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Treatment Outcomes of Metastatic Colorectal Cancer Patients Treated with Regorafenib as Third-Line Setting-A Multicenter Study

Üçüncü Basamakta Regorafenib ile Tedavi Edilen Metastatik Kolorektal Kanserli Hastaların Sonuçları-Çok Merkezli Çalışma

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ABSTRACT

Introduction: The clinical benefit of regorafenib therapy in metastatic colorectal cancer (mCRC) patients, who were previously treated with 5-fluorouracil (5-FU), irinotecan, or oxaliplatine based regimens with or without a biologic agent such as vascular endothelial growth factor (anti-VEGF) or anti epidermal growth factor receptor (anti-EGFR), has been shown in several previous phase III studies. In this study, we aimed to analyze the efficacy and toxicity profile of regorafenib in patients with mCRC.

Methods: This was a retrospective study of 23 mCRC patients from two different centers in Turkey. All patients were treated with regorafenib as third line setting after failure of two standard consecutive therapies including 5-FU, irinotecan, or oxaliplatine with or without anti-VEGF or anti-EGFR agent. Treatment outcomes along with drug efficacy and safety were analyzed retrospectively.

Results: Of the 23 patients, 13 were male (56.5%). Median age was 62 (35-76) years. The rates of RAS wild-type and RAS-mutated tumor were 43.5% and 56.5%, respectively. Eighteen patients (78.2%) received bevacizumab as first-line setting, whereas only five patients (28.8%) were given a prior anti-EGFR agent. Among the 23 patients, only one patient (4.3%) had a partial response. Median progression-free survival was 3.02 (2.6-3.37) months and median overall survival was 6.4 (2.6-10.1) months. There was no prognostic factor associated with survival. Grade 3-4 toxicities were observed in 30.4% of the patients, with hand-foot skin reaction being the most frequent adverse event (42.8%).

Conclusion: Although clinical and survival benefits of regorafenib have been demonstrated in previous studies, this advantage seems to be questionable in our study, with a significant toxicity profile making its use challenging. A treatment decision should be made considering the risk of mortality and toxicity profile.

Keywords: Metastatic colorectal cancer, overall survival, progression free survival, regorafenib, toxicity

ÖZ

Amaç: Daha önce 5-florourasil (5-FU), irinotekan veya oksaliplatin temelli rejimlerle tedavi edilen ve biyolojik ajan olarak vasküler endotelyal büyüme faktörü (anti-VEGF) veya anti epidermal büyüme faktörü reseptörü (anti-EGFR) alan veya almayan metastatik kolorektal kanser (mKRK) hastalarında regorafenib tedavisinin klinik yararı daha önceki faz III çalışmalarında gösterilmiştir. Burada mKRK'li hastalarda regorafenibin etkinlik ve toksisite profilini analiz etmeyi amaçladık.

Yöntemler: Çalışmamızda Türkiye'deki iki farklı merkezden takip edilen 23 mKRK hastasının retrospektif verileri incelenmiştir. Tüm hastalar anti-VEGF veya anti-EGFR ile kombine olarak veya olmaksızın; 5-FU, irinotekan veya oksaliplatin temelli rejimler ile, iki standart ardışık tedavinin başarısızlığı sonrasında üçüncü basamakta regorafenib ile tedavi edildi. İlaç etkinliği ve güvenliği ile birlikte tedavi sonuçları retrospektif olarak analiz edildi.

Bulgular: Yirmi üç hastanın 13'ü erkekti (%56,5) ortanca yaş 62 idi (35-76). RAS wild tip tümör oranı %43,5, RAS mutant tip tümör oranı ise %56,5'ti. On sekiz hasta (%78,2) birinci basamakta bevasizumab tedavisi almıştı. Yirmi üç hastanın yalnızca 1'inde (%4,3) kısmi yanıt elde edilmişti. Ortanca progresyonsuz sağkalım 3,02 (2, 6-3, 37) ay ve ortanca genel sağkalım ise 6,4 (2, 6-10, 1) aydı. Sağkalımla ilişkili prognostik faktör saptanmadı. En sık yan etki olarak el-ayak sendromu (%42,8) görülmekle birlikte, derece 3-4 yan etki %30,4 hastada saptandı.

Sonuç: Önceki çalışmalarda regorafenibin klinik ve sağkalım yararı gösterilmiş olmasına rağmen, bu avantaj, çalışmamızda kullanımını zorlaştıran önemli bir toksisite profili ile şüpheli görünmektedir. Mortalite riski ile toksisite profili göz önünde bulundurularak tedavi kararı verilmelidir.

