and carotene (4). It is used in the treatment of fever, tumors, pectoral pains, dysentery, aches, enteritis, cystitis, piles, and dysuria (2). Apart from its nutritional advantages, the sticks of *C. olitorius* can be gathered to be used as both fuel and for producing charcoal and gun powder (5).

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Medicinal plants have been known since the ancient times and have been used ever since to add flavor to food, to preserve food, to help promote good health, and to treat and prevent medical aliments (diseases), including infections. The reason for this are certain factors that include high costs of modern medicines, an onset of side effect when conventional pharmaceutical drugs are used, the rise in human population, and decreasing efficacy of modern synthetic drugs. Also, problematic are the emerging pathogenic microorganisms resistant to modern antibiotics and reduced effectiveness of these antibiotics. Several plants used traditionally have a potential antimicrobial property, and this has encouraged the optimism of scientists about the future of phytoantimicrobial agents (2, 6, 7).

MATERIAL and METHODS

A total of seven samples of seven different brands of the dried plant material (*C. olitorius* leaves) were collected from Lefkosa, Kyrenia, Guzelyurt, Lefke, Iskele, and Gazimagusa. All the *C. olitorius* leaf samples acquired from different regions of Northern Cyprus were grinded into powder using a porcelain mortar and then stored in the refrigerator at 4°C until further use. The leaf extracts were extracted with the methanol, ethanol, chloroform, and hexane solvents (1:10 [w/v]) at room temperature for 3 days under shaking conditions. After 72 hours, all the samples were filtered using the Whitman filter paper, and then all the methanol and ethanol leaf extracts were concentrated using a rotary evaporator, while the hexane and chloroform leaf extracts were evaporated under a fume hood, and then the extraction yield was calculated based on the dry weight of the leaves. After the evaporation of solvents, samples were suspended in methanol, ethanol, chloroform, and hexane at the final concentration of 100 mg/mL.

The antimicrobial activity was evaluated using the Kirby-Bauer disc diffusion method (8). For the antimicrobial test, *Staphylococcus aureus, Escherichia coli, Enterococcus faecalis, Bacillus subtilis, Staphylococcus epidermidis, Enterobacter cloacae, Klebsiella* spp., and *Candida albicans* were used. The antimicrobial activity for bacteria and yeast was performed on the Mueller-Hinton Agar. Sterile antimicrobial blank discs were placed strategically away from each other, and 15 mL of the appropriate samples was pipetted onto seven of the blank antimicrobial disc. Pure methanol, ethanol, chloroform, and hexane were used as negative control based on solvent of extraction. On the agar plate, the number 1 represented the Mulihiya, number 2 Othello, number 3 Karaca, number 4 Olkobirlik, number 5 Bafra, number 6 Baharyolu, and number 7 the Ender molokhia sample. As for the positive control, tetracycline (Bioanalyse Limited, 30 µg) was used as the positive control for *B. subtilis, S. aureus,* and *S. epidermidis*. Ciprofloxacin (Bioanalyse Limited, 5 µg) was used as the positive control for *E. coli, Klebsiella* spp., and *Enterobacter cloacae*. Nystatin (Oxoid, 100 units) was used as the positive control for *C. albicans*, while teicoplanin (Bioanalyse Limited, 30 µg) was used as the positive control for *E. faecalis*. All samples were incubated at 37°C for 48 hours. Following the incubation, the clear zones around the antimicrobial disc were examined and their diameters were measured.

The minimum inhibitory concentrations (MIC) of the *C. olitorius* leaf extracts that showed antimicrobial activity against test microorganisms were determined. This analysis was performed based on fact that the lowest inhibitory concentration determines to effective on test microorganisms. In this test, the 12.5, 25, 50, 75, and 100 mg/mL concentrations of the Baharyolu hexane leaf extract were investigated for their inhibitory effects against *B. subtilis* and *S. aureus*.

RESULTS

The highest extraction yield was found in the methanol extract, as an average 10.324%. The ethanol and chloroform extracts had an average extraction yield of 4.589% and 3.463%, respectively. The lowest extraction yield was recorded in the hexane extract with an average yield of 2.883% (Table 1).

TABLE 1. Extraction yield (%) for all leaf extracts

Name of the Molehiya Product	Ethanol Extracts (%)	Methanol Extracts (%)	Chloroform Extracts (%)	Hexane Extracts (%)
Olkobirlik	4.15	9.962	2.975	3.062
Othello	5.873	12.624	3.298	2.554
Mulihiya	4.007	9.648	3.732	1.84
Baharyolu	4.748	10.599	3.528	0.27
Bafra	4.523	10.171	2.405	2.296
Karaca	4.043	8.564	4.361	1.294
Ender	4.781	10.706	3.944	8.87

TABLE 2. Diameter of the inhibition zone (mm) (antimicrobial activity) of the methanol, ethanol, and chloroform leaf extracts (100 mg/mL concentration, 15 µL) against *Bacillus subtilis, Staphylococcus aureus*, and *Staphylococcus epidermidis*

Microorganisms Tested	Samples of Dried Molokhia								
	Mulihiya	Othello	Karaca	Olkobirlik	Bafra	Baharyolu	Ender	Methanol, Ethanol, Chloroform (NC)	Tetracycline (PC)
B. subtilis	-	-	-	-	-	-	-	-	32
S. aureus	-	-	-	-	-	-	-	-	25
S. epidermidis	-	-	-	-	-	-	-	-	-

(-) denotes a lack of antimicrobial activity toward both pathogenic microorganisms used.
PC: Positive control; NC: Negative control

All the leaf samples of the methanol, ethanol, and chloroform extracts displayed no antibacterial and antifungal activity against all the bacterial and fungus species used (Tables 2-5). As seen from Table 6, antimicrobial activity was only displayed by the hexane leaf extracts toward *B. subtilis* (10 mm) and *S. aureus* (12 mm) (Figure 1, 2).

As seen from Table 7, it was encountered any inhibitory effect of the hexane extract on *B. subtilis*. It was observed to low inhibitory effect for all tested concentrations on *S. aureus* as compared with the positive control. However, the growth of *S. aureus* was inhibited at the 12.5 mg/mL Baharyolu hexane leaf concentra-

TABLE 3. Diameter of the inhibition zone (mm) (antimicrobial activity) of the methanol, ethanol, chloroform, and hexane leaf extracts (100 mg/mL concentration, 15 µL) against *E. coli, Klebsiella* spp., and *E. cloacae*

	Samples of Dried Molokhia								
Microorganisms Tested	**Mulihiya**	**Othello**	**Karaca**	**Olkobirlik**	**Bafra**	**Baharyolu**	**Ender**	**Methanol, Ethanol, Chloroform, Hexane (NC)**	**Ciprofloxacin (PC)**
E. coli	-	-	-	-	-	-	-	-	30
Klebsiella spp.	-	-	-	-	-	-	-	-	28
E. cloacae	-	-	-	-	-	-	-	-	34

(-) denotes a lack of antimicrobial activity toward both pathogenic microorganisms used.
PC: Positive control; NC: Negative control

TABLE 4. Diameter of the inhibition zone (mm) (antimicrobial activity) of the methanol, ethanol, chloroform, and hexane leaf extracts (100 mg/mL concentration, 15 µL) against *C. albicans*

	Samples of Dried Molokhia								
Microorganisms Tested	**Mulihiya**	**Othello**	**Karaca**	**Olkobirlik**	**Bafra**	**Baharyolu**	**Ender**	**Methanol, Ethanol, Chloroform, Hexane (NC)**	**Nystatin (PC)**
C. albicans	-	-	-	-	-	-	-	-	25

(-) denotes a lack of antimicrobial activity toward both pathogenic microorganisms used.
PC: Positive control; NC: Negative control

TABLE 5. Diameter of the inhibition zone (mm) (antimicrobial activity) of the methanol, ethanol, chloroform, and hexane leaf extracts (100 mg/mL concentration, 15 µL) against *E. faecalis*

	Samples of Dried Molokhia								
Microorganisms Tested	**Mulihiya**	**Othello**	**Karaca**	**Olkobirlik**	**Bafra**	**Baharyolu**	**Ender**	**Methanol, Ethanol, Chloroform, Hexane (NC)**	**Teicoplanin (PC)**
E. faecalis	-	-	-	-	-	-	-	-	35

(-) denotes a lack of antimicrobial activity toward both pathogenic microorganisms used.
PC: Positive control; NC: Negative control

TABLE 6. Diameter of the inhibition zone (mm) (antimicrobial activity) of the hexane leaf extracts (100 mg/mL concentration, 15 µL) against *Bacillus subtilis, Staphylococcus aureus*, and *Staphylococcus epidermidis*

	Samples of Dried Molokhia								
Microorganisms Tested	**Mulihiya**	**Othello**	**Karaca**	**Olkobirlik**	**Bafra**	**Baharyolu**	**Ender**	**Hexane (NC)**	**Teicoplanin (PC)**
B. subtilis	-	-	-	-	-	10	-	-	32
S. aureus	8	-	9	9	10	12	8	-	25
S. epidermidis	-	-	-	-	-	-	-	-	-

(-) denotes a lack of antimicrobial activity toward both pathogenic microorganisms used.
PC: Positive control; NC:Negative control

TABLE 7. Minimal inhibitory concentration of the Baharyolu hexane leaf extract

	Samples of Dried Molokhia						
Concentration of the Hexane Extract	**12.5 mg/mL**	**25 mg/mL**	**50 mg/mL**	**75 mg/mL**	**100 mg/mL**	**Hexane (NC)**	**Tetracycline (PC)**
B. subtilis	-	-	-	-	-	-	32 mm
S. aureus	8 mm	9 mm	9 mm	11 mm	12 mm	-	25 mm

(-) denotes a lack of antimicrobial activity toward both pathogenic microorganisms used.
PC: Positive control; NC: Negative control

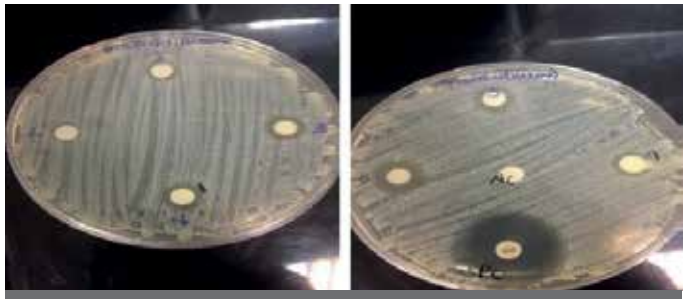

FIGURE 1. Antibacterial activity of the hexane extract toward *Staphylococcus aureus*

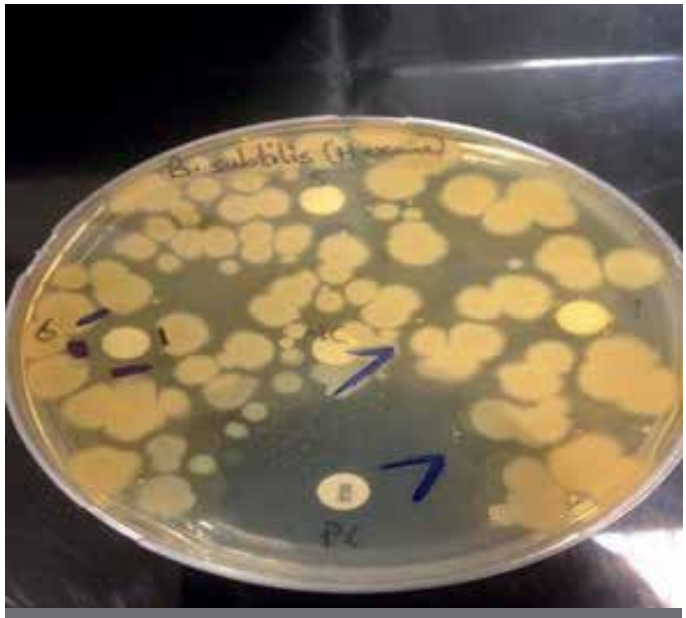

FIGURE 2. Antibacterial activity of the hexane extract toward *Bacillus subtilis*

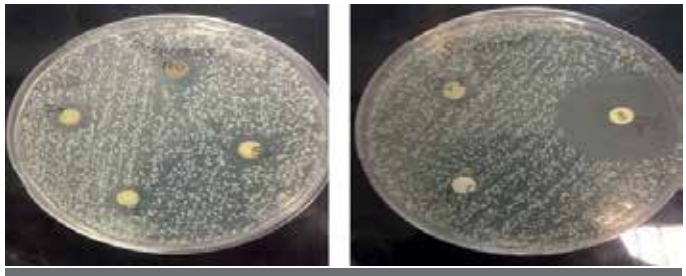

FIGURE 3. Clear indication of inhibition toward the growth of *S. aureus* at different concentrations of the Baharyolu hexane leaf extracts

FIGURE 4. No inhibition toward the growth of *B. subtilis* at different concentrations of the Baharyolu hexane leaf extract

tion (Figure 3, 4). Thus, the MIC value of the Baharyolu hexane leaf extract effective against *S. aureus* was 12.5 mg/mL. This result was similar to the inhibition zones recorded for the antimicrobial test.

DISCUSSION

The average extraction yields were 10.324% for methanol extracts, 4.589% for ethanol extracts, 3.463% for chloroform extracts, and 2.88% for hexane extracts. Sellami et al. (6) recorded the hexane extract (2.5%) with the lowest extraction yield between the ethanol (6.42%) and aqueous extract (10%) of *C. olitorius* leaves. This can be attributed to the fact that hexane is a non-polar solvent with a polarity index of 0.0. Also, different extraction yields (%) have been reported by Ilhan et al. (9). The yields of extraction for the petroleum ether extract, methanol extract, and ethyl acetate+water extract were found as 8%, 3.8%, and 2.2%, respectively.

The fact that all chloroform, ethanol, and methanol leaf extracts displayed no antimicrobial activity is not in line with other studies. Ullah et al. (10) concluded that the methanolic extract of different edible vegetables from Bangladesh showed antibacterial activity with the zone of inhibition ranging from 5 to 28 mm. The methanolic leaf extract of *C. olitorius* displayed the least antibacterial activity against *Shigella boydi* (6 mm) and *Vibrio mimicus* (5 mm). The methanolic leaf extract of *C. olitorius* displayed antibacterial and antifungal activities, with the diameters of zone inhibition ranging between 11 and 20 mm (9). In addition, Soykut et al. (11), reported that the *C. olitorius* ethanol leaf extract did not display any significant antimicrobial activity toward all tested bacterial and fungal strains.

The different finding was also stated for *C. olitorius* methanolic extract from Adegoke and Adebayo. The antibacterial activity of methanolic extracts against *S. aureus, E. coli, K. pneumonia*, and *S. typhi*. was observed at higher concentrations, such as 62.5, 125, 250, and 500 mg/mL. In these concentrations, the inhibition zone diameters against *S. aureus* were found as 5.0±0.3 mm, 6.0±1.0 mm, 7.0±0.6 mm, and 8.4±0.2 mm, respectively (2).

The zones of inhibition displayed by the hexane leaf extract against both *S. aureus* (12 mm) and *B. subtilis* (10 mm) were considerably lower than those displayed by the antibiotic (tetracycline) against those same bacteria. This can be attributed to the fact that the extract used was crude preparations. Further purifications or concentration enhancements might be needed to obtain more active compounds. Sellami et al. (6), also observed that the antibacterial activity displayed by different plant extract was relatively lower than the positive control (ampicillin). The *C. olitorius* hexane extract showed a low bactericidal activity with the diameter of inhibition <15 mm against *S. xylosus* (6).

In our study, the antimicrobial activity observed against *S. aureus* is similar to previous studies. It was reported to observe the antibacterial activity against *S. aureus,* these studies used the leaf and flower combination (essential oil from *C. olitorius*, 12.6±0.9 mm at 6 mg) (12) or just the leaf (methanolic extract of *C. olitorius*, 10.9±0.02 mm at 1.0 mg/mL) (7).

Also, the obtained antimicrobial activity against *B. subtilis* showed similarity to the results detected in another study car-

ried out by Driss et al. (12), where the zone of inhibition was recorded at 16.6±1.3 mm at 6 mg. It therefore stands to reason that an increase in the concentration of leaf extract used in this study might lead to a higher zone of inhibition.

S. aureus is the causative organism for urinary tract infections, food poisoning, abscesses, and respiratory infections. As for that, *B. subtilis* is the reason of food poisoning. So, the observed antimicrobial activity against these microorganisms is important to clinical treatment based on the medicinal plant.

The antimicrobial activity against tested gram-negative bacteria was not observed. This fact is similar to other studies concerning the antimicrobial activity against gram-positive and gram-negative bacteria. This is because the possession of an outer membrane by gram-negative bacteria that covers the cell wall limits the dilution of hydrophobic compounds, thus making them less likely to be affected by an antibiotic (9, 12).

Al-Yousef et al. (13) reported that the leaf and stem dry oils from *C. olitorius* showed an antibacterial and antifungal activity against all tested pathogen microorganisms. *S. aureus* was moderately sensitive with the 16 mm diameter of the inhibition zone against the obtained leafdry oil (13).

Table 7 shows the minimum inhibition concentration results of the *C. olitorius* hexane extracts against *B. subtilis* and *S. aureus*. Since there is no previous research on the hexane leaf extract of *C. olitorius*, the authors are not able to compare the results against anything.

As a result of our study, the methanol, ethanol, and chloroform extracts of the *C. olitorius* leaf were found to display no antibacterial activity against test microorganisms. However, the hexane extract developed an inhibitory effect against both *B. subtilis* and *S. aureus*. Especially, it was observed in the case of *S. aureus* that an increase in the extract concentration lead to an increase in the zone of inhibition based on the hexane extract. Therefore, the leaf of *C. olitorius* can be used by people with urinary tract infections, abscesses, skin infections, respiratory infections, endocarditis, osteomyelitis, and food poisoning to help them fight against infections caused by pathogenic microorganisms such as *S. aureus* and *B. subtilis*.

Ethics Committee Approval: Ethics committee approval was not required for this laboratory based study.

Informed Consent: N/A.

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Original Article

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Open Access Publishing in Otorhinolaryngology: An Emerging Trend among Turkish Scientists?

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BACKGROUND/AIMS
Scientific medical publishing has undergone significant changes in the last few decades, enabled by advances in technology. Together with these technological innovations, the development of alternative methods has become inevitable. Most authors have had difficulty in making decision between open access and the traditional subscription-based journals. In this study we aimed to compare the changes in citation numbers of open access vs. subscription-based journals in Otorhinolaryngology publishing among Turkish authors and institutions.

MATERIAL and METHODS
In this study we reviewed 28 Otorhinolaryngology (ORL) journals which have matched SCImago journal rank (SJR) values and included a total of 2,000 scientific papers published by Turkish authors between 2010 and 2015. All data extracted from SJR website and Google Scholar system.

RESULTS
There was statistically significant difference found between the subscription based (SB) and Open access (OA) according to the types of articles (p=0.000). The difference between the mean total cite number per article of SB and OA journals is not statistically significant but close to level of significance (p=0.061)

CONCLUSION
When choosing between open access and subscription based journals to publish, it is important to consider the journal's visibility, the cost of publication. Open access publishing trend is on the rise among Turkish researchers, though they still mostly prefer the subscription based journals in otorhinolaryngology category.

Keywords: Subscription based, open access, otorhinolaryngology

INTRODUCTION

In the last few decades, scientific medical publishing has undergone significant changes. These changes have been possible because of advances in internet technology and worldwide communication opportunities. Apart from printed traditional journals, electronic publishing has become widespread (1). These technological innovations have made the development of alternative methods inevitable, when compared with the classical publishing where the costs were traditionally provided from the readers or the public resources. Indeed, anyone with internet access can reach open access (OA) publications online with no boundaries. Thus, OA means unrestricted and free access to all available scientific information. Throughout the years, the authors were concerned about the concept of OA publishing and its potential damage to the system. The main reason for such worries has been the perception that in case the OA journals collected publication fee from authors rather than from readers, those journals would tend to easily accept substandard articles since their income would be directly proportional to the number of articles published. Thus, most authors have had difficulty in making decision between OA and the traditional subscription-based (SB) journals. Indeed four main factors gain importance when selecting a journal: visibility, cost, prestige, and speed.

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Impact factor (IF) is one of the most important criteria used to evaluate the quality of scientific journals. Despite its widespread use in the scientific world, the IF provided by Institute for Scientific Information (ISI) has recently been discussed (2). The main points of the opposition are the deficiency of citation quality assessment, poor comparability between the different areas of interest of the journals, and mainly English content of the publications. Self-citations, which are defined as referring articles from the same journal, are also considered a problem of this ranking system.