Anahtar Kelimeler: Metastatik kolorektal kanser, genel sağkalım, progresyonsuz sağkalım, regorafenib, yan etki

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Introduction

Despite recent advances in the treatment of metastatic colorectal cancer (mCRC), it is still the most frequent gastrointestinal system cancer in the western countries, with being an important cause of cancer mortality, affecting approximately 746.000 men and 614.000 women each year (1). Colorectal cancer is the third most common cancer worldwide and the second most common cause of cancer-related deaths in the United States (US), with 20% to 30% of patients having synchronous metastatic disease at the time of presentation andvvvvvatients eventually developing metastatic disease with unresectable metastases (2). After the introduction of chemotherapeutic agents such as fluoropyrimidines, oxaliplatine, and irinotecan along with monoclonal antibodies targeting vascular endothelial growth factor (VEGF) or epidermal growth factor receptor (EGFR), median overall survival (OS) duration of mCRC patients has improved approximately 30 months over the last 20 years (3), with a great extent of this progress being due to molecular targeted therapies, such as anti-angiogenic agents (bevacizumab) or EGFR signaling pathway inhibitors (cetuximab and panitumumab) (4).

Regorafenib, a novel oral multi-kinase inhibitor, has demonstrated antitumor activity in patients with mCRC who were previously treated with fluoropyrimidine-, oxaliplatine- and irinotecan-based chemotherapy +/- anti-VEGF therapy or anti-EGFR therapy through inhibiting a very diverse range of oncogenic gene products and growth factor receptors including KIT, RET, RAF1, BRAF, BRAFV600E, VEGFR, platelet-derived growth factor receptor PDGFR and fibroblast growth factor receptors (FGFR), hence being approved by FDA 2012 for use as monotherapy as last-line setting (5, 6). Anti-tumor activity and survival benefit of regorafenib were previously shown in two large randomized placebo-controlled trials, CORRECT (7) and CONCUR (8), which were performed in mCRC patients progressing on standard therapies. Survival benefit and efficacy of regorafenib were also confirmed by the large European REBECCA (9) cohort study in a real-world setting, with a similar toxicity profile as seen in previous randomized studies mentioned above.

Here, we performed a multicenter retrospective study to evaluate the efficacy and toxicity profile of regorafenib in mCRC patients in Turkey.

Methods

From October 2015 to December 2017, a total of 23 consecutive Turkish patients from two major centers receiving regorafenib monotherapy for refractory mCRC as third-line setting were analyzed. Patients with histologically confirmed mCRC were included in the study. The study was approved by the Necmettin Erbakan University Local Ethics Committee (Decision No. 2018/1319). This retrospective study was designed in accordance with the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", amended in October 2013. Since it was a retrospective study, no patient consent form could be obtained. We conducted a retrospective multi-center study to assess the efficacy and toxicity profile of regorafenib in mCRC, patients who were previously treated with fluoropyrimidine-, oxaliplatine- and irinotecan-based chemotherapy +/- anti-VEGF therapy (e.g. bevacizumab, ziv-aflibercept) or anti-EGFR (e.g. panitumumab, cetuximab) when appropriate. Baseline data of all patients, including disease characteristics, patient demographics, laboratory parameters, performance status (PS), treatments, response to treatments, and toxicities were carefully recorded.

After the failure of standard therapies, regorafenib was initiated as a monotherapy at 160 mg daily dose for 21 days with a 28-day repeating cycle. At the discretion of the physicians, a lower initial dose was allowed depending on the patient's clinical condition, and then the dose was increased by 40 mg per week until the maximum dose of 160 mg, relying on the patient's tolerability.

Evaluation of treatment responses was performed every 3 months by computed tomography (CT) or positron emission tomography (PET)-CT using the Response Evaluation Criteria in Solid Tumor version 1.1. National Cancer Institute Common Terminology Criteria of Adverse events version 4.0 was used to grade the adverse events. Dose reduction was allowed in case of drug intolerance or ≥ grade III toxicity. Regorafenib was given until disease progression, unacceptable toxicity or patient's withdrawal.

Statistical Analysis

All statistical analyzes were performed using Statistical Package for Social Sciences version 21.0 for Windows (SPSS, Inc. Chicago, IL, USA). Descriptive statistics were reported as percentage and median. Survival data were analyzed according to the Kaplan-Meier Method and were compared using Log-rank statistics. p value less than 0.05 was considered as statistically significant. Progression-free survival (PFS) was defined as the period between regorafenib initiation and disease progression or death due to any reason. Overall survival was defined as the period between regorafenib initiation and death due to any cause.

Results

A total of 23 patients were included in this study. Baseline characteristics are summarized in Table 1. Of the 23 patients, 13 were male (56.5%). Median age was 62 (35-76) years. The rates of RAS wild-type and RAS-mutated tumor were 43.5% and 56.5%, respectively.

Eighteen patients (78.2%) received bevacizumab as first-line setting, whereas only five patients (28.8%) were given a prior anti-EGFR agent. The primary tumor was located on the left side in 17 patients (73.9%). The number of patients who underwent palliative surgery and metastasectomy was nine (39.1%) and five (21.7%), respectively. Most of the patients (91.3%) had a PS of 0-1 at the beginning of regorafenib therapy.

Regarding survival, median PFS was 3.02 (2.6-3.37) months and median OS was 6.4 (2.6-10.1) months for regorafenib therapy during a median follow-up of 5.4 (2.4-23.4) months (Figures 1 and 2). Overall survival was 37 (23.9-50.4) months. The presence of comorbidity was the only prognostic factor in univariate analysis; however, no factors were found to be associated with survival (Table 2).