Based on the comparisons made by Falagas et al. (3), the SCImago journal rank (SJR) index might be a good alternative to the well-established journal IF, basing upon its OA nature, larger source database, and assessment of the quality of citations. It is recommended that the authors should consider all of these indices rather than just IF alone while assessing the influence and importance of medical journals in their respective disciplines. In this study, we aimed to compare the changes between citation numbers of OA and SB journals from 2010 to 2015 to explore the changing trends in otorhinolaryngology (ORL) publishing among Turkish authors and institutions.

MATERIAL and METHODS

In this study, we reviewed 28 (15 OA and 13 SB) ORL journals with matched SJR values (Table 1), and included a total of 2000 scientific papers published by Turkish authors between 2010 and 2015. All data extracted from the SJR website have been used as input for statistical analysis. The features of the articles were classified according to their institution (university, training and research hospital, state or private hospital), type of article (original research, letter to editor, case report, or review article), and subdivisions of ORL (otology-neurotology, rhinology-facial plastics, head and neck surgery, or others). Total and mean number of cites attributed to these articles were scanned using Google Scholar. The articles originating outside Turkey were not included in this study.

Statistical Analysis

All statistical analyses were performed with the Statistical Package for the Social Sciences version 20.0 (IBM Corp.; Armonk, NY, USA) statistical package. Student's t test, Mann-Whitney U test, and Chi-square test were used for comparison of groups, where required. A p of less than 0.05 was chosen as statistically significant.

RESULTS

There was no statistically significant difference between the mean SJR values of matched OA and SB journals in 2015 list (p=0.105) (Table 1). Among those 28 journals, the "Journal of Craniofacial Surgery", an SB journal, having an SJR index of 0.443 in 2015, was the host of the largest number of articles published by Turkish authors between years 2010 and 2015 (n=805). It was followed by "European Archives of ORL" (n=266), "International Journal of Pediatric Otorhinolaryngology" (n=183), and "The Journal of International Advanced Otology" (n=180).

This study included 2000 scientific papers (1604 in SB journals and 396 in OA) published by Turkish authors between 2010 and 2015. According to their institutions, 1280 of these articles originated from university hospitals, and 559 originated from training and research hospitals. There was no statistically significant difference between the SB and OA journals when compared with origin of the articles (p=0.197) (Table 2).

Statistically significant difference was found between the SB and OA journals according to the types of articles (p<0.001).

TABLE 1. List of matched subscription based (SB) and Open Access (OA) journals included in this study

Subscription-based journals and SJR values (2015)	Open access journals and SJR values (2015)
• Journal of Oral and Maxillofacial Surgery (0.938)	• Acta Otorhinolaryngologica Italica (0.877)
• European Archives of ORL (0.863)	• BMC Ear Nose Throat Disorder (0.780)
• Current Opinion in Otorhinolaryngology and Head & Neck Surgery (0.846)	• European Annals of Otorhinolaryngology Head and Neck Diseases (0.650)
• Journal of Otolaryngology Head and Neck Surgery (0.841)	• Noise & Health (0.563)
• Clinical Otolaryngology (0.779)	• Clinical and Experimental Otorhinolaryngology (0.552)
• International Journal of Pediatric Otorhinolaryngology (0.707)	• Journal of Oral& Maxillofacial Pathology (0.418)
• Cochlear Implants International (0.619)	• Head and Neck Oncology (0.452)
• Journal of Vestibular Research (0.610)	• Brazilian Journal of Otolaryngology (0.401)
• American Journal of Otolaryngology-Head and Neck Medicine and Surgery (0.586)	• International Tinnitus Journal (0.374)
• Journal of Craniofacial Surgery (0.478)	• Iranian Journal of Otorhinolaryngology (0.293)
• Journal of Laryngology & Otology (0.464)	• B-ENT (0.241)
• Oral and Maxillofacial Surgery Clinics of North America (0.401)	• Indian Journal of Otology (0.232)
• Indian Journal of Otolaryngology and Head & Neck Surgery (0.282)	• ENT Journal (0.231)
	• International Archives of Otorhinolaryngology (0.168)
	• Journal of International Advanced Otology (0.158)

*Mann-Whitney U test. p=0.105

SJR: SCImago journal rank

TABLE 2. Total number of published articles according to their institutions and type of the subscription

Type of the subscription	Institution				
	University	Training and research hospital	State hospital	Private hospital	Total
SB	1029 (%51.45)	437 (%21.85)	96 (%4.8)	42 (%2.1)	1604 (%80.2)
OA	251 (%12.5)	122 (%6.1)	15 (%0.75)	8 (%0.4)	396 (%19.8)
Total	1280 (%64)	559 (%27.95)	111 (%5.55)	50 (%2.5)	2000

*Chi-square homogeneity test. p=0.197

SB: subscription based; OA: open access

TABLE 3. Total number of published articles according to their type of article and type of the subscription

Type of the subscription	Type of article				
	Original research	Letter to editor	Case report	Review article	Total
SB	1051 (%52.55)	151 (%7.55)	383 (%19.5)	19 (%0.95)	1604 (%80.2)
OA	264 (%13.2)	4 (%0.2)	125 (%6.25)	3 (%0.15)	396 (%19.8)
Total	1315 (%65.75)	155 (%7.75)	508 (%25.5)	22 (%1.1)	2000

*Chi-square homogeneity test. p<0.001

SB: subscription based; OA: open access

TABLE 4. Total number of published articles according to their subdivisions of ORL-HNS and type of the subscription

Type of the subscription	Subdivisions of ORL- HNS				
	Otology neurotology	Rhinology facial plastic	Head and neck	Others	Total
SB	332 (%16.6)	475 (%23.75)	407 (%20.35)	390 (%19.5)	1604(%80.2)
OA	240 (%12)	53 (%2.65)	96 (%4.8)	7 (%0.35)	396(%19.8)
Total	572 (%28.6)	528 (%26.4)	503 (%25.15)	397 (%19.85)	2000

*Chi-square homogeneity test. p<0.001

SB: subscription based; OA: open access

TABLE 5. Total number of published articles according to their institutions and type of article

Institution	Type of article				
	Original research	Letter to editor	Case study	Review article	Total
University	822 (%41.1)	98 (%4.9)	339 (%16.95)	21 (%1.05)	1280 (%64)
Training and research hospital	379 (%18.95)	42 (%2.1)	138 (%6.9)	0	559 (%27.95)
State hospital	79 (%3.95)	9 (%0.45)	23 (%1.15)	0	111 (%5.55)
Private hospital	35 (%1.75)	6 (%0.3)	8 (%0.4)	1 (%0.05)	50 (%2.5)
Total	1315 (%65.75)	155 (%7.75)	508 (%25.4)	22 (%1.1)	2000

*Chi-square homogeneity test. p=0.197

TABLE 6. The standard error and the mean values of the total cites according to the type of subscription

Type of the subscription	Mean of total cite	Standard error
Subscription based	4.28	±1.370
Open access	5.76	±0.199
*Student's t test. p=0.061		

Original research articles were the most frequently published type in the SB journals (n=1051) (Table 3).

Among the ORL subdivisions, the most common topics were otology and neurotology (n=572) and rhinology and facial plastic (n=528). The SB and OA journals have statistically significant difference according to their subdivisions (p<0.001) (Table 4)

The types of articles were classified according to the origin of their institutions. The most frequent one was research articles from university hospitals among all institutions (n=822) (Table 5). Student's t test revealed that the difference between the mean total cite number per article of SB and OA journals is not statistically significant, but close to level of significance (p=0.061) (Table 6).

DISCUSSION

The SJR indicator is a measure of the scientific impact of medical journals. It explains the number of citations a journal receives,

and the value or dignity of the journals in which such citations come from. It is a numeric value that represents the average number of quotes received during the year selected in a document published in a medical journal over the last three years. The higher the SJR values, the higher is the prestige of the magazine (1). Different types of OA journals with various publishing modalities such as green, gold, and hybrid OA are currently in use. "Gold" OA is an example with unlimited instant access to all articles on the journals' website. With "Green" OA, researchers can reach the articles via the repositories of the institutions. In terms of "Delayed" OA, accessibility can be carried out after an embargo period. After a processing charge paid by the author in an SB journal, the article will be free to public access known as "Hybrid" OA (4). Thus, OA is not only a single unambiguous term, but is rather a set of possible strategies to distribute unrestricted scientific information accessible to all.

In the new era of constantly expanding internet technology, there are a large number of platforms, including social media sites and blogs, which can be accessed for free by anyone with an internet connection and a smartphone. Unlike traditional SB journals that require high registration fees from academic researchers to access journal content, the OA journals encourage authors to publish their findings online almost free of charge. This publishing modality plays an important role in the visibility and potential citations of an article required for the academic prestige. The "h-index", a new indicator proposed by Jorge E. Hirsch in 2005, is widely used today to evaluate scientists' research performance, rather than just the number of articles they produce. It measures the productivity of the scientist and the quality of that productivity altogether. To have a high h-index, it is necessary to publish significant number of articles. Each of these printed articles should have high citation numbers. At this stage, easy accessibility and high visibility of a printed article play a major role in achieving the desired high number of citations. Although the OA journals fulfill these criteria appropriately, they have been criticized for having a lower impact factor and poor peer review quality. However, the results of this study show that these determinations have begun to change with an increasing number of citations that the OA journals receive over the recent years in scientific indices. Although our quantitative findings were in accordance with the dominancy of the SB journals, the citation analyses revealed that as of 2015, the OA journals started to receive more citations than their SB equivalents did. This novel trend is on the rise among Turkish researchers. However, another interesting result of this study shows that the Turkish authors still prefer the SB journals for their academic visibility and prestige. The number of medical schools in Turkey ranked 8th in the 2014 list of top twenty world universities. This leads to a fierce competition for academic positions. Thus, the scientific publication rates are likely to increase even further (5, 6).

When choosing between the OA and SB journals to get the content published, it is important to consider the journal's visibility, the cost of publication, the IF or SJR of the journal, and the speed of publication. To the best of our knowledge, this is the first study in the English literature to compare the OA and SB journals in the ORL category, demonstrating the novel changing trends in medical publishing among Turkish scientists between 2010 and 2015. This type of scientific work on ORL can easily be replicated and applied to any other medical field or specialty. The current trends in medical publishing can be explored more specifically.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Original Article

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Can Preoperative Complete Blood Count Parameters Be Used as Predictive Markers for Lymph Node Metastasis in Endometrial Carcinomas?

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BACKGROUND/AIMS
To investigate the clinical utility of complete blood count (CBC) parameters in the preoperative diagnosis of lymph node involvement (LNI) in endometrial carcinomas (ECs).

MATERIAL and METHODS
We conducted a retrospective study of 159 patients with ECs who underwent complete staging surgery at a tertiary center between 2007 and 2017. After demographic characteristics and preoperative CBC parameters were retrieved from the patients' medical records, the patients were grouped according to lymph node status (positive and negative) and compared. Variables with $p<0.05$ were included in the logistic regression analysis, and receiver operating characteristic curve analysis was used to determine the cut-off values for predicting LNI.

RESULTS
The mean age of the patients was 59.1 years, and 14 (8.8%) patients had LNI. The mean white blood cell, neutrophil, and platelet counts; plateletcrit level; and neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios were significantly higher in patients with LNI. Logistic regression analysis identified an independent association between increased neutrophil count and LNI (odds ratio 5.12; $p<0.05$). The optimal cut-off value was 4.85 ($\times 10^3/\mu L$) (sensitivity, 77.4% and specificity, 74.2%). A cut-off of 6.25 ($\times 10^3/\mu L$) was used to identify LNI with 100% specificity.

CONCLUSION
An increased neutrophil count can be considered a useful additional tool for the preoperative diagnosis of LNI.

Keywords: Blood cell count, endometrial neoplasms, lymphatic metastasis, lymph node excision, neutrophils

INTRODUCTION

Endometrial carcinoma (EC) is the most common gynecological cancer among women in developed countries (1). Based on the GLOBOCAN estimates, which are produced by the International Agency for Research on Cancer, in 2012, there were approximately 160,000 new cases worldwide (1). Moreover, as risk factors, including obesity and advancing age, become more prevalent, the incidence will likely increase. Fortunately, an early diagnosis can be made in many patients (approximately 75%) based on signs and symptoms (abnormal uterine bleeding) (2).

Endometrial carcinoma is staged surgically and was first recognized by the International Federation of Gynecology and Obstetrics (FIGO) in 1988 (3). The staging guidelines were last revised in 2009, and total extrafascial hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymph node dissection remain the standard staging procedures (3). Among the many clinical and pathological factors (FIGO stage, age, histological type and grade, tumor size, presence of lymphovascular space invasion (LVSI), lymph node involvement (LNI), and positive peritoneal cytology), the FIGO stage is the most important variable that influences the likelihood of EC recurrence and the survival rate (2). Therefore, the American Congress of Obstetricians and Gynecologists recommended surgical staging, including lymph node sampling, for all women with EC, except for those at increased risk of mortality because of secondary co-

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morbidities (4). Despite these recommendations, recent studies have generated much debate on the benefit of lymph node sampling in low-risk ECs (5-8). Owing to this debate, staging practices vary widely based on the individual physician and institutional practices. Nevertheless, it is difficult to identify ECs with LNI preoperatively. In an attempt to resolve this challenge, various tools, including serum carcinoma antigen 125 measurement and magnetic resonance imaging, have been used; however, the sensitivity and specificity of these techniques are varied (7, 9).

In contrast, studies of gynecological and non-gynecological cancers have shown that preoperative complete blood count (CBC) is a useful diagnostic tool for predicting LNI and prognosis (10, 11). Similarly, studies conducted on ECs revealed that preoperative CBC parameters were not only able to predict cancerous lesions but might also be related to poor prognostic factors, including tumor stage and grade, LVSI, and LNI (12-20). However, the clinical utility of CBC parameters for predicting LNI has not yet been widely investigated.

The aim of the present study was to determine whether there is any significant relationship between LNI and CBC parameters in ECs. Furthermore, we investigated the clinical utility of these parameters in the preoperative diagnosis of LNI.

MATERIAL and METHODS

The medical files of 184 patients with EC who were staged surgically according to the recommendations of FIGO at a tertiary hospital between 2007 and 2017 were retrospectively analyzed. Patients who had acute inflammatory disease, myeloproliferative disorders, concomitant gynecological and other cancers, or autoimmune disease; were using any drug that affects CBC parameters including anticoagulants or hormonal contents; or reported smoking were excluded from the study. A total of 159 patients were enrolled in the study. Informed oral consent was obtained from all participants. The study was approved by the Ethical Review Board of Ankara Atatürk Training and Research Hospital (approval no.: 26379996/152) and was conducted in accordance with the World Medical Association Declaration of Helsinki (2000 revision).

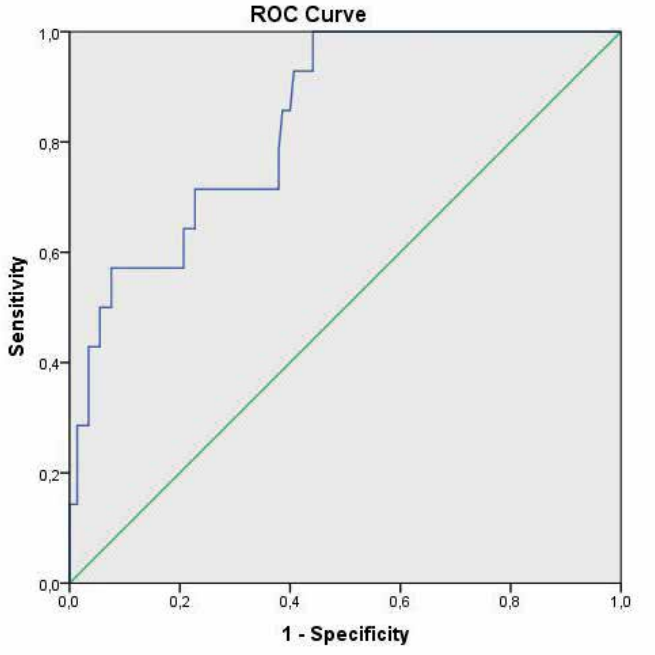

FIGURE 1. Receiver operating characteristic curve of serum neutrophil levels for discriminating lymph node positive from lymph node negative patients with endometrial carcinoma (area under the curve: 0.838; standard error: 0.048)

Data on demographic and pathological characteristics (age, gravidity, parity, histological type, FIGO stage, and LNI status) and preoperative CBC parameters (white blood cell (WBC), neutrophil, lymphocyte, and platelet counts; hemoglobin levels; mean corpuscular volume; mean platelet volume (MPV); platelet distribution width (PDW); plateletcrit levels; and neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte (PLR) ratios) were retrieved from the patient's medical files and hospital records. Blood samples were collected when the patients were admitted to the hospital for surgery and before receiving any medications. Specimens were analyzed within 2 h using a Sysmex XE-2100 Automated CBC Analyzer (Sysmex Europe, Germany).

After patients were grouped according to lymph node status (lymph node positive and lymph node negative), the groups were compared in terms of the examined CBC parameters. Once CBC parameters significantly associated with LNI were determined, the clinical utility of those parameters in the preoperative diagnosis of LNI was investigated.

Statistical Analysis

Data were expressed as mean±standard deviation. The groups (lymph node positive vs. lymph node negative) were compared using independent sample t-tests. Variables with $p<0.05$ were included in the binary logistic regression analysis, and the influence of each factor on the preoperative diagnosis of LNI was evaluated. The receiver operating characteristic (ROC) curve analysis was used to determine the cut-off values of the serum neutrophil level for diagnosing LNI. Statistical analyses were made using Statistical Package for the Social Sciences for Windows, version 21.0 (IBM, SPSS Corp.; Armonk, NY, USA). Odds ratios (ORs) and 95% confidence intervals (CIs) were determined. A $p<0.05$ was considered statistically significant.

RESULTS

Table 1 summarizes the demographic and pathological characteristics and preoperative CBC parameters of 159 patients with EC.

In the study group, 14 (8.8%) patients had LNI. While the mean serum WBC, neutrophil, and platelet counts; plateletcrit level; and NLR and PLR ratios were significantly higher in the lymph node positive group than in the lymph node negative group ($p<0.05$), the mean serum lymphocyte count and hemoglobin, hematocrit, MPV, and PDW levels did not differ significantly between the groups ($p>0.05$) (Table 2).

Binary logistic regression analysis revealed that among variables that differed significantly between the lymph node positive and lymph node negative groups, only an increased neutrophil count was independently associated with LNI (OR 5.12,

95% CI 1.168-22.452; -=0.03) (Table 3). The ROC curve analysis revealed that the optimal cut-off value of the serum neutrophil level for predicting LNI was 4.85 (×10³/μL). The sensitivity was 71.2%, and the specificity was 74.2% (Fig. 1). When the groups (lymph node positive vs. lymph node negative) were assessed in the ROC curve analysis using the 6.25 (×10³/μL) cut-off value, the sensitivity was 51.1%, and the specificity was 100%.

TABLE 1. Demographic and surgical characteristics and preoperative CBC parameters of 159 patients with endometrial carcinoma

Characteristics	Patients (n=159)
Demographic and surgical, mean±SD (range)	
Age (years)	59.1±10.0
Gravidity	4.45±3.02
Parity	3.54±2.51
Histological type, n (%)	
Type I (endometrioid type)	132 (83.0)
Type 2 (other types)a	27 (17.0)
FIGO stage, n (%)	
IA	97 (61.0)
IB	36 (22.6)
II	9 (5.7)
IIIA	2 (1.3)
IIIB	1 (0.6)
IIICI	4 (2.5)
IIIC2	6 (3.7)
IVA	2 (1.3)
IVB	2 (1.3)
Lymph node involvement, n (%)	
Yes	14 (8.8)
No	145 (91.2)
CBC parameter, mean±SD (range)	
WBC count (×10³/μL)	7.772±1.975
Neutrophil count (×10³/μL)	4.426±1.535
Lymphocyte count (×10³/μL)	2.231±0.645
Hemoglobin (g/dL)	12.858±1.56
Hematocrit (%)	38.91±4.312
MCV (fL)	84.67±6.27
Platelet count (×10³/μL)	288.415±81.072
MPV (fL)	10.33±1.41
PDW (fL)	14.0±2.57
Plateletcrit (%)	0.293±0.830
NLR (%)	2.180±1.193
PLR (%)	140.155±60.59

[a]Type II tumors include serous, clear cell, mucinous, mixed, and undifferentiated histological subtypes.
CBC: complete blood count; FIGO: International Federation of Gynecology and Obstetrics; MCV: mean corpuscular volume; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PDW: platelet distribution width; SD: standard deviation; WBC: white blood cell

DISCUSSION

The present study has shown that various CBC parameters, including WBC, neutrophil, and platelet counts; plateletcrit level; and NLR and PLR ratios, were significantly higher in ECs with LNI. Furthermore, it revealed that the neutrophil count was an independent predictor of a preoperative diagnosis of LNI, and a value >6.25 (×10³/μL) was able to identify ECs with LNI with a specificity of 100%. To our knowledge, this is the first study that widely investigates the clinical utility of CBC parameters for diagnosing ECs with LNI.

The influence of inflammation, caused by inflammatory cells and their mediators, in various aspects of cancer, including cancer initiation, promotion, progression, and metastasis, has recently been demonstrated (21). Similarly, it is suggested that changes in serum CBC parameters, including cell counts, cell size and shape, and cell-to-cell ratios, may reflect cancer and cancer-related characteristics. Studies of ECs revealed that various CBC parameters, such as WBC count, platelet count, PDW,

TABLE 2. The CBC parameters of patients with endometrial carcinomas according to lymph node status (positive or negative)

Characteristics, mean (±SD)	Lymph node positive (n=14, 9.8%)	Lymph node negative (n=145, 91.2%)	p
WBC count (×10³/μL)	9.492±2.123	7.611±1.887	0.001*
Neutrophil count (×10³/μL)	6.307±1.541	4.244±1.402	<0.001*
Lymphocyte count (×10³/μL)	2.067±0.598	2.247±0.649	0.321
Hemoglobin (g/dL)	12.342±1.364	12.904±1.572	0.199
Hematocrit (%)	38.0±4.655	38.996±4.284	0.414
MCV (fL)	86.535±6.047	84.495±6.047	0.246
Platelet count (×10³/μL)	358.642±76.436	281.634±78.476	0.001*
MPV (fL)	10.385±1.224	10.325±1.43	0.879
PDW (fL)	13.964±2.45	14.0±2.595	0.953
Plateletcrit (%)	0.34±0.11	0.288±0.079	0.026*
NLR (%)	3.285±1.155	2.075±1.145	<0.001*
PLR (%)	192.723±84.075	135.044±55.602	0.001*

*p<0.05.
CBC: complete blood count; MCV: mean corpuscular volume; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PDW: platelet distribution width; SD: standard deviation; WBC: white blood cell

TABLE 3. Binary logistic regression analysis of CBC variables of patients with respect to lymph node involvement

Variables	p	OR	95% CI
WBC count	0.855	1.052	0.613-1.804
Neutrophil count	0.03*	5.12	0.168-22.452
Platelet count	0.675	0.996	0.975-1.016
Plateletcrit	0.155	0.001	0.001-33.417
NLR	0.214	0.202	0.016-2.516
PLR	0.095	1.033	0.994-1.074

*p<0.05.
CBC: complete blood count; CI: confidence interval; NLR: neutrophil-to-lymphocyte ratio; OR: odds ratio; PLR: platelet-to-lymphocyte ratio; WBC: white blood cell

MPV, plateletcrit, and NLR, were significantly higher in ECs than in healthy and precancerous controls (12-17). Furthermore, some studies reported that serum WBC count, platelet count, and MPV may reflect both tumor stage and grade in ECs (12, 13, 17, 18). As a result, the authors proposed that CBC is a useful diagnostic tool for the preoperative early diagnosis of ECs in patients at a high risk of EC (i.e., those with abnormal uterine bleeding) (12-16).

Furthermore, several recent studies have investigated the relationship between CBC and LNI in ECs (13, 18-20). However, their results were inconsistent. For instance, Ekici et al. (13) found that both WBC and platelet counts are significantly higher in ECs with LNI than in others. Conversely, Takahashi et al. (18) found a significant relationship between increased platelet count and LNI, whereas there was no significant relationship between WBC count and LNI (19). In contrast, in their study, Suh et al. (20) found significant relationships between both NLR and PLR ratios and LNI, whereas there was no significant relationship between WBC count and LNI. In the present study, we found that preoperative serum WBC, platelet, and neutrophil counts; plateletcrit level; and PLR and NLR ratios were significantly higher in ECs with LNI. Furthermore, our study revealed that the neutrophil count was an independent predictor of the preoperative diagnosis of LNI.

An increased serum neutrophil count has been observed in many cancers with an advanced tumor stage and a poor prognosis (22, 23). Although the precise mechanism is still unknown, this condition was proposed to provide evidence for the concept of cancer-related inflammation inducing tumor progression (23, 24). Takahashi et al. (18) also found significant relationships between an increased neutrophil count and various poor prognostic factors associated with ECs (advanced surgical stage, LVSI, and cervical stromal involvement). In contrast to the previous study, the present study showed a significant and independent relationship between an increased neutrophil count and LNI. The inconsistency between studies may be the result of the diverse surgical and histological characteristics of the study populations, including FIGO stage and histological type and grade. It may also be the result of many variable characteristics of the study populations (i.e. race and harvested lymph node count).

Currently, there is no consensus on the benefit of lymph node sampling in all patients with ECs. Although a population-based retrospective study stated that lymph node sampling improved the survival of patients with ECs, another recent prospective study found no evidence of benefit from lymph node sampling in terms of overall or recurrence-free survival in women with early stage disease (3, 4). Thus, identification of patients with a high risk of LNI may improve survival by determining the extent of the lymph node sampling area and the administration of a suitable adjuvant therapy. With this aim, the usability of various diagnostic tools has been investigated. However, the sensitivity and specificity of commonly used preoperative diagnostic tools for LNI, such as serum carcinoma antigen 125 and magnetic resonance imaging, have been reported to be approximately 61.5%-77.8%/81.0%-94.9% and 50.0%-62.2%/92.0%-94.9%, respectively (7, 9). Similarly, the present study showed that the neutrophil count had 71.2% sensitivity and 74.2% specificity for diagnosing ECs with LNI preoperatively. Additionally, a cut-off value of 6.25 ($\times 10^3/\mu L$) was able to identify patients with EC with LNI with 100% specificity.

In conclusion, although the present study has its limitations, such as its retrospective single-center design and relatively small sample size, it revealed the potential predictive role of CBC for selecting patients with EC with LNI. To our knowledge, the present study is also the first to report the usability of the neutrophil count for diagnosing ECs with LNI. As the neutrophil level can be routinely determined using CBC tests preoperatively, this low cost and readily available parameter may be a new and promising marker to select patients with ECs for extended lymph node sampling. However, comprehensive studies on different histological subtypes are necessary to determine the utility of this marker for patients with ECs.

Ethics Committee Approval: Ethics committee approval was received for this study from Ankara Atatürk Training and Research Hospital. (Approval Date: 28/05/2018, Approval Number: 26379996/152).

Informed Consent: Oral informed consent was taken from the patients prior to the study.

Peer-review: Externally peer-reviewed.

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Review

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Common Benign Conditions of the Petrous Apex in the Pediatric Population

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Petrous apex lesions are rare. However, a wide number of entities may be seen during radiological studies of the head and neck. In addition to malignant pathologies, a variety of benign lesions can be discovered within this structure, such as cholesterol granuloma, cholesteatoma, cephalocele, mucocele, apical petrositis, and Langerhans cell histiocytosis. In addition to these lesions, a number of normal imaging variants may complicate the diagnosis. An understanding of the patterns and extent of disease processes of the petrous apex facilitates diagnosis and staging. Plain radiography, high-resolution computed tomography, and magnetic resonance imaging with diffusion-weighted sequences can be used in the assessment of petrous apex.

Keywords: CT, MRI, pediatric, petrous apex, temporal bone

INTRODUCTION

The petrous apex is the pyramidal shape medial projection of the temporal bone anteromedial to the inner ear and lateral to the petro-occipital fissure. It is subdivided by the internal auditory canal into larger anterior and smaller posterior segments (1). Petrous apex lesions are rare; however, a wide number of entities may be seen during radiological studies of this region incidentally for an unrelated disease. In addition, pseudolesions involving the petrous apex may make the diagnosis difficult and cause unnecessary treatment. Owing to its complex anatomical localization imaging, plain radiography, high-resolution computed tomography (HRCT), and magnetic resonance (MR) imaging with diffusion-weighted (DW) sequences play an important role in the assessment of petrous apex (2, 3). The aims of this pictorial essay were to describe the pseudolesions involving the petrous apex, to summarize the benign pathologies, and to recognize the patterns and imaging features of diseases that may involve the petrous apex.

Normal Anatomic Variants of the Petrous Apex

Mostly, the petrous apex is non-aerated and composed of dense bone and bone marrow (Figure 1). In up to 30% of the cases, variable degree of aeration of the petrous apex occurs. Approximately 4%-7% of the pneumatized petrous

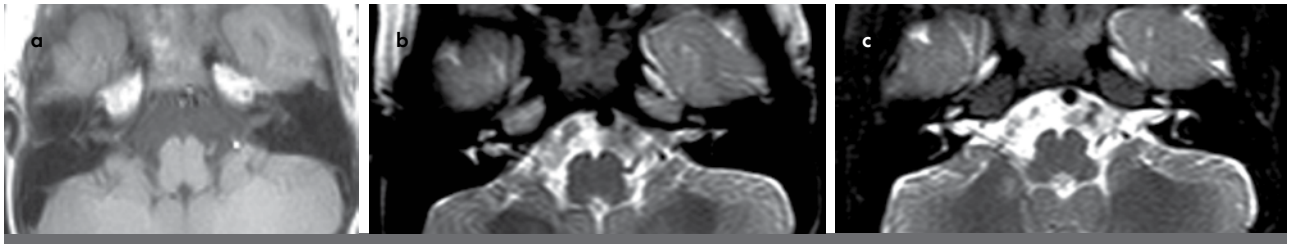

FIGURE 1. a-c. Non-pneumatized petrous apex. Bone marrow of both petrous apices reveals high TI (a) and intermediate T2 signal (b) that significantly decreased on fat-suppressed T2-weighted image (c).

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bones are asymmetric (4). When the pneumatization is not symmetric, the non-pneumatized petrous apex may be misinterpreted as pathologic (Figure 2). Absence of mass effect and close observation of the signal changes with fat-suppressed sequences prevent misinterpretation as cholesteatoma, effusion, or cholesterol granuloma. In addition, CT can easily visualize normal cortex or bony trabecula without mass effect. Asymmetric aeration is associated with asymmetric fatty marrow in the petrous apex. Typically, signal intensity of fatty marrow follows the signal of retro-orbital fat in all MR sequences. Fat-suppressed MR sequences or CT can confirm the normal fatty marrow (2, 3, 5).

Cephalocele

By definition, petrous apex cephalocele is the cystic expansion and herniation of the posterolateral portion of Meckel's cave into the superomedial portion of petrous apex. They are cerebrospinal fluid (CSF)-filled cystic structures. Except for fibers of the fifth cranial nerve, petrous apex cephalocele does not contain other neuronal tissues including the brain parenchyma. This entity is usually regarded as an incidental finding and believed to occur when CSF pressure caused over petrous apex roof dehiscence. On imaging, cephaloceles follow the CSF density or intensity on CT and MR imaging, respectively (Figure 3) (1, 3, 6).

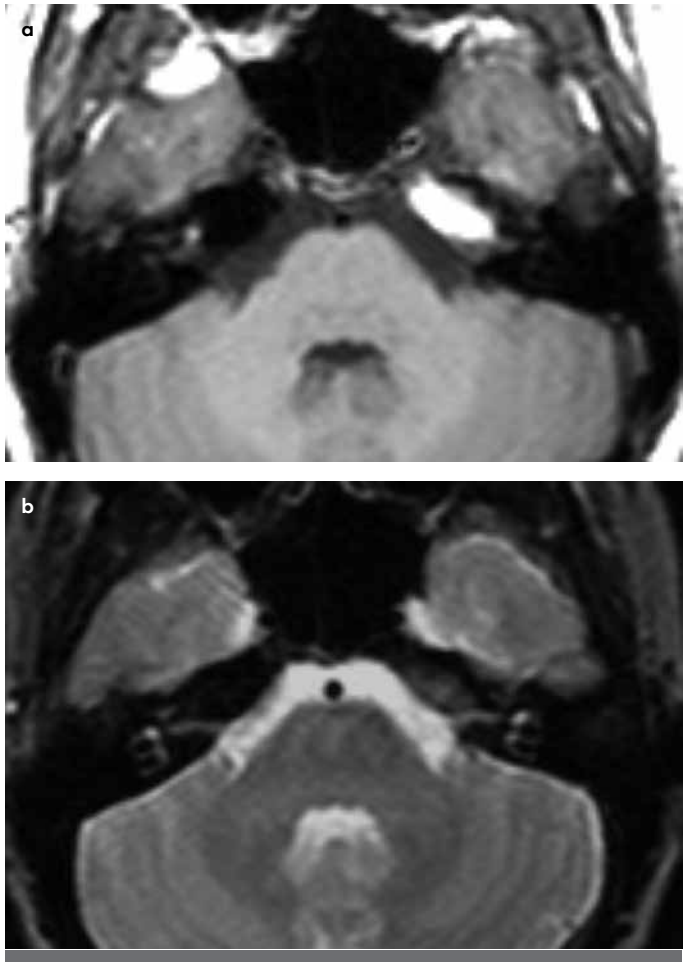

FIGURE 2. a, b. Asymmetric petrous apex. T1-weighted axial MR image shows high signal intensity of the left petrous apex suggesting cholesterol granuloma (a). T2-weighted axial MR image, however, reveals that these appearances follow the subcutaneous fat signal and consistent with non-pneumatized petrous apex (b).

Effusion and Petrous Apicitis

Petrous apex cells have communication with the middle ear; therefore, they are involved with similar disorders including inflammation and obstruction. Following a middle ear infection, a sterile fluid accumulation can be seen in petrous apex air cells; however, in the antibiotic era, extension of middle ear infection into the pneumatized petrous apex is rare. In addition to secondary involvement, isolated/primary mucosal inflammation and fluid retention can also occur due to viral agents and allergens. Isolated petrous apex effusion is a relatively frequent incidental imaging finding, and usually no follow-up or treatment is necessary (4). On imaging, fluid accumulation follows the CSF density and intensity on CT and MR imaging, respectively, with the preservation of internal septations (Figure 4). However, TI signal can be intermediate or high depending on the protein

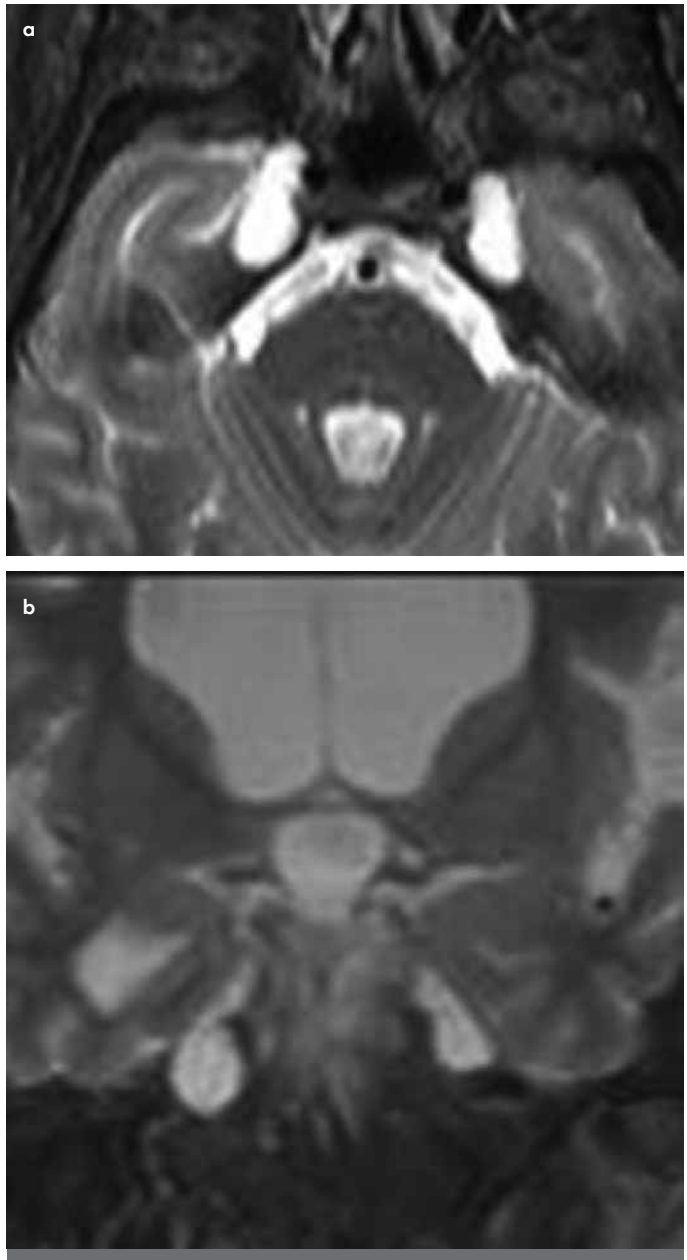

FIGURE 3. a, b. Petrous apex cephalocele. Axial and coronal T2-weighted images show bilateral, well-defined CSF isointense lesion extending into the petrous apex from the region of the Meckel's cave.

FIGURE 4. a, b. Petrous apex effusion. On T2-weighted image, there is a high T2 lesion in the left petrous apex (a). HRCT of the temporal bone reveals opacification of the left petrous apex with the preservation of air cells (b). Absence of expansion and presence of trabecular thinning suggest the diagnosis of effusion.

content of the fluid, which can cause confusion with cholesterol granuloma and mucocele. Lack of contrast enhancement and trabecular disruption can be helpful in differentiation from these lesions (5).

Mucocele

Mucocele is a rare inflammation that is believed to result from air cell obstruction. Accumulation of mucoid material within the obstructed air cells causes expansion, remodeling, and destruction of the bony septations. This disorder rarely primarily occurs in the petrous apex; instead, it usually extends from the adjacent structures. CT of the temporal bone reveals opacification of the air cells that is indistinguishable from cholesterol granuloma. Mucoceles have high T2 signal intensity with variable TI signal on MR imaging (3, 7, 8). It can also show peripheral enhancement without restriction in diffusion (Figure 5) (5).

Cholesterol Granuloma

Cholesterol granuloma is the most frequent adult petrous apex disorder that may occur in the mastoid, middle ear, and petrous apex; however, it is an uncommon petrous apex lesion in children. Its cause is unknown and believed to occur as an air cell obstruction, followed by mucosal edema, hemorrhage, inflammatory reaction, and bony expansion. Incidental small petrous apex cholesterol granulomas can be found on imaging studies that were performed for other symptoms. These asymptomatic lesions do not need any intervention until they progressively enlarge and cause symptoms. CT demonstrates an expansile, well-defined mass within the petrous apex with cortical thinning. Cholesterol granulomas classically have high signal intensity on both TI- and T2-weighted MR sequences

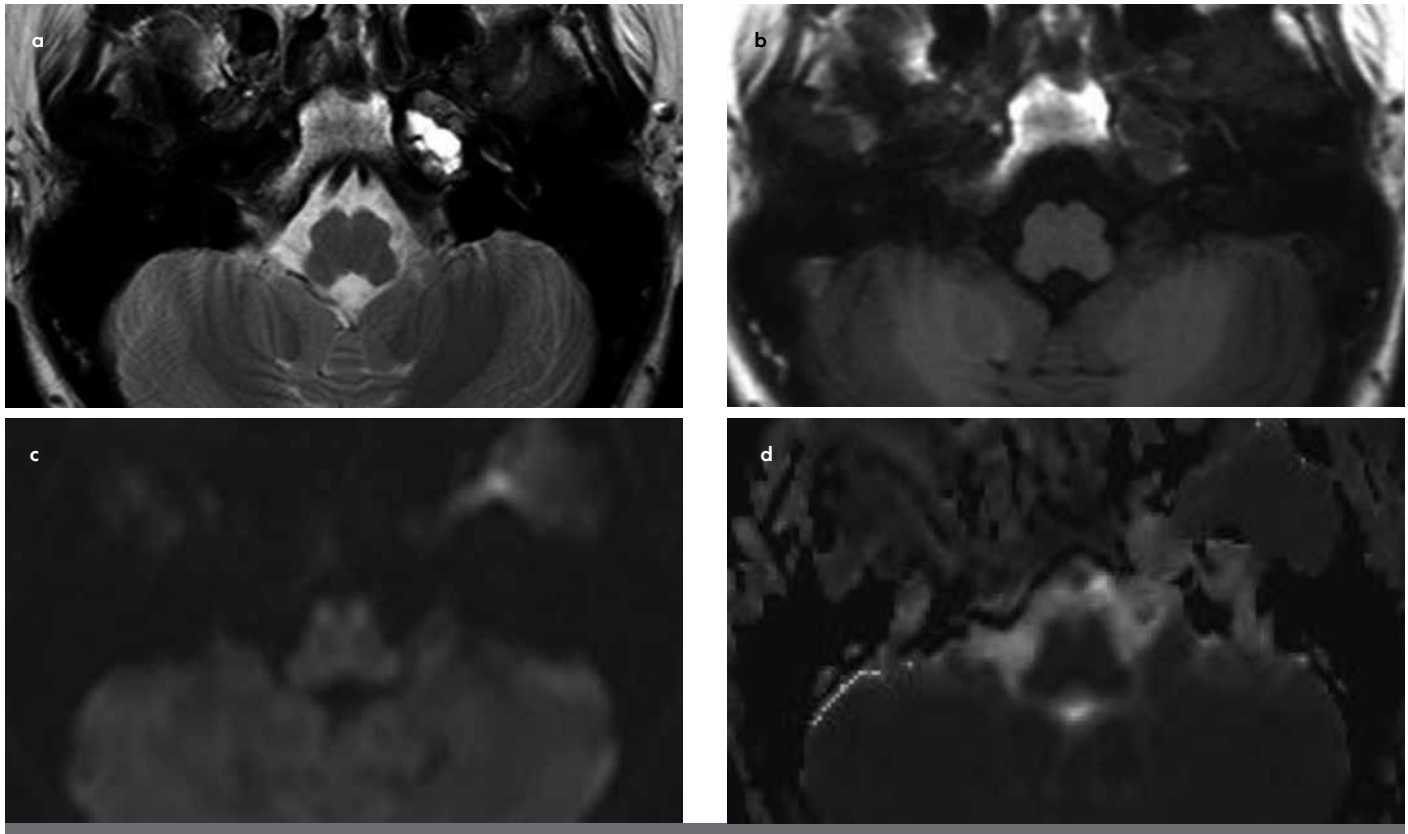

FIGURE 5. a-d. Petrous apex mucocele. Left petrous apex demonstrates mild expansion and high T2 (a) and low to intermediate signal intensity on TI-weighted image (b). The b1000 DW image (c) and corresponding ADC map (d) show that diffusion is not restricted.