Approximately 73.92% of patients were commenced on lower doses than standard. Starting dose of 160 mg was administered only in six patients. Dose modification was required in 69.56% of the patients (Table 3). Dose escalation could be performed once in four patients and twice in

Table 1. Baseline characteristics of patients (n=23)	
Number of patients	23
Median age (years)	62 (35-76)
Sex	
Male	13 (56.5%)
Female	10 (43.5%)
ECOG performance status	
0-1	21 (91.3%)
2	2 (8.7%)
Comorbidity (e.g DM, HT, Atherosclerosis)	
No	16 (69.6%)
Yes	7 (30.4%)
Tumor localization	
Right	6 (26.1 %)
Left	17 (73.9%)
Palliativesurgery	
Yes	9 (39.1%)
No	14 (60.9%)
Metastasectomy	
Yes	5 (21.7%)
No	18 (78.3%)
RAS mutation status	
Mutant	13 (56.5%)
Wild-type	10 (43.5%)
First-line therapy	
Folfox/xelox + Beva	9 (39.1%)
Folfox/xelox + Pan/Cet	2 (8.7%)
Folfiri + B	9 (39.1%)
Folfiri + Pan/Cet	3 (13.0%)
Response to first-line therapy	
Partial response	11 (47.8%)
Stable disease	4 (17.4%)
Progression	8 (34.8%)
Second-line therapy	
Folfox	2 (8.7%)
Folfiri	3 (13.0%)
Folfox/B	8 (34.8%)
Folfox + C/P	1 (4.3%)
Folfiri + B	4 (17.4%)
Folfiri + C/P	3 (13.0%)
Other	2 (8.7%)
Response to second-line therapy	
Partial response	8 (34.8%)
Stable disease	8 (34.8%)
Progression	7 (30.4%)
Response to third-line regorefenib	
Partial response	1 (4.3%)
Progression	22 (95.6%)

DM: diabetes mellitus, HT: hypertension, RAS: xxxxxxxxxxxxxxxxxxx

two patients. Dose reduction was required once in seven patients and twice in three patients. Approximately 13.04% of patients discontinued treatment due to toxicity. The median number of treatment cycles was three (1-11). The most common toxicities of any grade were hand-foot skin reaction (HFSR), fatigue, diarrhea, hypertension, mucositis and thrombocytopenia. Grade 3-4 toxicities were observed in seven patients (30.4%) with a descending order as follows, HFSR in 42.8%, fatigue in 28.5%, diarrhea in 14.28% and hypertension in 14.28% (Table 4).

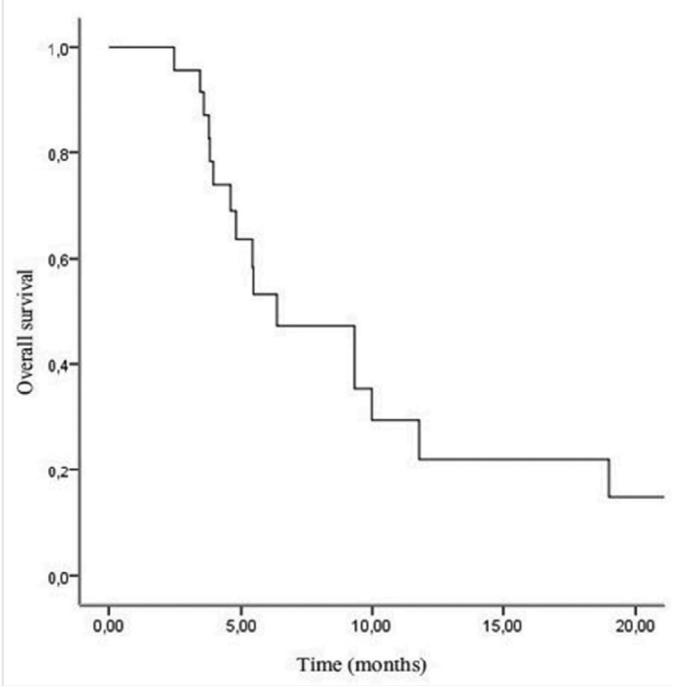

Figure 1. Overall survival curve

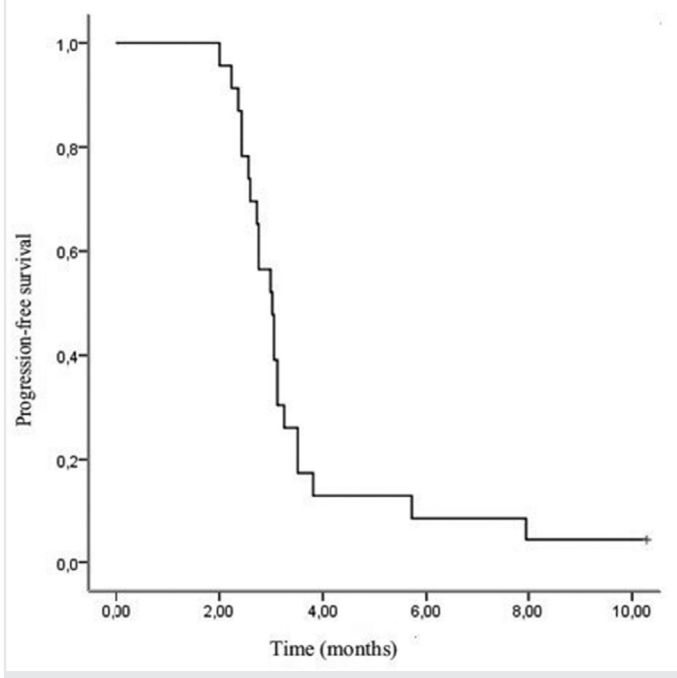

Figure 2. Progression-free survival curve

Table 2. Univariate analysis

Parameters	n (%)	Overall survival (month) univariate analysis	p
Age (years)			
≤60	10 (43.5)	37.1	0.46
>60	13 (56.5)	32.1	
Sex			
Male	13 (56.5)	45.7	0.12
Female	10 (43.5)	25.7	
ECOG performance status			
0-1	21 (91.3)	41.0	0.20
2	2 (8.7)	25.7	
Comorbidity (DM, HT, Atherosclerosis)			
No	16 (69.6)	45.7	**<0.001**
Yes	7 (30.4)	22.3	
Tumor localization			
Right	6 (26.1)	52.4	0.85
Left	17 (73.9)	37.1	
Palliative surgery			
Yes	9 (39.1)	45.7	0.15
No	14 (60.9)	32.1	
Metastasectomy			
Yes	5 (21.7)	45.7	0.69
No	18 (78.3)	32.1	
RAS mutation status			
Mutant	13 (56.5)	45.7	0.24
Wild-type	10 (43.5)	31.7	
First-line therapy			
Folfox/xelox + Beva	9 (39.1)	37.1	0.17
Folfox/xelox + Pan/Cet	2 (8.7)	31.7	
Folfiri + B	9 (39.1)	57.1	
Folfiri + Pan/Cet	3 (13.0)	26.7	
Response to first-line therapy			
Partial response	11 (47.8)	52.4	0.34
Stable disease	4 (17.4)	32.1	
Progression	8 (34.8)	25.7	
Second-line therapy			
Folfox	2 (8.7)	18.1	0.12
Folfiri	3 (13.0)	26.1	
Folfox/B	8 (34.8)	41.0	
Folfox + C/P	1 (4.3)	25.7	
Folfiri + B	4 (17.4)	NR not reached	
Folfiri + C/P	3 (13.0)	37.1	
Other	2 (8.7)	32.1	
Response to second-line therapy			
Partial response	8 (34.8)	45.7	0.01
Stable disease	8 (34.8)	37.1	
Progression	7 (30.4)	23.0	

Table 2. Continued

Parameters	n (%)	Overall survival (month) univariate analysis	p
Response to third-line Regorafenib			
Partial response	1 (4.3)	31.7	0.53
Progression	22 (95.6)	37.1	

DM: diabetes mellitus, HT: hypertension, RAS: xxxxxxxxxxxxxxxxxxxx

Table 3. Regorafenib administration

Median number or treatment cycles	3 (1-11)
Starting dōşe	**n (%)**
160 mgr.	6 (26.08)
120 mgr. or lower	17 (73.92)
Treatment discontinuation	**3 (13.04)**
Dose increase	6
Once	4 (66.6)
Twice	2 (33.3)
Dose reduction	10
Once	7 (70)
Twice	3 (30)

Table 4. Adverse events

	Any Grade, n=18 (78.26%)	Grade 3-4, n=7 (30.4%)
Hand-foot skin reaction	6 (33.3)	3 (42.8)
Fatigue	4 (22.2)	2 (28.5)
Diarrhea	3 (16.6)	1 (14.28)
Hypertension	2 (11.1)	1 (14.28)
Mucositis	2 (11.1)	-
Thrombocytopenia	1 (5.5)	-

Discussion

In the past 10 years, the availability of many drugs and the advent of new anti-angiogenic agents such as bevacizumab combined in standard regimens as first-line, second-line, or beyond progression setting have offered a considerable survival benefit with improved prognosis in patients with mCRC. Angiogenic regulation consists of a range of pathways and inhibition of a single target, such as VEGF, resulting in up-regulation of a diversity of pro-angiogenic factors (10), suggesting that a salvage treatment setting which includes a multi-kinase inhibitor with anti-angiogenic activity may be a plausible treatment option (11). Regorafenib, a novel agent, is a multi-kinase inhibitor targeting a range of receptors including VEGF 1-3, PDGF, tyrosine receptor kinase-2, FGFR, BRAF, KIT, and RET (12).