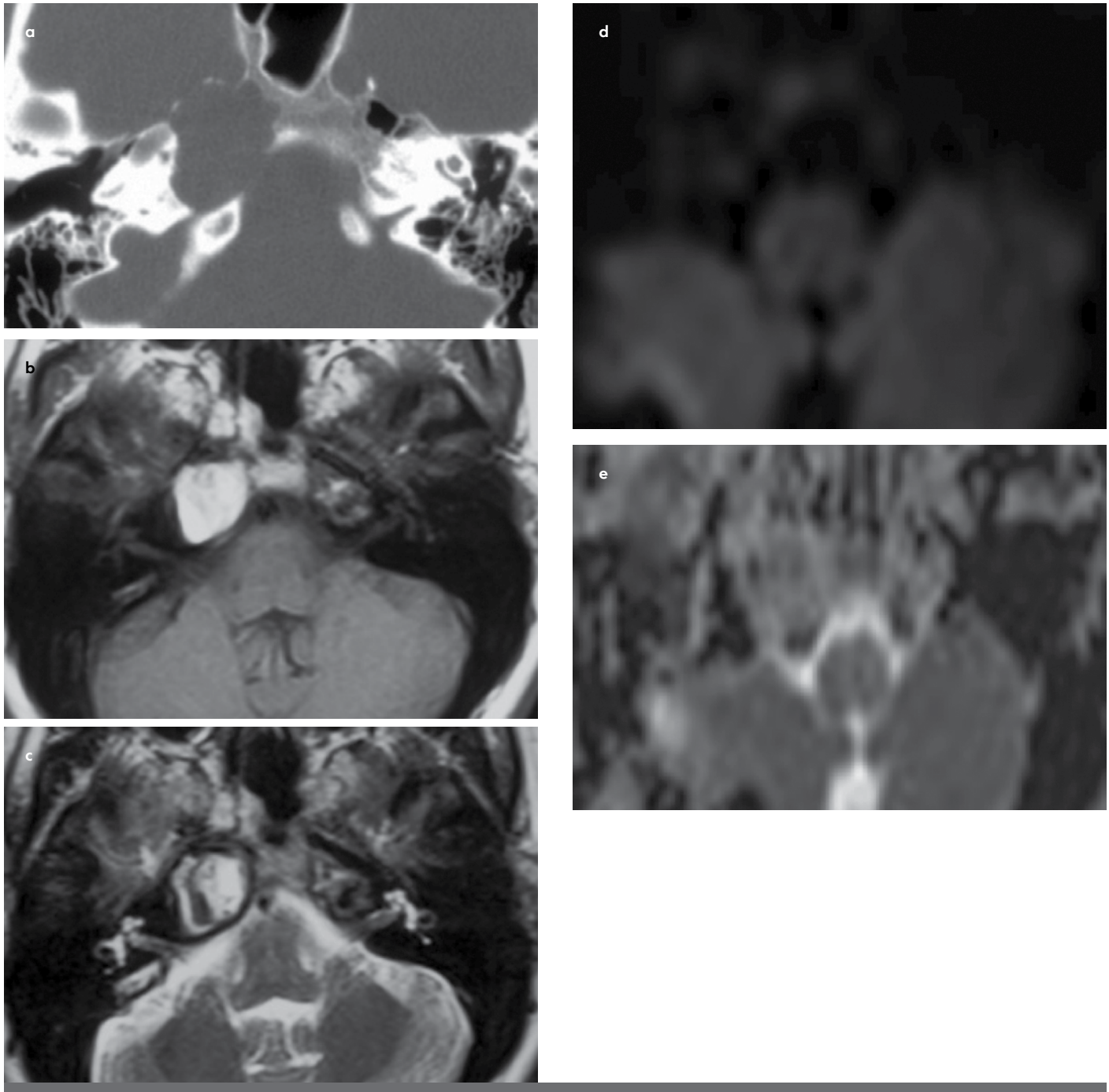

FIGURE 6. a-e. Cholesterol granuloma. An axial CT scan (a), TI- (b), and T2-weighted axial MR images (c) demonstrate expanded right petrous apex. The lesion shows high TI and high T2 signal intensity consistent with cholesterol granuloma. The bl000 DW image (d) and corresponding ADC map (e) show no restriction in diffusion. The dark peripheral rim is due to hemosiderin.

due to accumulation of blood products and proteinaceous debris (Figure 6). They also stay hyperintense after fat-suppressed MR sequences (8).

Cholesteatoma

Cholesteatoma or epidermoid cyst is a cystic mass-like lesion originating from the aberrant ectoderm trapped within the petrous apex. It can be seen at any part of the temporal bone including petrous apex. On imaging, they are expansile lesions with variable bone destruction. Typically, they have high T2- and low TI-weighted signal on conventional MR imaging sequences. Diffusion restriction is characteristic and helpful for distinguishing from mucocele (9). Half-Fourier acquisition single-shot turbo spin-echo DW imaging has high sensitivity and specificity in primary diagnosis and follow-up of possible residual/recurrence following surgery (I0). They also may show subtle peripheral contrast enhancement (Figures 7, 8) (5).

CONCLUSION

Imaging plays a pivotal role in assessing petrous apex lesions and normal variants. An understanding of the variants, pitfalls, and patterns of disease processes of the petrous apex facilitates diagnosis and staging. HRCT and MR imaging including DW sequences allow detailed evaluation of this region.

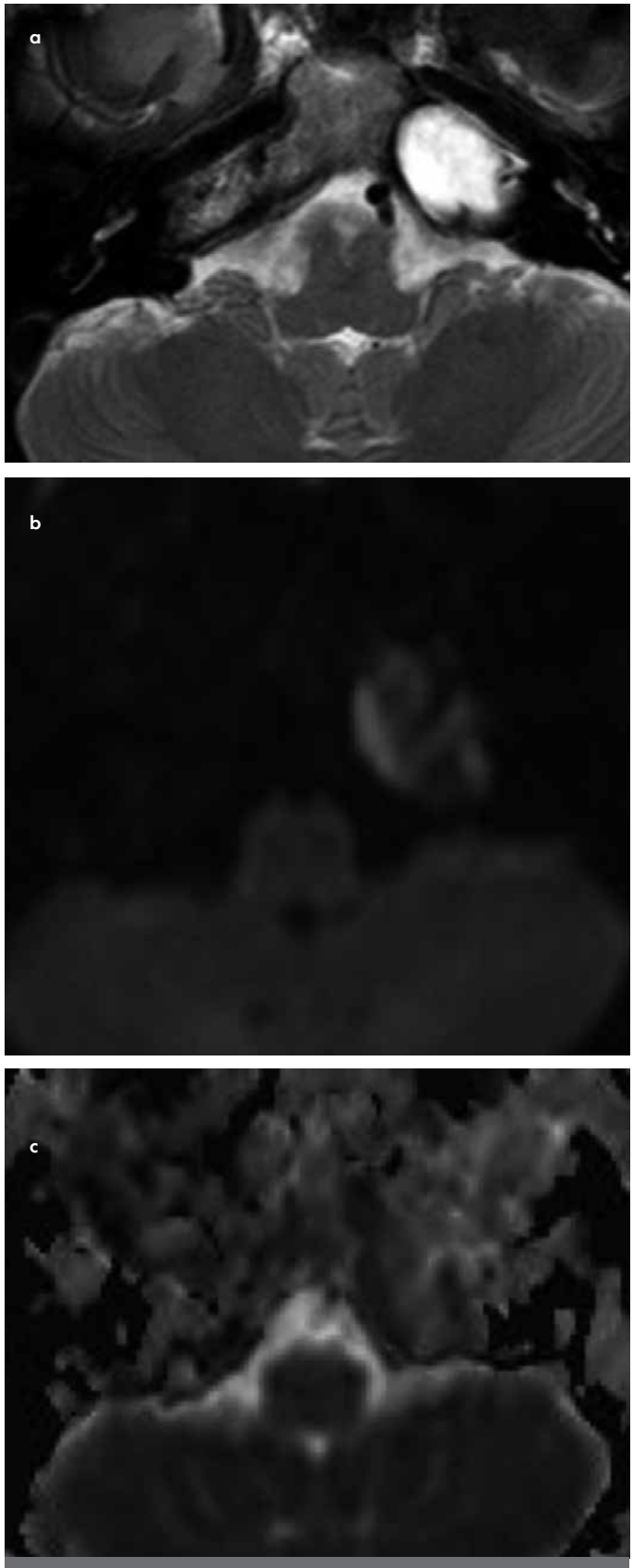

FIGURE 7. a-c. Cholesteatoma. On T2-weighted image (a), there is a well-defined, hyperintense expansile lesion in the left petrous apex. The b1000 DW image (b) and corresponding ADC map (c) show characteristic restriction in diffusion.

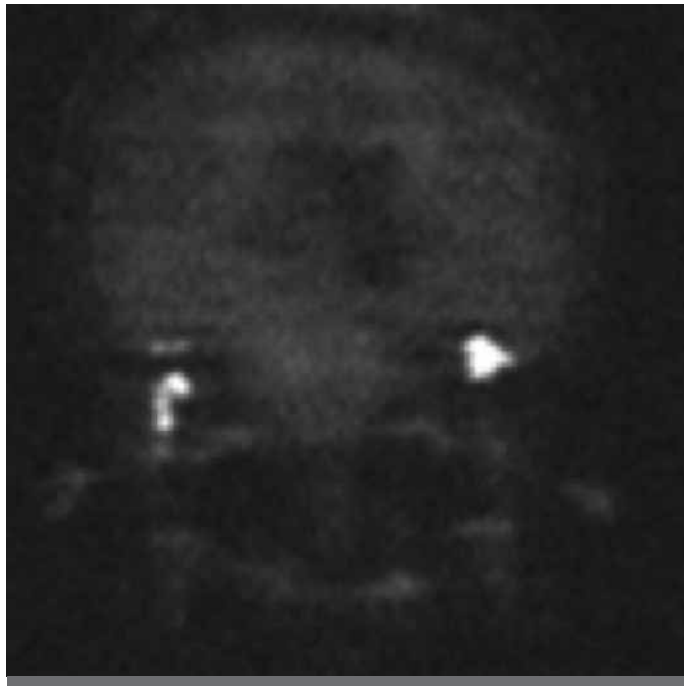

FIGURE 8. Cholesteatoma. A coronal half-Fourier acquisition single-shot turbo spin-echo DW image shows bilateral markedly high signal focal nodular lesions consistent with cholesteatoma

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Review

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Importance of Preoperative Magnetic Resonance Imaging Evaluation of the Anterior Cruciate Ligament Injuries

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Patients with a clinically suspected tear of the anterior cruciate ligament (ACL) are generally diagnosed using magnetic resonance imaging (MRI). It is accepted that MR is the most effective radiological modality for diagnosing ACL injuries. Formerly, the essential aim of MRI was to detect whether the ACL tear was partial or total. Recently, however, there has been an increasing interest in the region of rupture. In addition, it is highly important to focus on the tissue quality of the remaining ligament. These findings will help the orthopedic surgeon to choose the right surgical treatment technique. In this review, the classical MRI findings of the ACL injuries, as well as the location of the injured region and the quality of the remaining tissue, are addressed.

Keywords: Knee, magnetic resonance imaging, anterior cruciate ligament

INTRODUCTION

Every year, there is a statistically growing number of knee ligament injuries due to an increase in sports activities. The anterior cruciate ligament (ACL) tear or sprain is considered to be one of the most common sports injuries. The incidence of ACL rupture is 35 per 100,000 (1). An ACL injury may lead to pain, recurrent instability, progressive meniscus injury and cartilage damage, decrease in the quality of life, and finally osteoarthritis of the knees (2). The first surgical interventions for the ACL rupture were performed in the 1970s as open repair (3, 4). This treatment was abandoned after it was realized that the mid-term outcome was not satisfying. Arthroscopic ACL reconstruction is nowadays a standard treatment option following ACL rupture in active patients. The success rate of the arthroscopic ACL reconstruction has been reported as ranging between 70% and 90% (5, 6). In this standard treatment, the location of the tear and the quality of the remnant tissue was not important, so ruptured ACL debridement was the standard surgical procedure.

The ACL is composed of two functional bundles. These bundles are the anteromedial bundle (AM) and posterolateral bundle (PL), according to their insertion to tibia (7). An isolated PL or AM bundle reconstruction can be performed in the presence of clinical and magnetic resonance imaging (MRI) findings due to the inability of one bundle to function and the other to be inadequate (8, 9). With a selective bundle reconstruction in partial ACL tear, at least a full ACL reconstruction or even better results can be obtained. In addition, the advantages of preserving the proprioceptive functions of the ligament and having surgery with less morbidity are endured.

Despite anatomical and selective reconstruction techniques, the quest for ideal treatment in ACL surgery continues. Preservation of the injured ACL tissue can provide the maintenance of the proprioceptive and natural knee kinematics and is thought to accelerate healing by reducing surgical morbidity. More recently, arthroscopic primary repair of ACL tears is becoming popular again. DiFelice et al. (10) reported very successful results of the arthroscopic primary repair in patients with proximal tears, which are called type I, and good remnant tissue quality. Some authors agree with these findings (11, 12). This review emphasizes that the proximal ACL tear and good remnant tissue quality are critical for a successful outcome of the arthroscopic primary ACL repair.

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The assessment of soft tissue injuries in the knee joint with MRI has also established itself as the next diagnostic tool, following physical examination and x-ray. It is accepted that MRI is the most effective radiological method with 90% to 95% sensitivity and 95% to 100% specificity when assessing ACL injuries. In addition, if the MR images are not optimized, the technique can be less reliable in partial or chronic ruptures (13, 14). When direct and indirect findings in MRI of knee are evaluated together, much information can be obtained about the affected bundle, rupture site, and the residual tissue quality of the ACL tear.

The aim of this review is to emphasize the importance of the affected bundle, the location of the injury and the structure of the remnant ACL tissue, as well as to discuss the classical findings of MRI with the ACL injury. These findings may guide the orthopedic surgeon to choose the right surgical treatment technique.

Knee MRI

All examinations were performed with a 3.0T MRI machine (Siemens, Magnetom, Skyra, Erlangen, Germany) and a 16-channel knee-dedicated tx rx in our clinic. We used our standardized protocol, which has three sequences in the sag-

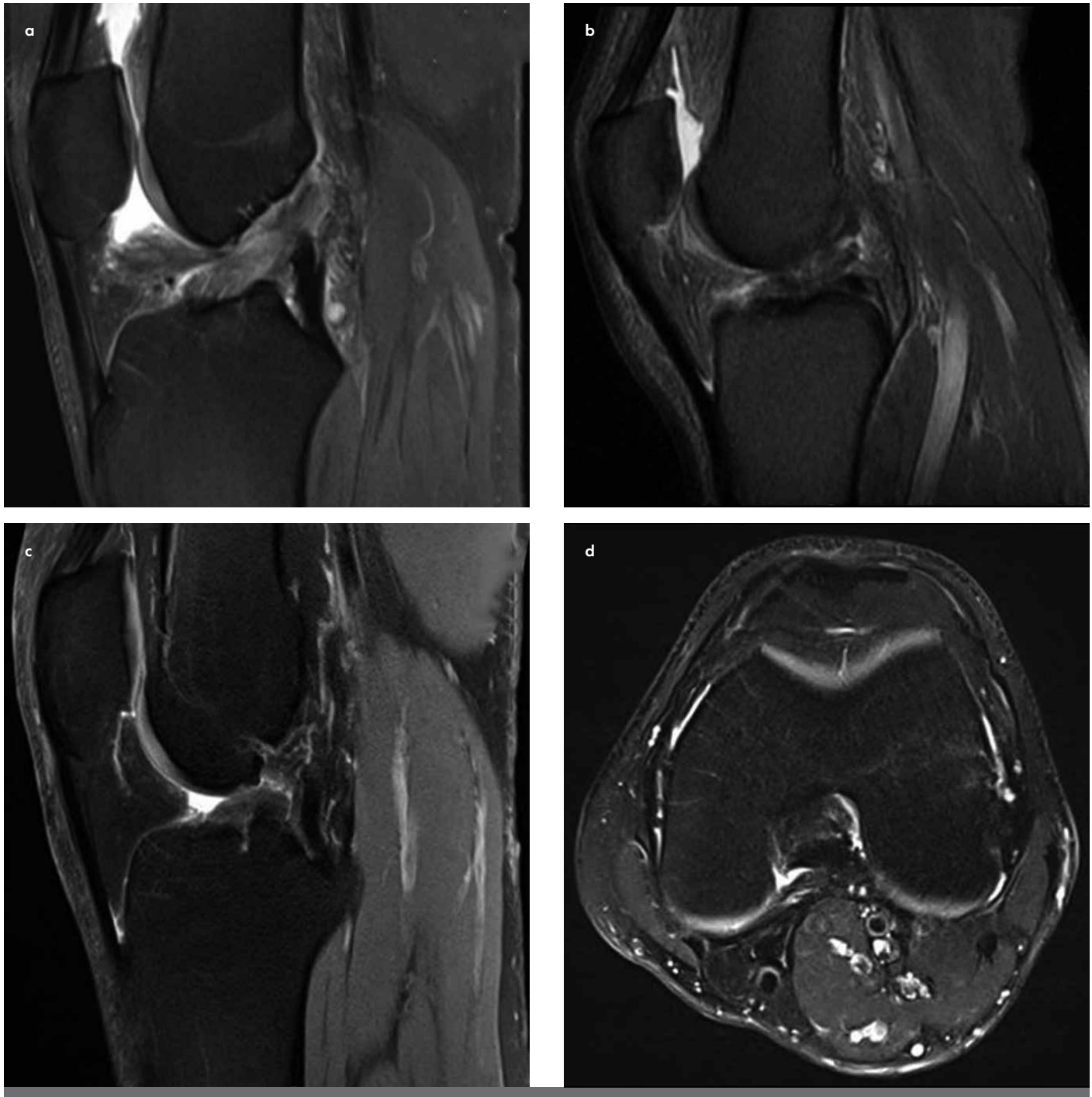

FIGURE 1. a-d. Three separate sagittal proton-density MRI images of the knees depict the anterior cruciate ligament disruption. Acute injury (a) subacute injury (b) chronic injury (c). Axial proton-density MRI images of the knee depicting a chronic anterior cruciate ligament disruption and "empty notch sign" (d).