Here, we aimed to evaluate the efficacy and safety of this new kinase inhibitor, although not including a representative sample. The median OS and median PFS in our study were 6.4 and 3.02 months, respectively. These findings are comparable to those reported in previous randomized studies. The CORRECT study was an international, randomized, and placebo-controlled phase-III trial including 760 patients who were

randomized 2:1 to receive either regorafenib 160 mg daily or placebo. It demonstrated an improved median OS for regorafenib group compared to the placebo (6.4 months vs. 5.0 months, p=0.0052) (7), showing similar results to our findings. Another international phase III trial, CONCUR, which also confirmed the OS benefit of regorafenib in 204 Asian patients who were randomized 2:1 to receive either regorafenib or placebo (8.8 months vs. 6.3 months, p=0.00016) (8), had a better median OS than that observed in our study. Median PFS durations for CORRECT and CONCUR trial were 1.9 and 3.2 months in the regorafenib arm, gaining only 0.2 and 1.5 months, respectively, compared to placebo group. The median PFS in our study was similar to that reported in CONCUR trial and higher than in the CORRECT trial. The REBECCA trial, a cohort of 1178 patients with mCRC, was an open-label and single-arm study of 654 patients (in full analyze) treated with regorafenib after a failure on standard therapies. This study demonstrated a median OS of 5.6 months and median PFS of 2.9 months with 12-month survival rate of 22% (9), indicating a similar median PFS but a lower median OS duration compared to those reported in our study, despite the higher number of patients starting with a lower dose of regorafenib in our study (73.9% in our study vs. 18% in REBECCA).

The most common toxicities of any grade in our cohort were HFSR, fatigue, diarrhea, hypertension, mucositis and thrombocytopenia. HFSR, fatigue, diarrhea and hypertension were the most common grade 3-4 toxicities. This toxicity profile is substantially consistent with the adverse events reported in the REBECCA real-world cohort (9), CORRECT trial (7), and CONCUR trial (8). Most adverse events were similar in the CONCUR (8) and CORRECT (7) trials, with the only exception of any-grade HFSR (74% vs. 47%, respectively) and impaired liver function tests (37% vs. 20%, respectively), which were more frequent in CONCUR trial (8). The most common reason leading to drug-discontinuation in our study was the toxicity, similar to REBECCA cohort (9). Most of the patients in our cohort (69.56%) required dose modifications and this was higher than those reported in CORRECT (7) (20% of patients required a dose reduction) and CONCUR trials (8) (40% of patients required a dose reduction). Compared to the REBECCA (9) cohort, a larger proportion in cohort started at a lower dose of regorafenib (18% vs. 73,9%, respectively). Patients should be informed about the prophylaxis and management of regorafenib-related adverse events prior to treatment to minimize the incidence of adverse events and to ensure that patients take full advantage of regorafenib treatment, thus optimizing treatment outcomes. Therefore, the most common adverse events should be discussed with the patient before the treatment.

The REBECCA real-world analysis (9) reported that high ECOG PS, a shorter time from the initial diagnosis of metastasis, starting at a lower initial dose of regorafenib, more than 3 metastatic sites, the presence of liver metastasis and KRAS mutation were the factors associated with shorter OS. However, there was no predictive factor associated with survival in our cohort, which might be due to the small sample size of our cohort.

So far, some studies have explored some biomarkers of efficacy for regorafenib, but no useful pretreatment biomarker in clinical practice has yet been determined (13, 14). Indeed, there is no predictive biomarker to allow the selection of patients most likely to benefit from regorafenib (11). However, Komori et al. (15) reported that serum CA19-9 response was an early predictive marker of efficacy of regorafenib in mCRC.

The major limitation in our study was the small sample size, resulting in a suboptimal evaluation of outcome predictors in cox regression analysis. Hence, the results of this study should be interpreted with caution. In addition, selection bias and the absence of independent monitoring were other limitations inherent in retrospective studies, which might affect our results. Furthermore, identifying patients who will tolerate full-dose or a reduced dose of regorafenib is pretty important to optimize the study design. Nevertheless, our findings support the available data in the literature and provide useful information regarding the results of mCRC patients treated with regorafenib.

Conclusion

Regorafenib, a novel agent, is a multi-kinase inhibitor for use as monotherapy at last-line setting in mCRC. Although regorafenib shows a small but significant survival benefit in patients with mCRC who do not have any further treatment options after the failure over standard therapies, its toxicity profile along with the absence of predictive factors suggest a careful evaluation for the benefit/risk ratio before its use in clinical practice.

Ethics Committee Approval: The study was approved by the Necmettin Erbakan University Local Ethics Committee (Decision No. 2018/1319).

Informed Consent: Since it was a retrospective study, no patient consent form could be obtained.

Peer-review: Externally peer-reviewed.

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

Conflict of Interest: No conflict of interest was declared by the authors.

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Comparison of Long-Term Survival Rates of Primary Surgery and Surgery After Neoadjuvant Chemotherapy in Ovarian Cancer

Over Kanserinde Neoadjuvan Kemoterapi Sonrası Cerrahi ile Primer Cerrahinin Uzun Dönem Sağkalımların Karşılaştırılması

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ABSTRACT

Introduction: To compare long-term survival of primary debulking surgery (PDS) and interval debulking surgery (IDS) after neoadjuvant chemotherapy (NAC) in patients with advanced ovarian cancer.

Methods: Patients who underwent debulking surgery for ovarian cancer between 2001 and 2014 were included in the study.

Results: Of 378 patients, 191 (50.5%) underwent PDS and 187 (49.5%) underwent IDS. Compared with PDS group, IDS was associated with higher optimal surgical performance (residual <1 cm) (83% vs. 65%, p<0.001), lower visible tumor rate in the upper abdomen during surgery (12% vs. 46%, p<0.001), lower intraabdominal ascites rate (2% vs. 64%, p<0.001), lower postoperative (within 30 days) mortality (0 vs. 5) and lower bowel resection/colostomy rate (3% vs. 11%, p=0.001). The median follow-up period was 43 (1-161) months. Overall survival (OS) was longer in the PDS group [56.8 months (95% CI: 48.2-65.4] vs. 43.5 [95% CI: 38.1-48.8], log-rank test p=0.026). PDS was superior in both residual subgroups, 64.9 vs. 44.6 months (p=0.008) in ≤1 cm group and 41.6 vs. 25.3 months (p=0.044) in >1 cm group. The 8-year OS was higher in the PDS group (31.8% vs. 12.7%). According to multivariate Cox analysis, age, suboptimal debulking, IDS and presence of tumor in the upper abdomen were independent factors associated with shorter OS duration (hazard ratio: 1.013; 1.606; 1.456 and 1.495, respectively).

Conclusion: NAC in patients with FIGO 2010 stage 3 ovarian cancers is useful in reducing tumor spread, surgical morbidity and suboptimal surgery rates. However, long-term survival rates were shorter than the PDS group.

Keywords: Chemotherapy, cytoreduction, FIGO, ovarian carcinoma

ÖZ

Amaç: İleri evre over kanserli hastalarda primer debulking cerrahisi (PDS), neoadjuvan kemoterapi sonrası cerrahisi (NAC), aralıklı debulking cerrahinin (IDS) uzun dönem sağkalım açısından karşılaştırılması.

Yöntemler: 2001-2014 yılları arasında yumurtalık kanseri nedeniyle opere edilen hastalardan evre 3 olanlar çalışmaya alındı.

Bulgular: Toplam 378 hasta, 191'i (%50,5) PDS, 187'si (%49,5) IDS olarak ayrıldı. PDS grubu ile karşılaştırıldığında, IDS grubunda optimal cerrahi (rezidüel <1 cm) performansı daha yüksek (%83-%65, p<0,001), ameliyat sırasında üst batında makroskopik tümör görülen hasta oranı daha az (%12-%46, p<0,001), 1 litreden fazla intraabdominal asit daha az (%2-%64, p<0,001), postoperatif (30 gün içinde) exitus daha az (0-5), bağırsak rezeksiyonu/kolostomi oranı daha az (%3-%11, p=0,001) izlendi. Ortanca takip süresi 43 (1-161) aydı. Genel sağkalım (GS), PDS grupta daha uzundu (56,8 ay [%95 CI: 48,2-65,4] vs. 43,5 (%95 CI: 38,1-48,8), log-rank testi p=0,026). Rezidüel hastalık ≤1 cm ve >1 cm olan her iki alt grupta PDS üstündü (sırasıyla 64,9 ay -44,6, p=0,008; 41,6-25,3, p=0,044). 8 yıllık GS oranı, PDS hastalarında daha yüksekti (%31,8'e karşılık %12,7). Çok değişkenli Cox analizine göre, yaş, suboptimal cerrahi, IDS ve üst batın bölgesindeki tümör varlığı, kısa GS süresi ile ilişkili bağımsız faktörlerdi (sırasıyla tehlike oranı: 1,013; 1,606; 1,456 ve 1,495).

Sonuç: FIGO evre 3 over kanserli hastalarda neoadjuvant-kemoterapi, tümör yayılımını azaltmada, cerrahi morbiditeyi azaltmada ve optimal storedüksiyonun azaltılmasında yararlıdır. Ancak uzun dönem sağkalım oranları primer cerrahi grubuna göre daha kısa bulundu.

Anahtar Kelimeler: Kemoterapi, sitoredüksiyon, FIGO, yumurtalık karsinomu

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Introduction

Three-quarters of patients with ovarian cancer are diagnosed with advanced-stage disease (FIGO 2010 stage 3/4) at presentation. Primary debulking surgery (PDS) followed by chemotherapy with paclitaxel and carboplatin, and neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) are two main treatment approaches (1,2). According to randomized controlled trials, survival is similar for both treatment approaches (3-5). These studies showed that postoperative complication rates were lower and the optimal surgery rate was higher in IDS after NAC. Therefore, over the past decade, the use of NAC has increased and PDS rates are showing a negative trend (6).

Recently, several studies have shown poorer survival in IDS compared to PDS (4,7-12).