FIGURE 2. a-b. Sagittal proton-density MRI image of the knee: The asterisk marks the hemarthrosis. (a) Axial proton-density MRI image of the knee: The asterisk marks the hemarthrosis (b).

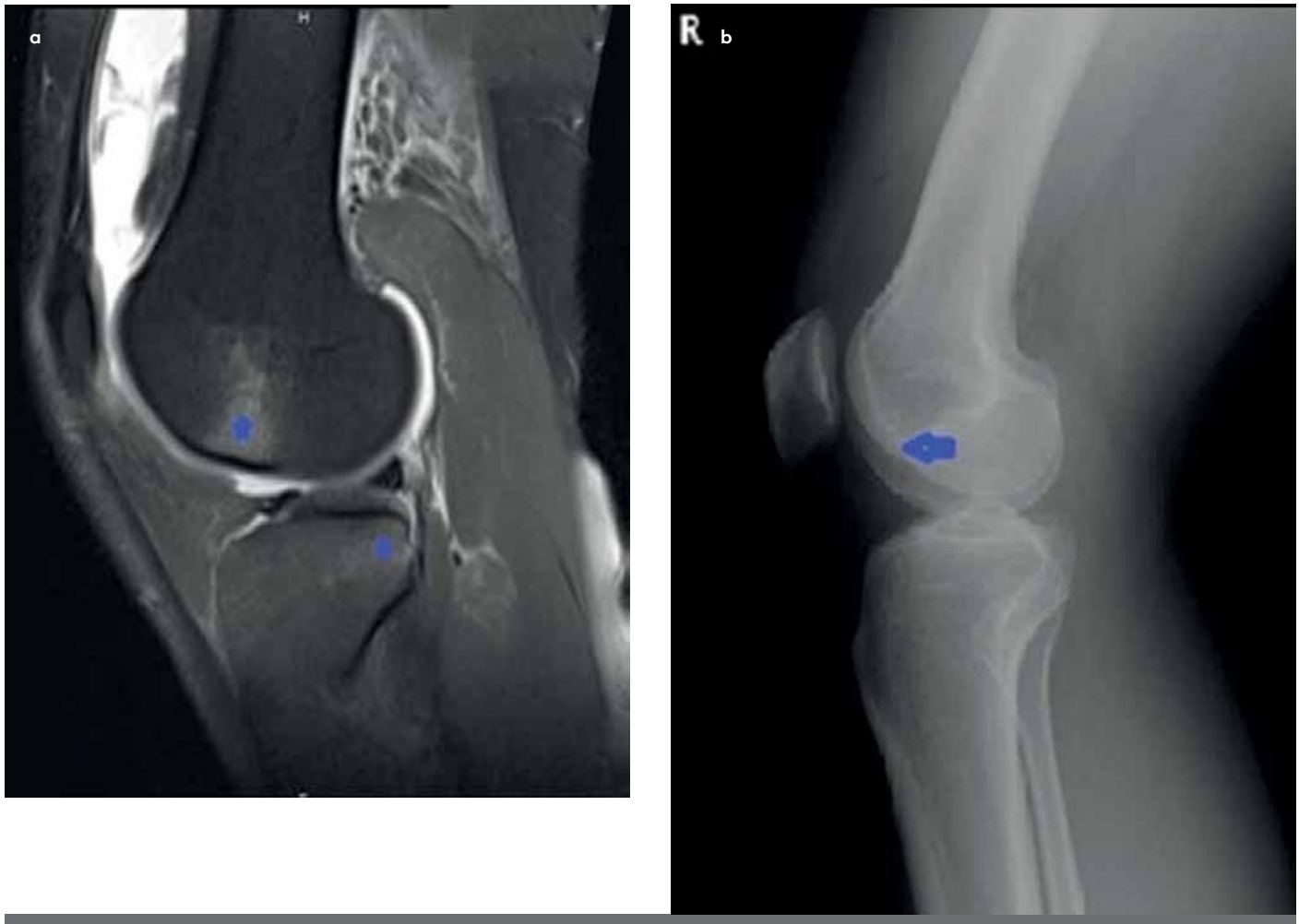

FIGURE 3. a, b. Sagittal T2 proton-density of knee: The asterisk marks the central third of the lateral femoral condyle and posterior third of the lateral tibial plateau bone bruise (a) Lateral knee direct graphy: The arrow marks deep sulcus (terminalis) sign (b).

ittal orientation [I- fat-suppressed proton-density weighted turbo spin-echo (FS PD TSE) sequence 2; TI-weighted turbo spin-echo sequence 3; T2 with water excitation (T2 DE3D WE) sequence]; two sequences in the coronal orientation [I- fat-suppressed proton-density weighted turbo spin-echo (FS PD TSE) sequence 2; T2 turbo inversion recovery magnitude short tau inversion recovery (T2_TIRM_COR(STIR) sequence], and one sequence in the axial orientation [I- fat-suppressed proton-density weighted turbo spin-echo (PD_TSE_FS_TRA) sequence]. The parameters used for image acquisition were a 320X256 matrix and 3.0 mm slice thickness with 0.3 mm inter-slice gap.

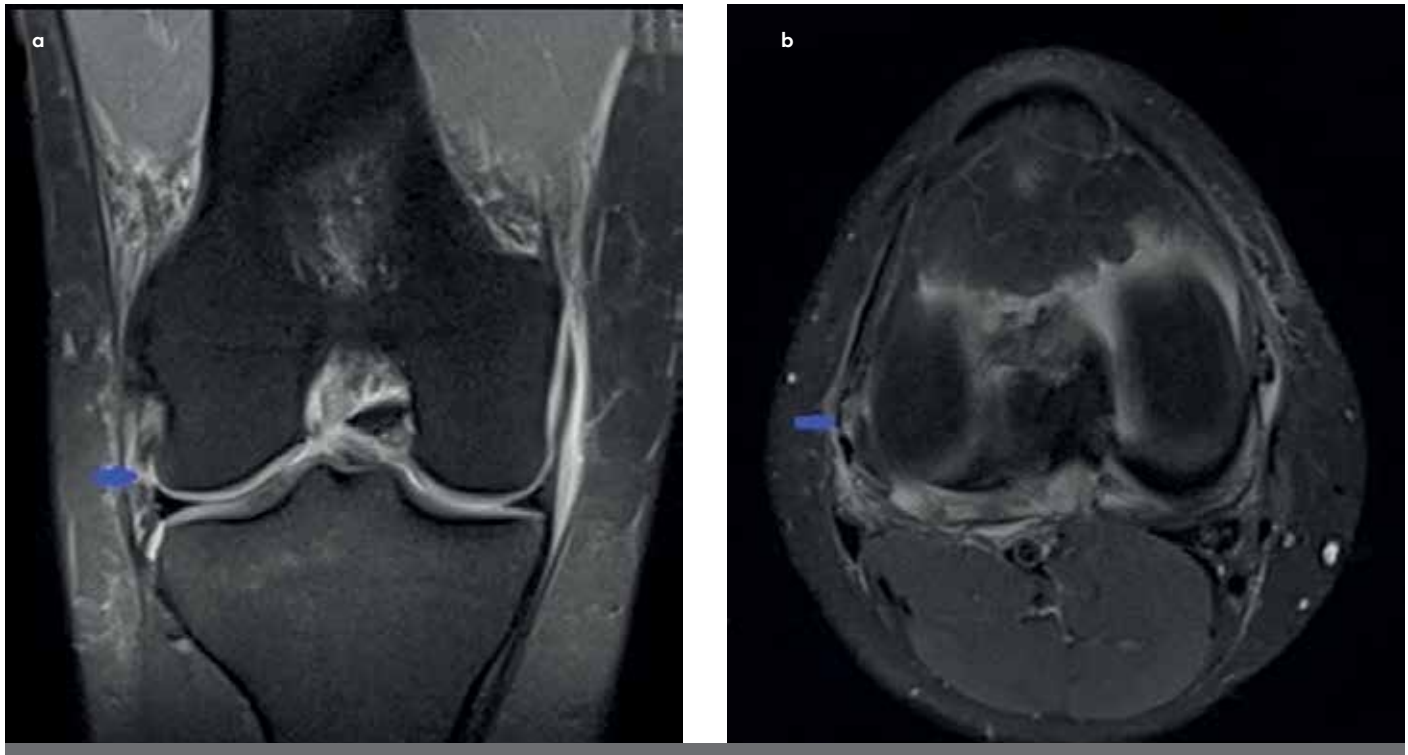

FIGURE 4. a, b. Coronal proton-density MRI image of the knee: The arrow marks disruption of the femoral part of the anterolateral ligament (a) Axial proton-density MRI image of knee: The arrow marks anterolateral ligament (b).

FIGURE 5. a, b. Sagittal proton-density MRI image of the knee: The amount between two longitudinal lines shows the anterior tibial translocation. (a) Sagittal TI MRI image of the knee: The angle between the two blue lines shows the PCL buckling (b).

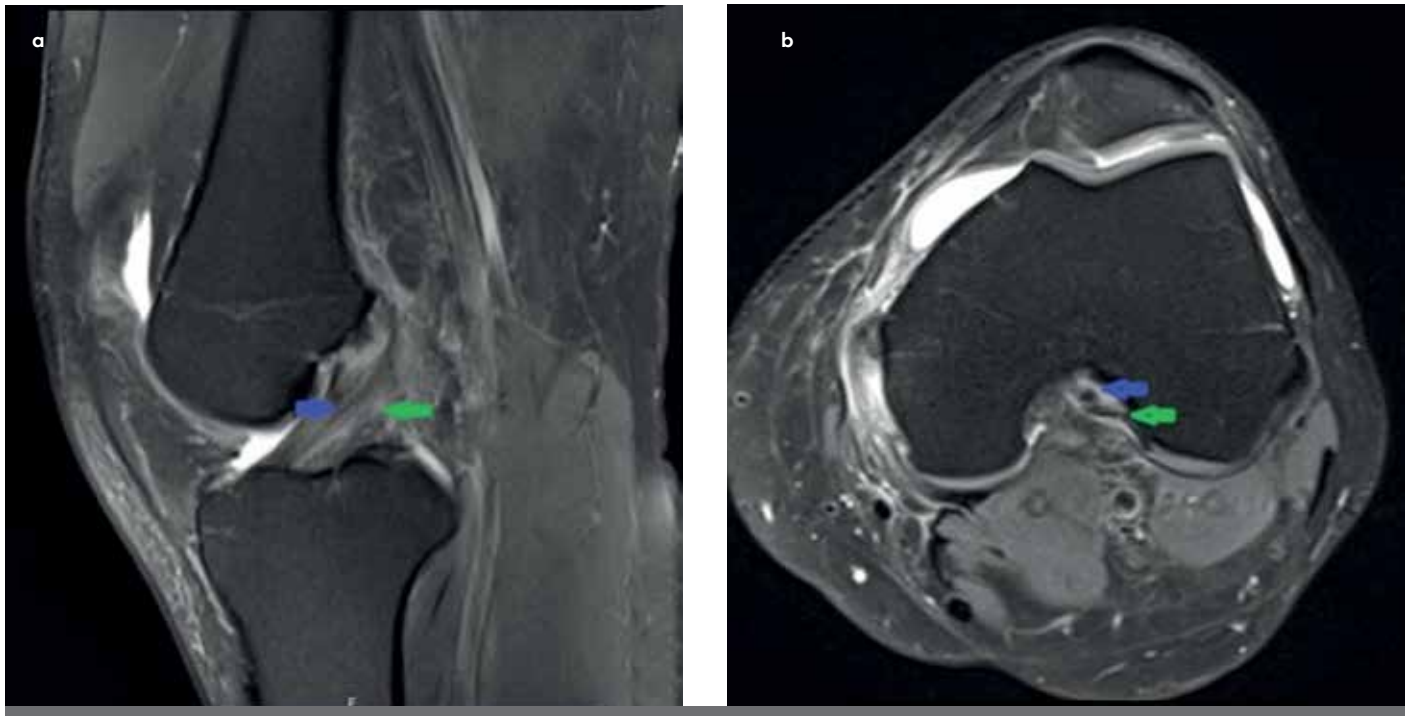

FIGURE 6. a, b. Sagittal proton-density MRI image of the knee: The blue arrow shows intact anteromedial bundle; the green arrow shows disrupted posteromedial bundle. (a) Axial proton-density MRI image of the knee: The blue arrow shows disrupted posterolateral bundle femoral attachment; the green arrow shows intact anteromedial bundle femoral attachment (b).

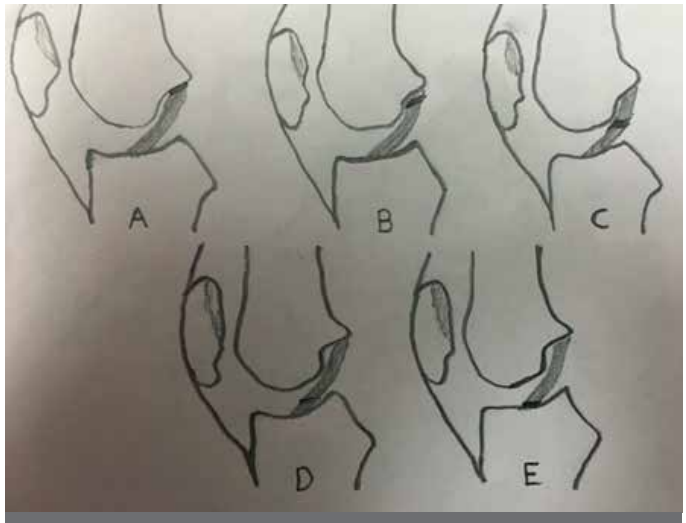

FIGURE 7. a-e. Tear type classification (Drawings by B. Polat). Type I proximal avulsion tear (a). Type II proximal tear (b). Type III midsubstance tear (c). Type IV distal tear (d). Type V distal avulsion tear (e).

A normal ACL is characterized by continuous, homogeneous low-signal intensity fibers, extending from the intercondylar notch of the tibial plateau to the medial aspect of the lateral femoral condyle. The ACL is best visualized with a turbo spin echo (TSE) sagittal intermediate weighted sequence and axial intermediate weighted with fat-suppression sequence. In addition, tibial attachments of the AM and PL bundles can be seen with coronal images.

Knee MRI scans were evaluated for the presence or absence of the following direct and indirect signs. These signs are discussed below.

DIRECT SIGNS

The direct signs of acute ACL tears consist of a structural integrity at any plane (axial, coronal, or sagittal) in the morphology of ACL, abnormal ligament contour, and abnormal MRI signal characteristics of the ligament itself. MRI studies performed in the acute period may show hyperintense appearance in the sagittal T2 sequences and are indicative of the loss of integrity and edema (Figure Ia). In the subacute period, the edematous appearance gives place to the fragmented appearance of lower intensity (Figure Ib). In the chronic period, the ACL may appear to be completely absent or undulated in the T2-weighted sagittal and axial sequence (Figure Ic, d) which can be named "empty notch sign" (15).

INDIRECT SIGNS

Hemarthrosis

Anterior cruciate ligament injury is the most common reason of traumatic knee hemarthrosis. The reason for acute hemarthrosis is injury to the branches of the middle geniculate artery. Bomberg et al. (16) reported that acute traumatic hemarthrosis in 71% of patients is caused by an ACL tear. Other most common causes of traumatic knee hemarthrosis are patellar dislocation and meniscal tear. Hemarthrosis is not considered a specific finding indicative of ACL injuries. It can be seen in the overall joint, particularly in the suprapatellar pouch, presenting as hyperintense in TI and intermediate to hyperintense in T2 sequence (Figure 2a, b).

Bone Bruise and Deep Sulcus Sign

When the ACL is torn, anterior translation of the tibia leads to abnormal contact of the lateral femoral condyle and lateral tibial plateau. This abnormal contact leads to microtrabecular fractures, edema, and hemorrhage on the subchondral bone. This condition is called bone marrow edema or bone bruise on

MRI. Generally, it is accepted that most common bone bruise locations in case of an acute ACL tear is the central third of the lateral femoral condyle and posterior third of the lateral tibial plateau (Figure 3a). This bone bruise pattern is sometimes seen in the medial compartment during severe injuries. Dunn et al. (17) reported that 418 of 525 (80%) patients with ACL tear had bone bruise imaging findings. Osteochondral depression of lateral femoral condyle in sulcus terminalis where a junction between the weight bearing tibial articular surface and the articular patellar surface of the femoral condyle, can be called "deep sulcus terminalis sign" (18). An average of 2 mm of collapse on the lateral femoral sulcus can be seen on direct graphy, as well as on MRI (Figure 3b). In a MR review study, bone contusions or bruise in the lateral compartment of the knee increased the specificity and positive predictive value in the ACL injury (19).

Segond Fracture or Anterolateral Ligament (ALL) Rupture

The abnormal varus stress and internal rotation of the tibia during the ACL injury causes the avulsion fracture of the lateral tibial condyle, which is called the Segond fracture. The Segond fracture is actually a bony avulsion of the ALL (20). This lesion, which is better seen on a direct graph, may also be detected on MRI.

Anterolateral ligament originates from the lateral femoral epicondyle, and it has a diagonal course and inserts at the anterolateral part of the tibial plateau, which is posterior to Gerdy's tubercle (21). Based on previous anatomic studies, the ALL has been divided into three segments: femoral (from the origin to the bifurcation point); meniscal (from the meniscal insertion to the bifurcation point); and tibial (from the tibial insertion to the bifurcation) parts (21, 22). Fat-saturated T2 weighted, proton-density weighted coronal and axial images of magnetic resonance generally show ALL precisely. With the coronal view, the meniscal part, the femoral part and the tibial part of the anterolateral ligament are easily observed (Figure 4a). With the axial view, ALL can be seen just in front of the lateral collateral ligament (Figure 4b) (23). Helito et al. (24) found that 32.6% of patients with a torn ACL had ALL injuries.

Anterior Tibial Translocation

Magnetic resonance studies of the sagittal section of the lateral femoral condyle were described as an indirect finding if there was a 7 mm or greater anterior translocation of the tibia relative to the femur (25). The amount of anterior tibial translocation is measured by calculating the distance between the posterior edges of lateral femoral condyle and the posterior edges of the tibia by drawing tangential vertical lines. The measurement should be made in the middle of the lateral femoral condyle of the sagittal plane images (Figure 5a). The mean anterior translocation amount in chronic ACL tears is 8.7 mm on average, while in acute ACL tears, it is 5.4 mm on average. The anterior tibial translocation has been shown to increase with time (26). This finding is considered equivalent to the physical examination of the anterior drawer test. According to Vahey et al. (25), the tibial anterior translocation was a specific finding for the ACL tear. It is accepted that subluxation of at least 5 mm has 58% sensitivity and 93% specificity for an ACL tear.

Buckling of the Posterior Cruciate Ligament

In the sagittal imaging of knee MRI with ACL tears, the sigmoidal orientation develops in the posterior cruciate ligament (PCL) due to the anterior translation of the tibia relative to the femur (27). This sign is called buckling of the PCL, and it can be observed with acute or chronic ACL tears (Figure 5b). In some studies, it has been reported that sigmoidal or curved appearance of PCL is more common in chronic ACL tears than in acute ACL tears (28). Yoo et al. (29) found that the reason for PCL buckling is the anterior subluxation of the tibia with ACL tears, and they also noted that hyperbuckling disappears after ACL reconstruction. For this reason, the PCL buckling observed after an ACL reconstruction is an indication of ACL laxity.

Tear Location of and the Residual Tissue Quality of ACL

Partial ACL injuries that affect the AM or PL bundle constitute approximately 30% of all ACL injuries (Figures 6a, b) (30). Biomechanical studies have shown that the PL bundle affects the rotational stability (pivot shift test), and the AM bundle affects the antero-posterior translational stability (anterior drawer test) (31). It is easy to diagnose complete ACL tears, compared to partial tears (sensitivity of 62%-81%; specificity of 19%-97%; and accuracy rates of 25%-53%) (32). An oblique axial sequence, thin slice, and the use of 3 Tesla MRI may increase these accuracy rates (33, 34). In contrast to physical examination and MR assistance, a definitive diagnosis of partial ACL tears is determined during arthroscopy. Although a definitive decision of selective reconstruction for partial ACL injury is given during arthroscopy, a well-evaluated MRI will guide to the surgeon before surgery.