In this study, we compared the outcomes of patients with advanced stage (FIGO stage 3) ovarian cancer treated with IDS after NAC or PDS.

Methods

The study included patients who underwent surgery for advanced stage ovarian, tubal, or peritoneal cancer at İstanbul University İstanbul Faculty of Medicine Hospital between 2001 and 2013 (decision number: 05, date: 19.03.2018). A total of 378 patients were evaluated retrospectively. Clinical data were obtained from medical records of the patients. Inclusion criterion was a diagnosis of advanced stage high grade (FIGO stage 3C) epithelial ovarian, tubal, or peritoneal cancer according to postoperative pathology reports. Patients were triaged to undergo PDS followed by adjuvant chemotherapy (PDS group) or to receive neoadjuvant chemotherapy with IDS (IDS group).

Patients

All patients were evaluated by a multidisciplinary team of gynaecologic oncologists, radiologists, gynaecopathologists, radiation oncologists and medical oncologists. For patient evaluation, we used magnetic resonance imaging and computerized tomography, tumor markers (CA-125, CA19-9, CEA) and computed tomography for lung examination. According to these evaluations, patients planned for primary surgery were directed to preoperative preparation. Patients planned for NAC were referred to the Department of Interventional Radiology for ascites cytology or tru-cut biopsy from tumoral tissue and directed to the NAC protocol after pathological confirmation. NAC consisted of carboplatin (area under the curve 5-6) and paclitaxel (135-175 mg/m^2) every 3 weeks. The number of planned chemotherapy cycles was 3-4 prior to surgery.

As a standard surgical procedure in both groups (IDS-NAC and PDS), bilateral salpingo-oophorectomy, hysterectomy, appendectomy, and omentectomy were performed, and all visible tumors were removed if possible. Pelvic/para-aortic lymphadenectomy or sampling was performed in some patients. The decision to perform pelvic/para-aortic lymphadenectomy was determined by the surgical team. Other surgical procedures, the most common of which were large/small bowel resection and splenectomy, were performed when necessary. Optimal surgery was defined as the absence of a tumor larger than 1 cm at the end of the surgical procedure. After surgery, all patients were treated by the same team of medical oncologists and received the same regimen of chemotherapy (paclitaxel plus platinum-based chemotherapy).

Follow-up

All patients underwent a follow-up protocol after postoperative chemotherapy. The patients were evaluated with a gynecological examination and CA-125 markers every 3-4 months in the first two years. After two years, patients were evaluated every six months. If recurrent disease was suspected, patients were assessed by magnetic resonance imaging and by positron emission tomography, if necessary.

The overall survival (OS) was defined as the time from initial treatment to death or to the last follow-up examination. The primary endpoint of this study was OS.

The Statistical Package for the Social Sciences (SPSS) for Windows version 21 was used to perform all analyzes. Kaplan-Meier method was used for survival distributions and significance for survival duration was determined by the log-rank test. Differences between groups were analyzed using Fisher's exact and chi-square tests. p values less than 0.05 was considered significant.

Since this study is a retrospective review, the permission of the local ethics committee has not been obtained. However, all patients signed an informed consent for the use of their clinical data.

Results

A total of 378 patients, 191 in the PDS group and 187 in the IDS group, were analyzed. Clinical and survival features are presented in Table 1. During 43 months of median follow-up period, 128 (67%) patients from the PDS group and 137 (73%) patients from the IDS group died ($p=0.185$). The optimal surgery rate was higher in the IDS group (83% vs. 65%, $p<0.001$). The mean age was higher in the PDS group (56.3 ± 13.2 vs. 59.7 ± 10.5). In the PDS group, there was more tumor in the upper abdomen (46% vs. 12%, $p<0.001$), intraabdominal ascites more than 1 liter (64% vs. 2%, $p<0.001$), higher lymphadenectomy rate (53% vs. 13%, $p<0.001$), higher bowel resection/colostomy rate (11% vs. 3%, $p=0.001$), and higher postoperative mortality (within 30 days) (5 vs. 0) (Table 1).

Survival Analysis

The PDS group had a higher median OS duration than the IDS group (56.8 vs. 43.5 months, log-rank test $p=0.026$). 2-year OS rates were higher in the IDS group (85% vs. 77%) and 3-year, 5-year, and 8-year OS rates were higher in the PDS group (64.3% vs. 60.6%, 47.1% vs. 36.6%, 31.8% vs. 12.7%, respectively) (Figures 1-2).

Subgroup Analysis (Table 2)

Each group was subdivided in terms of optimal surgery. OS times of subgroups based on optimality are presented in Table 2. The best survival was in the PSD group with optimal surgery (64.9 months). The IDS group undergoing suboptimal surgery had the worst survival (25.3 months).