Current ACL reconstruction procedures, which are called anatomic or double-bundle reconstruction, have limitations. Approximately, the failure rate of 10% can be found in the ACL reconstruction surgery. Limitation of movement, arthrosis, and recurrent instability are the main reasons of such failure (35). Recent biomechanical studies have suggested that the ACL reconstruction is not always successful with regard to gaining normal knee kinematics and does not totally prevent early osteoarthritis in the knee (36, 37). Arthroscopic ACL repair has many theoretical advantages over reconstruction. These advantages have gradually increased the interest in this surgical technique in recent years. With this technique, a normal knee kinematics is more effectively preserved, and the development of osteoarthritis is prevented as the patient's ACL is preserved (38). Arthroscopic ACL repair does not require graft tissue and bone tunnels, which provides shorter surgical time and recovery with fewer complications than the ACL reconstruction surgery (39). A detailed MRI evaluation is mandatory preoperatively if arthroscopic ACL repair is considered. The success of the surgery is directly affected by the remnant tissue quality and the localization of the tear. The modified Sherman classification system helps to classify the tear localization in five types (Figure 7). In Type I tear, the femoral part of ACL is avulsed, but more than 90% of the distal ACL is intact. In Type 2, there is a proximal tear with 75%-90% of intact distal ACL. In Type 3, there is midsubstance tear between 25% and 75% of the ACL. Types 4 and 5 are the distal tears, with 10%-25% of the distal ACL remaining intact in Type 4, and less than 10% of the distal ACL left intact. Type 5 tears can be divided into two groups, as soft tissue avulsions (type VA) or bony avulsions of tibial insertion (type VB). In the decision of arthroscopic primary ACL repair, this classification is very helpful.

In addition, the tissue quality can be classified as good, fair, and poor. If all fibers are intact in the same direction with a homo-

geneous signal, it is called a good quality tissue. If some fibers are in the same direction with a mildly heterogeneous signal, it is called a fair quality tissue, and if most fibers are in different directions with heterogeneous signal, it is called a poor quality tissue. Tears with good tissue quality must be preferred for an arthroscopic ACL repair.

CONCLUSION

Patients with a suspected ACL tear are diagnosed with an MRI scan. It is accepted that MRI is the most effective radiological modality, with 90%-95% sensitivity and 95%-100% specificity for detecting ACL injuries. Historically, MRI is mainly used to determine the ACL injury and to discern whether the tear is partial or complete. However, recently the MRI targeting has been expanded. Nowadays, the MRI classification of the remnant tissue quality and the localization of the ACL tear are the most important findings for primary arthroscopic ACL repair. As a result, choosing the right surgical technique for the ACL tear treatment is easier with these findings and the MRI help.

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Review

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Three-Dimensional Printing in Medicine: Current Status and Future Perspectives

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Three-dimensional (3D) printing has emerged as a defining component of the medical research and manufacturing industry in the past 10 years. The main applications of 3D printing in medicine are the development of educational and simulation models, patient-specific surgical guides and implants, and rapid prototyping of medical devices and biofabrication. 3D printing for preoperative planning in orthopedic, maxillofacial, spinal, cardiac, and oncologic surgery is currently the most prominent topic in published literature. At the same time, the models acquired via medical imaging may be used for 3D print custom implants tailored to patient's needs. Yet, the most promising field where 3D printing is being used in medicine is biofabrication of cell and tissue constructs, and this technology will possibly change the whole approach both to organ transplantation and drug research in the near future. 3D printing is expected to have a huge impact on the future of medicine. Current hype emerging from simple curiosity is steadily transitioning to a more structured approach through unbiased scientific research.

Keywords: 3D printing, medicine, future

INTRODUCTION

The production of solid objects by adding them layer by layer is called additive manufacturing. This term was popularized in the early 2000s and evolved to a more popular one called "3D printing", which describes the processes used in additive manufacturing. Initial 3D printers were developed in the 1980s but the real hype started in the late 1990s after commercial 3D printers were introduced to the masses. The real popularity was achieved through the community, which called themselves "the makers". These enthusiasts used common designs and introduced them to the public via open source codes. With the development of social media, video streaming, and online 3D printer spare parts shopping, kits with online assembly instructions have become available to common users, which has led to great reduction of the printer prices. The health sector rapidly integrated 3D printing in its workflow and 3D printing became one of the locomotives of the industry. In this article, we will describe the process of 3D printing, the technologies used, their applications, and current status in medicine.

How Is It Done?

All processes start with a 3D model acquired via a computer-aided design, 3D scanner, photogrammetry or medical imaging software. Prior to printing, the model should be examined for errors, because 3D printers do not recognize holes, faces, self-intersections, and manifold errors. This issue is particularly encountered in models acquired by 3D scanning. After this "digital cleaning and preparation", the 3D file is processed by software called slicer which turns the model into thin layers and produces a code that is recognized by a 3D printer.

This code is called G-code and contains a series of coordinates and commands specific to the machine. Until this part, the process is much the same for all manufacturers. The real difference starts with the method used for 3D printing, and there are approximately 20 different technologies. The most common ones are fused deposition modeling, stereolithography, selective laser sintering, and material jetting. Fused deposition modeling (FDM) describes the process of adding layers of molten thermoplastic on each other through a moving extrusion hot end onto a bed. This is the process most frequently adopted by makers worldwide because of the ease of use and wide availability of cheap machines and supply materials.

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Stereolithography (SLA) is the process where, instead of melting, an ultraviolet (UV) curable resin is polymerized by high precision lasers in a tank. This technique produces the most precise models and is widely adopted in the field of dentistry. Selective laser sintering (SLS) uses laser to cure the powder polymer layer by layer. This method produces sophisticated durable parts mainly for engineering purposes. Material jetting is a process which uses powder, which is sprayed layer by layer with immediate curing via laser or a heat source. The last two technologies need full-time technical support, are more industrial in nature, and the machines are not affordable for ordinary users. More recently, the term "metal 3D printing" was introduced to the industry and has already been used for the production of custom surgical guides and implants. This technology is based on layer-by-layer laser or heat fusion of metal powder.

FIGURE I. Image segmentation of tibial fracture

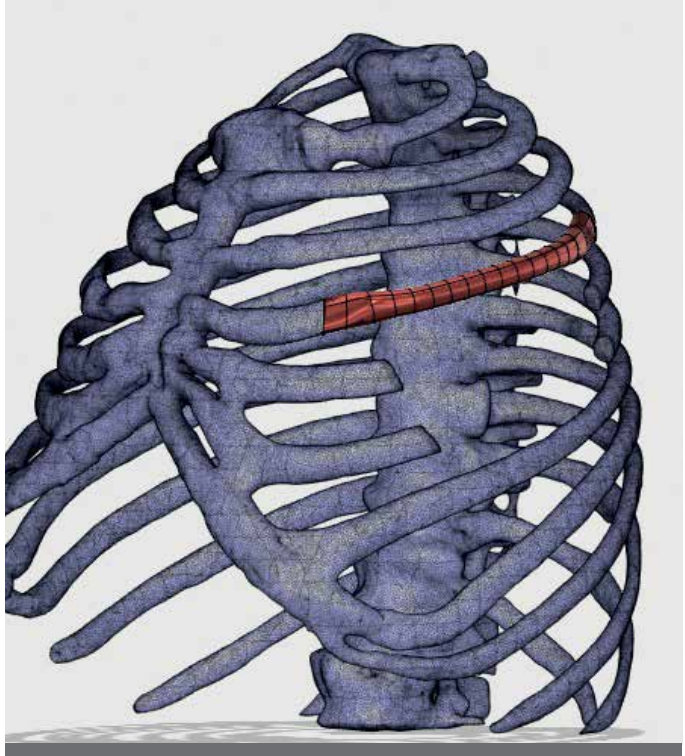

FIGURE 2. Patient-specific rib implant modeling

All these technologies have different resolutions, printing times, and price per part and use different materials with variable strength properties. For example, an SLA print offers a highly detailed model with a high price per part but with moderate strength and is mostly suitable for printing 3D models prior to dental and vascular procedures. SLS print is strong and detailed because it is mostly printed with polyamide; however, it requires a powder cleaning station and is more expensive than FDM and SLA prints. FDM printed model is cheaper and stronger than SLA printed model; however, it offers lower print detail and often requires printing of separate removable support structures besides the print itself. Therefore, the knowledge of these technologies is crucial before deciding to acquire a particular machine for research purposes.

CURRENT APPLICATIONS IN MEDICINE

Surgical Planning and Education

3D printing for preoperative planning in orthopedic, maxillofacial, spinal, cardiac, and oncologic surgery is currently the most prominent topic in published literature. Modern medical imaging workstations offer the possibility of converting patient images into 3D models. This process is also possible by uploading the DICOM images into freely available open source imaging software options. The software allows segmentation of the image, which means selecting the region of interest in slices and converting it to a solid 3D object (Figure I). This object is further transferred to the mesh software for digital cleanup and preparation for printing. This method allows the surgeons to prepare for surgery and reduce intraoperative decision time, particularly in complicated cases. Sodian et al (1) showed that 3D printed stereolithographic replicas were extremely useful in planning reoperations for previous coronary bypass surgery. At the same time, this method also allows the surgeon to manufacture patient- and lesion-specific guides for orthopedic, spinal, and maxillofacial surgeries (2-7). Printed models may also aid the patient to understand the planned surgical procedure better, and, at the same time, the models may be reserved for both student and resident training. However, current literature lacks randomized controlled studies to prove the proposed positive effects of 3D printing on surgical planning. We may see studies on these aspects after the current hype slows down leaving space for unbiased research.

Patient-Specific Implants

This is perhaps the most promising aspect of 3D printing in the field of surgery. The images obtained from patients allow the surgeon to plan the surgery with a 3D printed model. At the same time, this image may be reconstructed, and an implant tailored for the specific needs of the particular patient may be modeled with the dedicated software (Figure 2). This approach is already being practiced by several centers and commercial companies, and patient-specific implants are being manufactured using 3D printing (8, 9). In a case documented by Phan et al (10), 3D printed spinal implant reduced the overall surgery time and risk of neurovascular compromise in a patient with C1/C2 fusion. Unfortunate-

ly, research in this area mostly comprises case reports and case series for the treatment of specific pathologies.

Bioprinting

The most promising application of 3D printing is in the field of biofabrication. The term bioprinting refers to the process of layer-by-layer deposition of live cells suspended in a biocompatible hydrogel or via the spheroid formation. The deposition is achieved through extrusion or jetting based techniques (11). The polymers used for bioprinting are natural, such as gelatin, alginate, collagen, fibrin, or synthetic, such as polyethylene glycol, polycaprolactone (PCL), and polylactide co glycolide (PLGA) (12). Current research is mainly focused on the development of deposition systems and polymers to provide the most suitable environment for long-term survival of cells in vitro. However, the main challenge is the inability to fully mimic the natural extracellular matrix and provide exact cell to cell signaling and interactions. Therefore, this process is extremely complex and requires a high level of expertise, both in the field of engineering and polymer and cell sciences. Printed cell aggregates are further matured in bioreactors to form a functional tissue construct. With the current pace of research in this field (13-21), it is possible to foresee 3D printed tissue and organs in future.

Future Perspectives

Three-dimensional printing is definitely a niche area in medicine. The most striking future perspective is definitely in the area of 3D bioprinting. Currently, budget 3D bioprinters capable of performing basic tasks are becoming widely available due to reduced prices. At the same time, many centers are building their own printers for research purposes. Even the current status of research predicts 3D printed organ and tissue constructs in the near future.

Another definite surge is expected in the field of production of patient-specific implants and prostheses. Many companies are presenting their implants printed with different materials, including titanium, and this approach will possibly be a surgical routine in the near future.

Other fields like 3D printed surgical instruments and guides and educational models are highly dependent on the mass availability of affordable 3D printers in every hospital and university.

CONCLUSION

Three-dimensional printing is expected to have a huge impact on the future of medicine. Current hype emerging from simple curiosity is steadily transforming to a more structured approach via unbiased scientific research.

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Review

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Pharmacologic Effect of 5-Methoxytryptophol

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5-methoxytryptophol (5-MTX) is an indolamine synthesized from the pineal gland hormones. This indolamine, synthesized from serotonin and melatonin, has been shown to be biologically active in different species. In particular, its activation is regulated by radiation stimuli such as sunlight. 5-methoxytryptophol-mediated receptors play a role in the regulation of cerebral artery contractility, intracarrhythmia, and the regulation of the renal function. It also shows immunomodulator, antioxidant, and anxiolytic properties with different mechanisms. To date, studies examining the mechanism of 5-MTX have been done, but these are insufficient to explain it. In our study, all of these studies were examined, and we aimed to explain the pharmacological and therapeutic effect of 5-MTX as a review. In particular, the fact that melatonin secreted in the dark and 5-MTX released in the light create a 24-hour protective effect will bring a new perspective to new studies. This will lead to the creation of a new clinical and scientific research, which will lay groundwork for the creation of alternative treatment regimens.

Keywords: 5-methoxytryptophol, melatonin, serotonin

INTRODUCTION

5-methoxytryptophol (5-MTX) is a hormone synthesized from the pineal gland hormones. This indolamine, synthesized from serotonin and melatonin, has been shown to be biologically active in amphibians, reptiles, fish, birds, and mammals and is physiologically regulated by radiation stimuli such as sunlight. Some researchers report that 5-MTX has a similar endocrine effect as melatonin and has a 24-hour circadian pattern in blood. This indolamine, unlike melatonin, is photoperiod dependent and oscillates in the daytime, whereas its levels in blood are inversely proportional at nighttime (1).

Circadian and "seasonal" rhythms of 5-MTX have been identified in studies on various vertebrate species and gastropods. For example, in a human study, the levels of 5-MTX were investigated between January and March, which is called the short photoperiod, and it was found to have higher concentrations during the day and lower concentrations during the night. As a matter of fact, during the summer months, 5-MTX was found in higher concentrations in plasma at night due to a high production related to the photoperiod, compared with the winter months. As a result, it was determined that the pineal gland is affected by photoperiods in the synthesis of 5-MTX (2).

Synthesis

There are two ways to synthesize 5-MTX.

The first way begins with the deamination of serotonin by oxidative monoamine oxidase (MAO). Serotonin is deaminated by MAO through the oxidation mechanism into the 5-hydroxyindole acetaldehyde. With the catalytic activation of the enzyme aldehyde reductase (AR), 5-hydroxyindole acetaldehyde is reduced down to 5-hydroxytryptophol. 5-hydroxytryptophol is methylated by the 5-hydroxyindole-O-methyltransferase enzyme to form 5-MTX (Figure 1) (3).

Along with this method, 5-MTX is made from melatonin alongside another metabolic mechanism in the retina, kidney, and liver. Melatonin is converted to 5-methoxytryptamine by deacetylation. 5-methoxytryptamine then forms 5-methoxyindolacetic acid and 5-MTX through deamination (Figure 2) (4).

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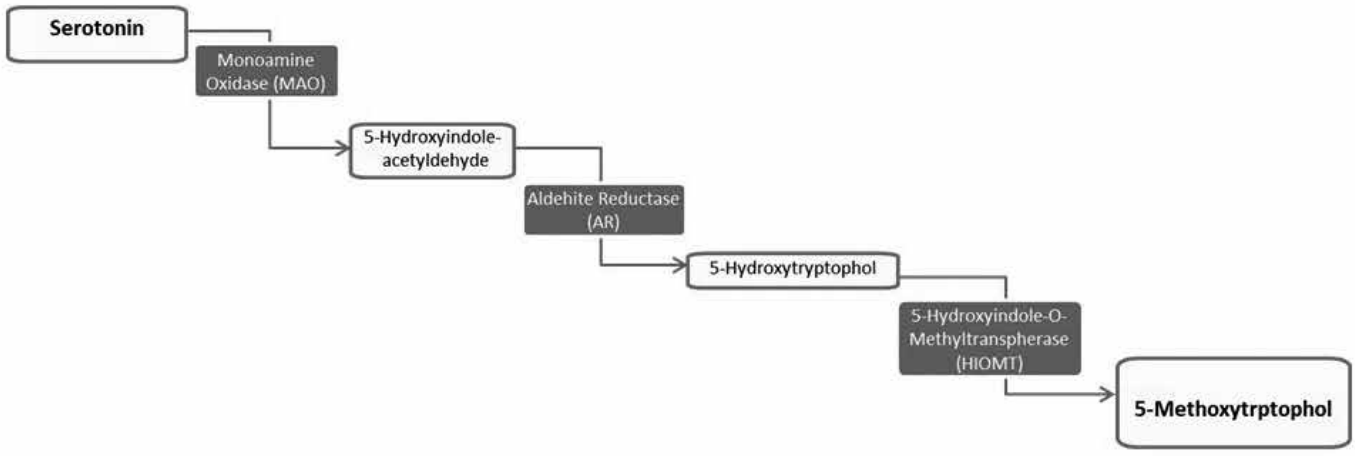

FIGURE I. 5-Methoxytryptophol (5-MTX) synthesis pathway from serotonin

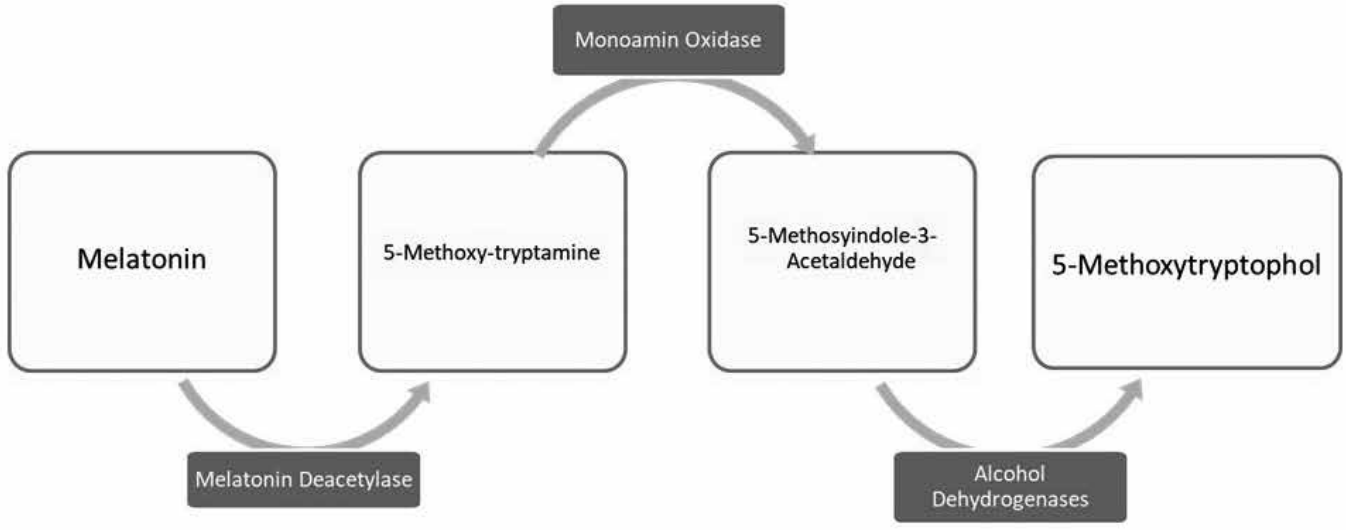

FIGURE 2. 5-Methoxytryptophol (5-MTX) synthesis pathway from melatonin

Receptors

In the receptor studies using radioligand 2-[125I]-iodomelatonin, the MT_1 and MT_2 receptor affinity of MTX-5 in different species shows variance (5). The affinity is high in the receptors of chicken brains and retinas and rabbit retinas solely for the MT_1. MT_2 receptors have affinity in the hamster brain (6, 7). In humans, these two receptor subtypes are thought to be found intensely in the suprachiasmatic nucleus (SCN) and affect the entire biological system by spreading to other brain regions. MT_1 receptors are responsible for renal function, dermal function such as hair growth, sleep, circadian rhythm, and cerebral artery contractility (1). These receptors play a role in light-dependent events such as Ca-dependent dopamine release in mammalian retinas and phagocytosis of retinal photopigment discs (8). The MT_1 receptor activation causes G_i adenylate cyclase inhibition via proteins. Also, only MT_1 receptors have been shown to stimulate arachidonate release via phospholipase activation. Low-affinity MT_2 receptors are claimed to be closely connected with G proteins and to behave in a similar way to MT_1 receptors. However, unlike MT_1 receptors, MT_2 receptors have been indicated to cause phosphoinositide hydrolysis (9).

It has been found during studies that 5-MTX, just like melatonin, has the ability to enter many organelles. In particular, it can pass to the blood-brain barrier receptors. It can be found in high concentrations in the thyroid and adrenal glands, ovaries, and uterus cells, and it can be metabolized in urine as well (1). Although some studies have shown that there is a correlation between the concentration of 5-MTX in the pineal gland and serum levels, conflicting results arise. This is due to turnover, secretion, and the fact that the turnover to 5-MTX from 5-methoxyindoline does not follow a rhythmic course (10). In addition, human organic anion transporter (hOAT) 1 and hOAT 3 of the solute carrier family carrier proteins efflux the 5-MTX from the cerebrospinal fluid to the choroid plexus, because of which this correlation does not occur. These carrier proteins play a facilitating role in the uptake of the drug into the cell, and they dynamically affect the accumulation of 5-MTX and its translocation in the cell (11).

The Role in Physiological and Pathological Events

5-MTX plays a part in physiological and neuroendocrine functions, although the cellular and molecular mechanisms of its release are still unknown. However, because it helps to remove free

radicals and their antioxidant activity, it resembles melatonin (12). In particular, the studies of 5-MTX have shown that it increases superoxide dismutase and glutathione peroxidase levels and prevents lipid and protein oxidations, and thus has been caused by FeCl3 and ascorbic acid and has protective properties similar to melatonin (13, 14). In a study conducted in 1996 by Lissoni et al., it was found that 5-MTX reduced IL-6 levels, which are the immunostimulatory cytokines in serum, and increased the synthesis of immunosuppressive IL-2 and IL-12. Since opposing circadian rhythms of melatonin and 5-MTX have been established, Lissoni suggest that these two indolamines, which act at different times of the day, should be used together to benefit from immunostimulatory effects (15). In a study by Savtekin and colleagues, it was also indicated that 5-MTX shows protective qualities by affecting matrix metalloproteinases 2 and 8 and TNF-α and IL-Iβ levels in zymosan-induced synovial inflammation (16).

It was also shown that by affecting human gingival fibroblasts, 5-MTX stimulates the healing of wounds in periodontal disease or dental implantology by reducing the expression of collagen III al, a decorin tissue inhibitor of metalloproteinases I, and IL-10 (17). Potential use of this agent in the treatment of periodontal diseases is being considered due to its properties that increase the collagen synthesis and improve scar tissue healing, reduce the ROS levels, stimulate immunologic response, have antibacterial activity, and slow down the alveolar bone loss (18).

In addition to the antioxidant and immunomodulatory properties of 5-MTX, there are also hypothermic and hypotensive effects (19). In studies conducted on rats, it has been proposed that it shows an anxiolytic effect by the modulating of stress response (20). It is possible that its effects are the result of increased GABA-ergic activity, decreased metabotropic glutamatergic activity, and modulation of the opioidergic system just like melatonin does. Alongside melatonin, it is present in the regulation of the sleep cycle (21). In vitro studies conducted on hormones have indicated that 5-MTX increases the osteoblastic activity and inhibits the osteoclastic activity in bone cells. According to this study, 5-MTX was found to stimulate the osteoblast differentiation more than melatonin, clearly showing an increased secretion of osteocalcin (22). It has been suggested that by blocking the nicotinic and muscarinic acetylcholine receptors, 5-MTX inhibits the FSH and LH, the anterior pituitary hormones, and has antigonadotropic effects by affecting the gonads. In toxicological studies performed, fetotoxic and teratogenic effects were observed even at normal doses (23, 24).

CONCLUSION

In all these findings, it is understood that 5-MTX released in the light with the hormone melanin released in the dark has a 24-hour protective effect on the body. Therefore, in studies concerning melatonin, the application of 5-MTX alongside it, as it imitates the daytime rhythm, will lay a foundation for alternative treatment regimens to emerge as it brings a new perspective, causing new clinical, scientific studies to arise.

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Review

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Cystic Echinococcosis in Northern Cyprus: A Literature Review

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Cystic echinococcosis is a zoonotic disease caused by the larval stages of *Echinococcus granulosus* sensu lato (s.l.). The life cycle of the parasite consists of dogs and other canids as the definitive hosts and ungulates, such as sheep and goats, as the intermediate hosts. Humans are accidental intermediate hosts in the life cycle of the parasite. The island of Cyprus is located in the eastern part of the Mediterranean region where echinococcosis is endemic. The disease was common in the island until the 1970s. In Southern Cyprus, two control programs for echinococcosis were implemented; the first one was initiated in 1971 and continued until 1985, and the second one was introduced in 1993 and implemented for 5 years. The control programs resulted in a decrease of the prevalence in both dogs and livestock. In Northern Cyprus, a control program was implemented between 1997 and 2005 that also resulted in a decrease of the disease rates in definitive and intermediate hosts. However, termination of the program led to an increase in the prevalence. Recent data suggest that sporadic cases of echinococcosis still exist; therefore, control programs should be continued in order to prevent the disease in Northern Cyprus.

Keywords: Cystic echinococcosis, *Echinococcus granulosus*, prevalence, Northern Cyprus

INTRODUCTION

Echinococcosis, also referred to as hydatid disease, is a zoonosis developed by the larval stages of *Echinococcus*, which is a cestode parasite (1). It is one of the neglected tropical diseases and also listed among the priority neglected zoonotic diseases defined by the World Health Organization (2).

Different clinical forms of echinococcosis in humans include cystic echinococcosis (CE), which is caused by *Echinococcus granulosus* sensu lato (s.l.) (3); alveolar echinococcosis (AE), developed by *Echinococcus multilocularis*; and polycystic echinococcosis, caused by *Echinococcus vogeli* and *Echinococcus oligarthrus* (4). CE and AE are the most common clinical forms of the disease, and they cause health and financial problems especially in low-income countries (5). The highest rates of *E. granulosus* are documented from Eurasia, Africa, Australia, and South America (6). *E. multilocularis* is limited to the Northern Hemisphere, whereas it is widespread in this region (7). Polycystic echinococcosis is restricted to Central and South America and reported rarely in humans (1).

Cystic echinococcosis has a worldwide distribution and is endemic in areas including Peru, Chile, Argentina, Uruguay, Southern Brazil, Mediterranean region, Central Asia, Western China, and East Africa. It is a particular concern in poor rural regions where livestock and dogs are typically present and maintain transmission of the infecting parasite (4).

Cystic echinococcosis has significant impact on human health (6). It is estimated that >1 million people are infected globally, with >1 million disability-adjusted life-years lost each year. Furthermore, the economic burden of human CE is estimated to be >$750 million, whereas the estimated cost of the infection in livestock was reported to be >$2 billion per year globally (8).

The Mediterranean region is one of the areas in which the highest rates of zoonotic diseases are recorded (9). The annual incidence rate of human CE was reported to be 4-8/100,000 in this region (10). Furthermore, CE was indicated as one of the five most common zoonotic diseases in the Mediterranean region (9).

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Cyprus is a Mediterranean island where CE was commonly encountered in the past. The disease was detected not only in animals but also in humans. In order to prevent the further spread of CE in the island, control programs were implemented, and these campaigns resulted in substantial reductions of the prevalences in both dogs and livestock (11, 12). In Northern Cyprus, a control program for echinococcosis was also implemented; however, after termination of the program, the disease re-emerged in the country (13).

In this review, first, the transmission of *E. granulosus* and the clinical manifestations of CE are summarized. Then, the presence of CE in Cyprus is discussed with a focus on Northern Cyprus. In addition, the impacts of the control programs on animal hosts and the reported human CE cases are reviewed.

CE and the Life Cycle of *E. granulosus*

CE is caused by the larval stages of *E. granulosus* sensu lato (s.l.). This complex includes five species: *E. granulosus* sensu stricto (s.s.) (genotypes G1-G3), *Echinococcus equinus* (G4), *Echinococcus ortleppi* (G5), *Elodea canadensis* (G6, G7, G8, and G10), and *Echinococcus felidis* (3). Among these, *E. granulosus* sensu stricto (s.s.) is considered to be the most important human pathogen (14).

In the life cycle of the parasite, dogs and other canids are the definitive hosts, whereas ungulates (e.g., sheep and goats) are the intermediate hosts. Humans are accidental intermediate hosts for the parasite (1).

Dogs have an easy access to the viscera of livestock particularly in rural regions (15). For this reason, the definitive hosts can also ingest the offal that contains the hydatid cysts. In this case, the adult form of the parasite develops in the small intestine of a canine. The eggs are passed in the stool of an infected animal. After ingestion of the eggs by the intermediate hosts, the larva (oncosphere) hatches from the egg, penetrates the intestinal mucosa, reaches the bloodstream, and migrates to the liver, lungs, and other internal organs. Here, the oncosphere develops into the metacestode (hydatid cyst) (1).

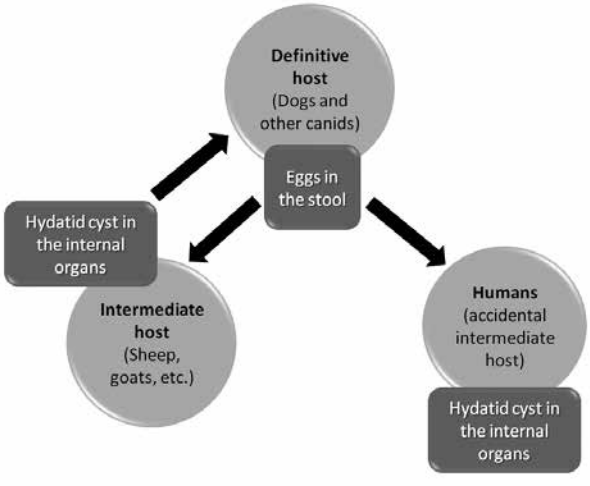

FIGURE 1. Transmission of CE between the definitive and intermediate hosts

Within the cyst, brood capsules and protoscolices bud from the germinal layer, and daughter cysts are generally formed. When the organs of the intermediate hosts that contain the cyst are ingested by the definitive hosts, the life cycle of the parasite can start again. In the definitive hosts, the protoscolices evaginate, attach to the intestinal mucosa, and develop into the adult form in 30-80 days (1).

Humans can be infected via the fecal-oral route when dogs pass *E. granulosus* eggs in their stool. Humans can ingest the parasite eggs directly through close contact with dogs or indirectly by consuming contaminated water and uncooked meat (15).

A number of factors can facilitate the transmission of the parasite between animals and humans. Potential risk factors that are related with CE include free dog roaming, feeding dogs with viscera, dog ownership, slaughtering at home, insufficiently controlled slaughterhouses, living in rural regions, and low income (16).

Figure 1 summarizes the transmission of CE between the definitive and intermediate hosts.

Clinical Manifestations of CE

Cystic echinococcosis most frequently involves the liver. The second most commonly affected organ is the lung. Apart from these, the cyst can also reach other organs and structures in the body (4).

Generally, the cyst grows slowly; therefore, CE is mostly asymptomatic for a long time. Usually, primary infections comprise a single cyst; however, nearly 20%-40% of the individuals can have more than one cyst. Enlargement of the liver, right upper abdominal pain, nausea, and vomiting are the signs and symptoms of liver hydatidosis. Leakage or rupture of the cyst can result in anaphylaxis (1).

Secondary CE can develop as a result of cyst rupture in the peritoneal cavity, and the protoscolices and/or small cysts can form larger cysts. The growing cysts can lead to obstruction in the portal vein or bile duct, which may cause segmental or lobar atrophy of the liver. Other complications include cyst rupture in the biliary tree and secondary cholangitis, obstruction of the bile duct by daughter cysts, and development of fistula (1).

Since the infection can be asymptomatic for a long period, the clinical diagnosis of CE is generally difficult. Therefore, physical examination, radiological techniques, and serological tests are performed for the diagnosis of CE (6, 17).

The Island of Cyprus and its Importance for Echinococcosis

Cyprus is situated in the east of the Mediterranean region, between 34°33′-35°42′ northern latitudes and 32°16′-34°36′ eastern longitudes (18). In the island, agriculture is an important source of income, where crop and livestock production is common (11). Echinococcosis was commonly encountered in Cyprus until the 1970s. The intermediate hosts were seriously affected by the parasite, and also the disease was an important public health issue. The annual surgical incidence rate was recorded as 12.9/100,000, which was one of the highest proportions recorded for echinococcosis worldwide (12). The high prevalence of infec-

tion was attributed to several factors including the abundance of stray dogs, improper slaughter of animals, inappropriate disposal of the infected offal, poor awareness of the parasite's life cycle in the community, and climate, which is favorable for the survival and dispersal of the parasite eggs (19).

Implementation of Two Echinococcosis Control Programs in Southern Cyprus

In 1971, the first control program for echinococcosis was initiated in the island. The program continued in Southern Cyprus (Greek Cypriot community) until 1985; however, it was abandoned in Northern Cyprus (Turkish Cypriot community) after 1974 (12). The control program achieved successful results in both dogs and livestock. During the implementation of the program, the infection rates were reduced from 14.1% to 0% in dogs, from 50%-60% to 0.11% in sheep, from 14.5% to 0.01% in goats, from 18.6% to 0.04% in pigs, and from 38.9% to 0.87% in cattle (11). By the year 1985, echinococcosis was considered to have been eradicated in both definitive and intermediate hosts; therefore, the program was terminated. After 1985, sporadic cases were detected in livestock, and transmission of echinococcosis continued between dogs and livestock. Eventually in 1993, the second control program for echinococcosis was initiated in Southern Cyprus (12) and implemented for 5 years (11). The infection was detected in 16 dogs in 1993, but this number was reduced to zero by 1997. The infection rates declined from 0.088% to 0.011% in cattle, from 0.033% to 0.007% in sheep, and from 0.0112% to 0.0006% in goats between 1994 and 1999 (12).

Northern Cyprus and Implementation of the Echinococcosis Control Program

The area of Northern Cyprus covers approximately one-third of the island. The population of the country was reported to be 286,257, whereas the numbers of people living in urban and rural regions were documented as 197,484 and 88,773, respectively, according to the 2011 census (20). The economy of Northern Cyprus is based primarily on the public sector, trade, tourism, and education (21). The main economic activities include agriculture and animal husbandry in the rural areas of the country (22).

In 2010, the numbers of sheep, goats, and cattle were documented to be 186,424, 54,440, and 47,972, respectively, in Northern Cyprus. Importantly, the presence of inadequately supervised slaughterhouses and slaughtering of small ruminants outside the abattoirs were also reported. Moreover, the number of dogs was estimated to be 15,000, whereas the number of registered dogs was noted to be 13,500. The number of stray dogs was shown to be increasing (13). Taken together, these suggest that the possible risk factors for CE are present in Northern Cyprus (16).

The echinococcosis control program that was initiated in 1971 did not continue in Northern Cyprus (Turkish community) after 1974, and the disease was detected in both humans and livestock (12). A study conducted in Northern Cyprus documented the prevalence rates of echinococcosis in sheep and cattle processed in slaughterhouses of Famagusta and Nicosia between 1993 and 1998. The rates of echinococcosis were reported to be 71.1% in sheep and 46% in cattle in the slaughterhouse of Famagusta. The prevalences in the slaughterhouse of Nicosia were reported to be 30.33% and 13.16% in sheep and cattle, respectively (23). Owing to the high prevalence rates, a control program for echinococcosis was implemented between 1997 and 2005 in Northern Cyprus (13). During the period of 1997 and 2002, the rate of CE declined from 0.9% to 0.0% in sheep <2 years, whereas this percentage was reduced from 48% to 4% in sheep >2 years. The prevalence of the infection also declined in cattle and goats. The rate of CE in dogs decreased from 1.95% to 0.0% between 1998 and 2004. Termination of the control program resulted in an increase in the prevalences, and finally, CE re-emerged in Northern Cyprus (13). In 2010, the prevalences of CE were reported to be 14.9%, 5.57%, and 3.16% in sheep, goats, and cattle, respectively. Furthermore, the rate of *E. granulosus* infection in dogs was estimated to be 5% (13).

Human Echinococcosis Cases in Cyprus

Apart from the cases in dogs and livestock, disease in humans was also demonstrated in the island. According to data collected from government hospitals, 160 surgical operations of CE were performed between 1980 and 1998 in Southern Cyprus. The operations in the private clinics were excluded in the data; therefore, the actual number of cases was noted to be >160. Among individuals <20 years old, no case of CE was detected in Southern Cyprus; however, three cases were documented in this age group from Northern Cyprus. Cases from Southern Cyprus primarily consisted of latent infections, and as a result of the control program, the transmission cycle between dogs and humans was blocked (11).

A report from Cyprus demonstrated four cases of isolated cardiac echinococcosis in the 12 years prior to 2000 (24). After this period, sporadic cases appear to have occurred in the island. Data obtained from the European Centre for Disease Prevention and Control (ECDC) suggest that echinococcosis has been detected at very low levels in Cyprus. A total of four (two in 2011 and two in 2015) confirmed echinococcosis cases were reported from Cyprus between 2011 and 2015. The first three countries that reported the highest number of cases in 2015 were Bulgaria (n=313), Germany (n=145), and Spain (n=83) according to the ECDC report (25).

In Northern Cyprus, 80 surgical cases were documented between 1990 and 1996. The annual incidence rate was recorded as 5.7/100,000. Together with the number of individuals operated abroad, the estimated rate for 1995 was noted to be a minimum of 25/100,000. As the proportions were determined according to data obtained from surgical operations, the number of actual cases was suggested to be higher (13). Echinococcosis was detected in the radiological examination of 43 (1.73%) out of 2480 individuals between 1996 and 1999 (23). In 2010, the surgical prevalence of human CE was documented to be 4/100,000 (13).

More recently, a preliminary investigation in Northern Cyprus included 688 individuals to evaluate the presence of human echinococcosis by serological tests. Seven (1.0%) out of 688 samples were found to be positive by Western blot. Four out of seven individuals were detected to be positive for *E. granulosus*, whereas the remaining three were positive for *E. multilocularis* (26).

CONCLUSION

In the island of Cyprus, sporadic cases of echinococcosis appear to occur at low levels. Implementation of control programs

in Southern Cyprus achieved successful results in both definitive and intermediate hosts. The control program in Northern Cyprus also resulted in a decrease of the CE rates. However, the prevalences increased in Northern Cyprus after termination of the program.

Previous and recent findings on echinococcosis suggest that the disease cannot be ignored in Northern Cyprus. The possible transmission of *E. granulosus* can be prevented by control measures, such as management of stray dog population, deworming of dogs with praziquantel, administration of the EG95 vaccine to sheep and goats, maintaining hygiene at slaughterhouses, and raising public awareness by education programs, particularly in the rural settings. In addition, more studies should be conducted to evaluate the presence of CE in humans, dogs, and livestock in Northern Cyprus.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Case Report

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Iris Fixated Intraocular Lens Implantation

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Management of dislocated lens is one of the challenges faced in ophthalmology practice. Here we reported the case of patient with dislocated lens and its management with pars plana anterior vitrectomy, intraocular lens (IOL) exchange, and fixation of new 3 pieces IOL to iris with a Siepser suture technique.

Keywords: Dislocated IOL, iris fixated IOL, pars plana anterior vitrectomy

INTRODUCTION

Dislocated Intraocular lens (IOL) might be presented during or after cataract surgery, trauma, insufficient capsular support, or zonular dehiscence (1). There are several surgical methods for the management of dislocated IOL. The ones applied mostly are anterior chamber IOL, scleral fixation of same or new IOL, and iris fixation of same or new IOL (1-5). Here we reported the management of the case of a patient with traumatic dislocated IOL with pars plana anterior vitrectomy and implantation of 3-piece IOL to iris.

CASE PRESENTATION

An 80 years old male patient complaining of decrease in sight in his right eye after accidental hit with a peanut was admitted to our department. He had a history of right eye cataract surgery 7 years ago. Physical findings revealed hand motion vision and dislocated IOL in his right eye; the left eye was normal. The patient underwent pars plana anterior vitrectomy, dislocated IOL explantation through corneal incision, and fixation of 3-piece posterior chamber IOL (Alcon Acrysof MA60AC, Alcon Laboratories, USA) to iris under general anesthesia. Initially, 2 transconjonctival 23-gauge (G) trocars were inserted at distance 3.5 mm periphery to the limbus. One of them was infusion for balanced salt solution (BSS, Alcon Laboratories, USA) and the other one was for vitrectomy probe. Then, pars plana anterior vitrectomy was performed. The vitreous around the dislocated IOL was cleared. Dislocated IOL was taken to the anterior chamber. Temporal corneal incision was performed with a corneal knife (Ophthalmic knife, MST 45 straight, Mani Inc., Japan) between 9 and 12 o'clock position. Dislocated IOL was explanted through corneal incision. Then new 3-piece IOL (Alcon Acrysof MA60AC, Alcon Laboratories, USA) was inserted into the anterior chamber through corneal incision (Figure Ia). The anterior chamber was filled with cohesive viscoelastic substance (0.50 mL in volume; sodium chondroitin sulfate 4%, sodium hyaluronate 3% with 27 G canula, Viscoat, Alcon Laboratories, USA). Corneal incision was closed with 3 separate 10/0 nylon sutures. One of thehaptic segments of IOL inserted to the posterior chamber. Paracentesis was made at 1 o'clock with a 20 G MVR knife (MV2 20, Mani Inc., Japan) for the insertion of needle (Mani L2460, Mani Inc., Japan). A long curved needle was passed from paracentesis through the iris then under the haptic up to the anterior chamber and lastly went out through the cornea (Figure Ib). Hook inserted through the paracentesis grasps the distal strand of the suture out of the eye. Distal strand forms a loop outside the eye adjacent to the proximal strand. The distal loop was grasped with a tying forceps, triple throw was made. So knot was slided by pulling proximal and distal strands. The hook was used again to create a loop of the distal strand through that proximal strand. Reverse single throw of the distal loop was made and the proximal strand was grasped to slide the distal loop, thus tightening the suture. A microscissor was used to cut suture ends (Figure Ic). Other haptic segment of IOL was inserted into the posterior chamber and the long needle was passed from corneal incision, iris, under the haptic, and out from the limbal cornea (Figure Id). The Siepser knot suture technique was used to fixate the iris (Figure Ie). The optic segment of IOL was inserted into the posterior chamber behind the iris. Viscoelastic was cleared

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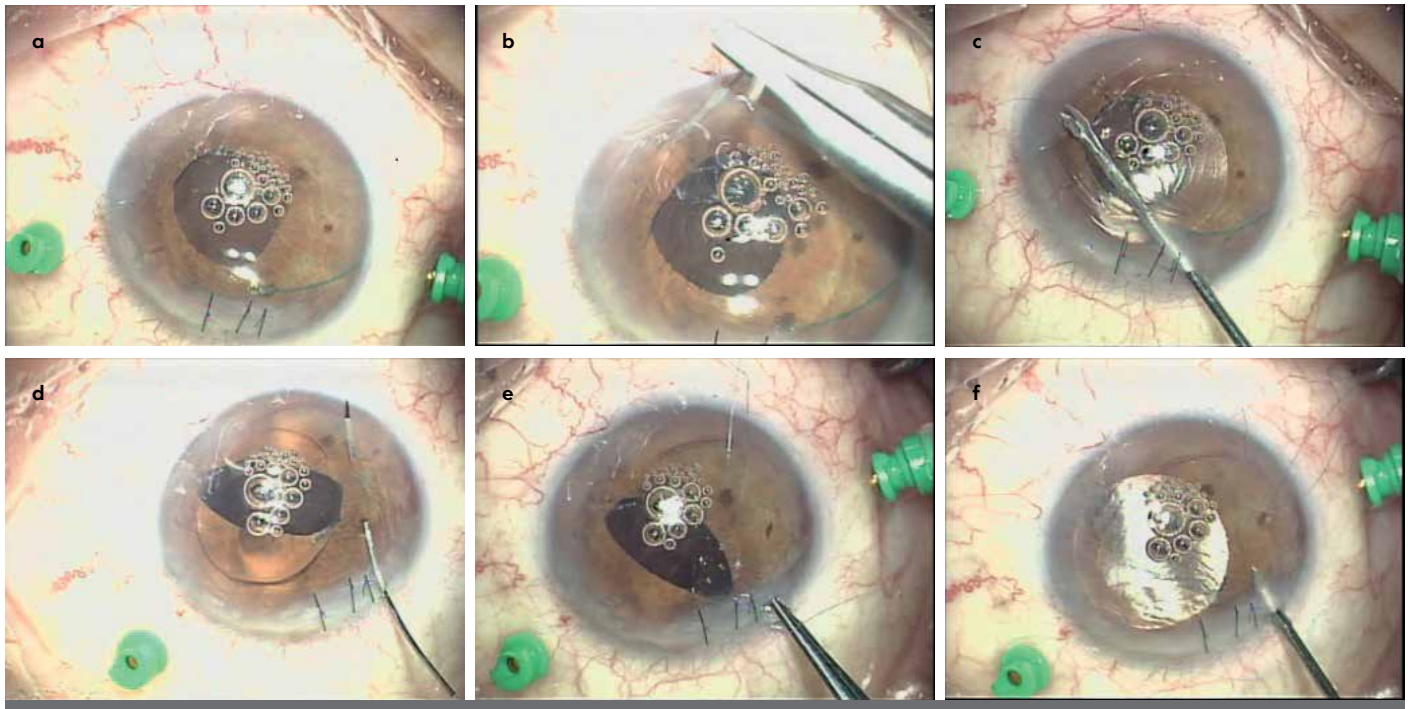

FIGURE 1. a-f. Three-piece IOL insertion to the anterior chamber (a). Long curved needle passed from paracentesis through the iris then under the haptic up to the anterior chamber and cornea out of the eye (b). Microscissors used to cut the suture ends (c). Other haptic inserted into the posterior chamber and long needle passed through the corneal incision, iris, under the haptic, and out from the limbal cornea (d). Siepser knot suture technique used again to fixate iris (e). Viscoelastic was cleared through paracentesis and trocars were removed (f).

FIGURE 2. Postoperative one month later IOL was well centered and vision is 8/10.
IOL: Intraocular lens.

through paracentesis and trocars were removed (Figure 1e). Mix of dexamethasone and gentamicin injected by subconjunctival route at the end of operation. After 3 months of operation vision was 0.8 with Snellen chart. IOL was centrally located. There was no pathologic fundus finding (Figure 2). Informed consent was obtained from the patient prior to the study.

DISCUSSION

Management of dislocated IOL is one of the challenges in ophthalmology practice. Each option has its advantages and disadvantages. Applying the anterior chamber IOL after removal of dislocated lens is easy, but this may cause corneal endothelial cell insufficiency that may result in bullous keratopathy and sight loss (1, 3, 4). Scleral fixated IOL implantation has advantages with less endothelial cell loss; however, tilted IOL and suture exposure are the major problems of this type IOL application (1). Iris fixated IOL application has advantages, such as less endothelial cell loss like scleral fixated IOL implantation and less tilted IOL compared with scleral fixated IOL, but contact of IOL may cause iris pigment discharge and an inflammatory reaction (1, 2, 5). In our case, we preferred iris fixated IOL implantation with the Siepser knot technique with 10/0 nylon suture, following pars plana vitrectomy and dislocated IOL exchange. We preferred this option to protect corneal endothelial cells, to decrease the risk of tilted IOL, and to prevent the complications of other methods.

Management of dislocated IOL secondary to trauma, ruptured capsule, implantation of IOL, and choice of IOL implantation method is one of the challenges in ophthalmology practice. Fixation of 3- piece IOL to iris with a Siepser knot of 10/0 nylon suture after pars plana vitrectomy and IOL exchange is an option for the management of such cases. To assess the safety of this method case series are needed.

Informed Consent: Informed consent was obtained from the patient who participated in this study.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Case Report

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Barotrauma Induced Incus Dislocation

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Ossicular chain injuries are infrequent complications mostly caused by skull trauma and penetrating injury through the external auditory meatus. Blast, barotrauma and lightning are the other occasional causes.

Keywords: Ossicular chain, incus dislocation, barotrauma

INTRODUCTION

Ossicular chain injuries are rare complications of skull trauma through the temporal bone. Penetrating injury through the external auditory meatus and barotrauma are other frequent causes. Ossicular injury should be considered in patients with persistant hearing loss following trauma.

High-resolution CT is the method of choice for the evaluation of ossicular chain.

In the present report, we present high-resolution CT findings of incus dislocation in a scuba diver.

CASE PRESENTATION

A 20-year-old male scuba diver with hearing loss in his right ear was refered to our department. The patient denied any history of trauma. Otoscopic examination revealed a bony protrusion abutting the tympanic membrane in the right ear. High-resolution computerized tomography (256-detector multislice CT scanner, Somatom Definition Flash, Siemens Healthcare, Erlangen, Germany) demonstrated the dislocated incus protruding from the external auditory canal (Figures 1 and 2).

Written consent was obtained from the patient.

DISCUSSION

Ossicular chain injuries have various etiologies. The main cause is skull trauma (1, 2). Penetrating injury through the external auditory meatus (cotton-tipped applicators, stone, etc.); surgical trauma; blast; barotrauma through the external auditory canal or through the Eustachian tube; and lightning are the other causes (2).

Traumatic ossicular injuries are usually associated with longitudinal temporal bone fractures (1, 3). Temporary hearing loss following trauma is frequent due to tympanic membrane perforation or hemotympanium (4). Ossicular injury should be considered when conductive hearing loss lasts for two months following trauma (3, 5).

Types of the ossicular injuries include incudostapedial joint separation; incudomalleolar joint separation; incus dislocation; malleoincudal complex dislocation; stapediovestibular dislocation; and fractures of malleus, incus, and stapes (1). Incudostapedial joint separation is the most frequently occurring type of the ossicular injuries and dislocations are more common than fractures (5, 6).

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FIGURE I. Axial computerized tomography image through the right temporal bone

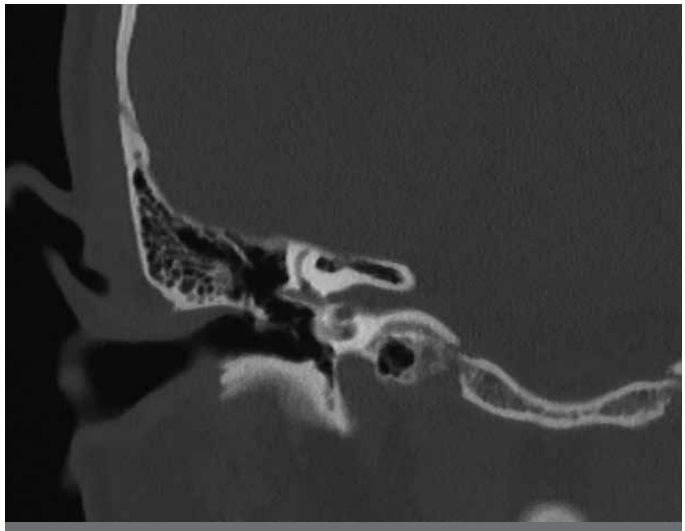

FIGURE 2. Coronal computerized tomography image through the right temporal bone

Incus is more vulnerable to traumatic injury, being the heaviest and weakly anchored ossicule, while malleus is stabilised by the tensor tympani tendon and stapes by the stapedial tendon (2, 6, 7). Dislocated incus may remain in the epitympanic recess or prolapse into the hypotympanium or external auditory canal (2).

High-resolution CT is the method of choice for evaluation of the ossicular chain patologies (1, 3). Axial and coronal planes are necessary for identifying the position of the incus and its relationship with the malleus and stapes.

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

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Case Report

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Colon Cancer Presenting as Abdominal Wall Abscess

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Malignant colon cancer rarely present with anterior abdominal wall abscess. Here we present the case of a patient who underwent radical surgery. A 62-year-old man presented with a locally advanced sigmoid malignant colon tumor with an anterior abdominal wall abscess as preliminary symptom, with no evidence of metastasis to distant organs. We performed sigmoid colectomy with full-thickness resection of the anterior abdominal wall including the abscess. Pathological examination revealed a moderately differentiated adenocarcinoma with no tumor tissue in the surgical margins. Postoperative clinical course was entirely uneventful. The patient remained well for the 2-year follow-up period without recurrence. In this study, we aim to show that radical surgery for locally advanced colon cancer in tertiary care centers procures satisfactory results with regards to disease-free survival and quality of life.

Keywords: Abdominal wall abscess, locally advanced colon cancer, radical surgery

INTRODUCTION

Locally advanced disease, which involve 5%-22% of all colorectal cancers, is a subgroup of colorectal tumors and is characterized by the invasion of adjacent organs without distant metastases (1). Of the estimated 100,000 new colon cancer cases that are diagnosed each year in the United States, locally advanced disease with invasion of adjacent organs or abdominal wall constitutes approximately 10%-20%. These cancers are classified as T4 lesions by the American Joint Committee on Cancer staging schema (2). The formation of an abscess is seen in only 0.3%-4% of all colon cancer cases, and anterior abdominal wall abscesses occur due to malignant tumor invasion and perforation, as reported previously (1, 2). Radical surgery has been rarely performed due to unacceptable high risks and also poor prognosis.

Here we present the diagnosis and treatment of a man treated with radical surgery for locally advanced sigmoid malignant colon tumor complicated by an abscess of anterior abdominal wall.

CASE PRESENTATION

A 62-year-old man was admitted to a district hospital with the symptoms of skin edema and redness in the left anterior abdominal wall. Antibiotic therapy for 7 days did not improve his condition. He developed necrotic skin changes on a fluctuant and indurated area in the left anterior abdominal wall, suggesting an abscess formation, and the patient was referred to our clinic (Figure 1) Contrast-enhanced abdominal computed tomography (CT) scan revealed a gross mass with fluid inside in the lower left quadrant. Separating the mass from the sigmoid colon was challenging (Figure 2). Colonoscopy confirmed a tumor of the sigmoid colon. Carcinoembryonic antigen level was normal. Blood tests revealed white blood cell (WBC) count of 11.200 /mm^3 (reference range: 3.500-8.500/mm^3) and a C-reactive protein level of 14.58 mg/dL (reference range: <0.3 mg/dL). Drainage of the abdominal wall abscess was performed under local anesthesia. Surgery was planned after symptoms and induration of the abscess had regressed. A sigmoid colectomy with full-thickness resection of the anterior abdominal wall, including the abscess pouch, was performed (Figure 2). Abdominal defect was closed using an AlloDerm regenerative tissue matrix (LifeCell Corporation, Bridgewater, N.J.). The postoperative course was entirely uneventful, and the patient was discharged on the 17th day after surgery. Pathological examination revealed a moderately differentiated adenocarcinoma, ulcerated type with a clear margin, with subserosal invasion and nodal involvement classified as stage IIIC: T4N1M0 according to the Tumor-Node-Metastasis (TNM) classification. Adjuvant therapy was administered, and the patient has remained well for 2 years after surgery without any evidence of tumor recurrence. Written informed consent was obtained from the patient.

This study was presented at the 15th Turkish Colon and Rectal Surgery Congress. 19-23 May, 2015. Antalya, Turkey.

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FIGURE I. Erythematous, tender, fluctuant area seen in the left lower quadrant

FIGURE 2. Axial computed tomography of lower abdomen shows a large mass encasing the colon near the junction of the descending and sigmoid portions (arrow)

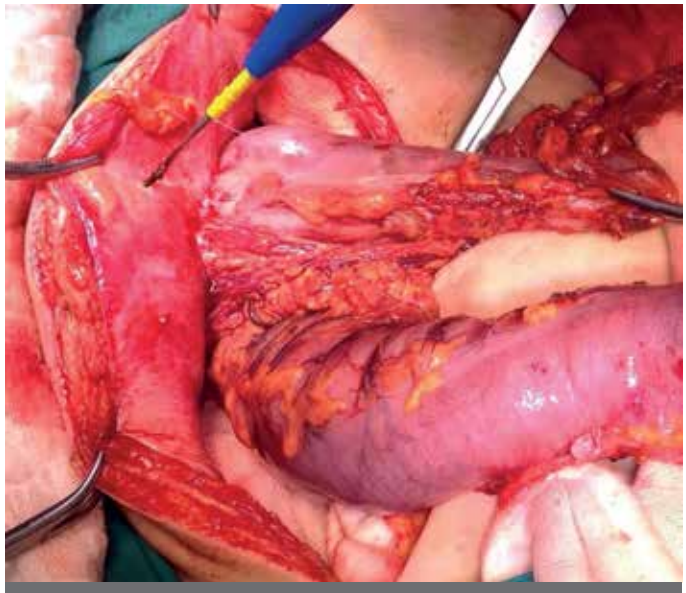

FIGURE 3. Postoperative finding

DISCUSSION

Abdominal wall abscess due to invasion and perforation of the colon tumor is a rare occurrence. Preoperative diagnosis of abdominal wall abscess associated with colon cancer is considered as difficult. However, the source of abscess must be detected by clinicians as quickly as possible. While taking history of the patient and conducting a physical examination, the significant features of abscess, such as fever, pain, skin reddening, or a palpable mass, may be determined (1). WBC count generally increases in the presence of an abscess. Owing to its peerless imaging sensitivity, CT is an ideal technique to evaluate suspected abscesses, and colorectal cancer appears as wall thickening of colon or a separate mass. Colonoscopy is advantageous to investigate the features and structure of tumor (3).

Complete resection of the malignant colon tumor and the abscess wall is the preferable method. Unless surgery is contraindicated by the patient's general condition, percutaneous aspiration and drainage by indwelling catheter combined with broad-spectrum antibiotics may be applied without further diagnostic work-up (4, 5). However, the drainage procedure may alleviate the toxemia, and, if possible, simultaneous colon resection should be performed to eradicate the main source of sepsis.

Radical surgical approaches are associated with a high rate of morbidity and mortality (1). Radical resection is a challenging procedure for surgeons because, in the presence of local invasion, multivisceral resection is required. Although radical resection is essential in patients for cure, unfortunately, most of patients exhibit bad general conditions. Abdominal wall reconstruction is necessary in terms of resection of the abdominal wall muscles and fascia. Primary repair of abdominal wall often fails owing to high tension, and the failure rate of the primary repair may reach up to 50% (1, 2). On the other hand, large abdominal wall defects related to full-thickness resection of the invasive malignant tumors are not recommended to be closed by primary sutures.

Therefore, perforated colon cancer with abscess formation may be first treated with local drainage of the abscess and the use of appropriate antibiotics and then the resection of the colon and anterior abdominal wall with adequate drainage.

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

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Author contributions: Concept - E.K., S.K.; Design - A.E., F.C.; Supervision - E.K., M.P.; Resource - S.K., A.E.; Materials - F.C., S.K.; Data Collection and/or Processing - E.K., A.E.; Analysis and/or Interpretation - F.C., M.P.; Literature Search - S.K., F.C.; Writing - E.K., S.K.; Critical Reviews - E.K., M.P.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Letter to the Editor

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Our Anesthetic Management for Brainstem Evoked a Response Audiometry in a Child with Ondine's Curse

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Dear Editor,

Congenital central hypoventilation syndrome (CCHS), also known as Ondine's curse, is a rare disease characterized by autonomic respiratory dysfunction without any pulmonary, cardiac, or neuromuscular disorder (1). This syndrome may be accompanied by seizures, gastroesophageal reflux disease (GERD), Hirschsprung's disease, and dysrhythmia (2). However, there are limited data on the anesthetic management of patients with CCHS (2-4).

A 2-year-old girl, 14 kg in weight, presented with hearing loss. Brain stem evoked audiometry (BERA) under general anesthesia was planned. The patient was diagnosed with CCSH 2 months after the delivery due to apnea attacks and multiple seizures. She showed mild symptoms related to GERD. However, she had no history of respiratory distress, seizures, or gastrointestinal symptoms for the last 1 year and thus did not take any medication.

Results of physical examination and routine laboratory tests were normal. Airway assessment was consistent with Mallampatti class I.

Monitoring included electrocardiography, noninvasive blood pressure measurement, and pulse oximetry. After preoxygenation, inhalation induction was performed with 8% sevoflurane in oxygen. Subsequently, anesthesia was induced with remifentanyl (2 µg/kg), lidocaine (2.5 mg/kg), and propofol (4 mg/kg), without a muscular relaxant. Laryngeal mask anaesthesia was performed using 2.5 size of mask. Anesthesia was maintained with (50%/50%) medical air/oxygen and 2% sevoflurane (via inhalation). The test lasted 1 h without any complication. She was closely followed up in the ward for 24 h and was uneventfully discharged the next day.

The main concern among anesthesiologists is the failure to control ventilation. Patients with CCHS are sensitive to central respiratory depressant effects of opioids, preoperative anesthetics, anxiolytics, inhalation agents, muscular relaxants, and benzodiazepines. Sevoflurane seems to be more suitable due to its rapid establishment of an anesthetic concentration and lack of airway irritation (5). CCHS is often accompanied by GERD, which is associated with increased risk of aspiration.

Central control of temperature may be problematic. Several preventions, such as increasing the room temperature and warming the respiratory gases and intravenous fluids, should be suggested (5).

Cardiovascular status should be taken into account in the maintenance of anesthesia. Anesthetic agents with short activity, such as sevoflurane, remifentanil, and nitrous oxide, may be suitable choices. Because seizures are common, anticonvulsant drugs should not be discontinued throughout the perioperative period. Additionally, the use of enflurane should be avoided because of its seizure-like effects (5).

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In conclusion, anesthetists should be aware of this syndrome and associated disorders. Detailed preoperative evaluations along with appropriate medications and techniques are of great importance for successful anesthetic management.

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