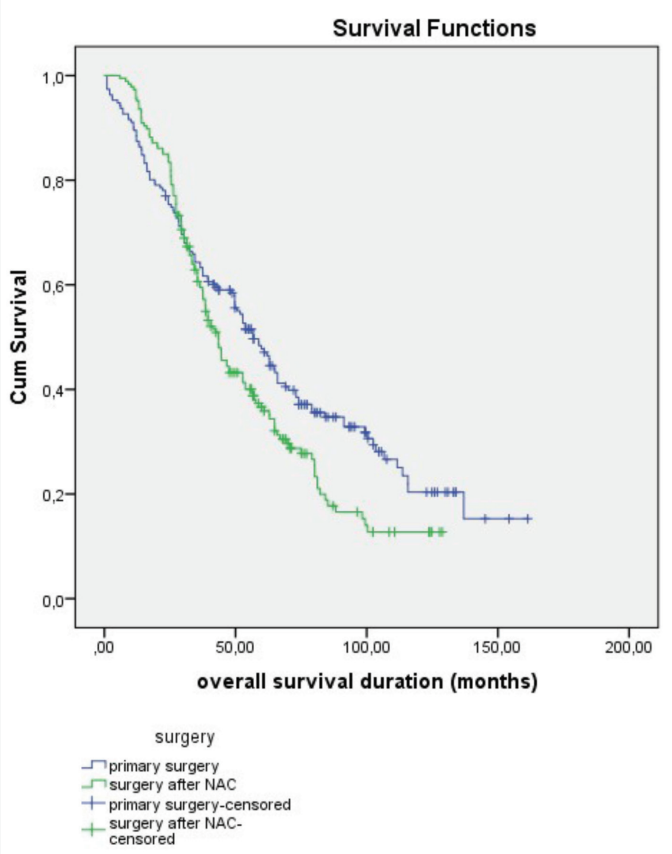

Figure 1. Overall survival of patients grouped according to neoadjuvant chemotherapy (log-rank test p=0.026)

NAC: neoadjuvant chemotherapy

Table 1. Clinical and survival results of patients based on PDS/IDS

Feature	Primary debulking surgery (n=191)	Interval debulking surgery (n=187)	p
Age, (years) mean ± SD	56.3±13.2	59.7±10.5	**0.007**
>60 years	72 (37.7%)	93 (49.7%)	
Performance of optimal surgery	124 (65 %)	156 (83 %)	**<0.001**
Presence of visible tumor at upper abdomen during surgery	88 (46 %)	23 (12 %)	**<0.001**
Ascites (more than 1 liter)	123 (64 %)	5 (2 %)	**<0.001**
Lymphadenectomy	102 (53 %)	24 (13 %)	**<0.001**
Bowel resection/colostomy	21 (11 %)	6 (3 %)	**0.001**
Total exitus	128 (67 %)	137 (73 %)	0.185
Postoperative (within 30 days)	5 (2.6 %)	-	
Median overall survival	56.8	43.5	**0.026**
(months) 95% CI	48.2-65.4	38.1-48.8	
2-year survival rate	77.0 %	85.0 %	
3-year survival rate	64.3 %	60.6 %	
5-year overall survival rate	47.1 %	36.6 %	
8-year overall survival rate	31.8 %	12.7 %	

SD: standard deviation, CI: confidence interval, PDS: primary debulking surgery, IDS: interval debulking surgery

Cox regression analysis (Table 3)

Factors related to OS were analyzed by univariate and multivariate analyses (Table 3). The examined factors included age, optimal surgery, presence of tumor in the upper-abdomen, lymphadenectomy and treatment option (PDS or IDS). According to multivariate analysis, suboptimal surgery [hazard ratio (HR), 1.606; (95% CI, 1.184-2.177); p=0.002], presence of tumor in the upper-abdomen [HR, 1.495; (95% CI, 1.113-2.006); p=0.007], IDS [HR, 1.456; (95%CI, 1.076-1.970); p=0.015], and age [HR, 1.013; (95% CI, 1.002-1.024); p=0.025] were associated with shorter survival duration. Lymphadenectomy was associated with OS in univariate analysis, but not in multivariate analysis.

Discussion

The NAC-IDS approach has been undertaken for patients with advanced stage ovarian cancer over the last 25 years, as an alternative option to PDS. This approach is increasingly preferred and the use of PDS is decreasing in clinics (6,13). Comparative survey outcomes for PDS and IDS continue to be published. To date, more than 20 studies comparing survival have been published (Table 4). In some studies, NAC-IDS seems advantageous in terms of survival, whereas others have reported that the PDS approach is preferable (Table 4). However, there is consensus that IDS is superior to PDS in terms of performance of optimal debulking (12-14).

In this study, optimal debulking and absence of upper abdominal metastasis were independent positive prognostic factors according to multivariate analysis (Table 3). These factors were higher in the NAC group. Despite these good results in the NAC group, survival was lower (median OS duration was 43.5 vs. 56.8 months, p=0.026) (Table 1). The survival advantage of PDS has become more prominent in the long-term survival analysis (Figures 1-2). In addition, PDS was superior in terms of survival in subgroup analysis based on performance of optimal surgery (Table 2). Interestingly, patients with NAC have a shorter survival rate compared to patients with PDS, even though optimal surgery has been achieved. Similarly, in a recent study, Kessous et al. (15) reported that

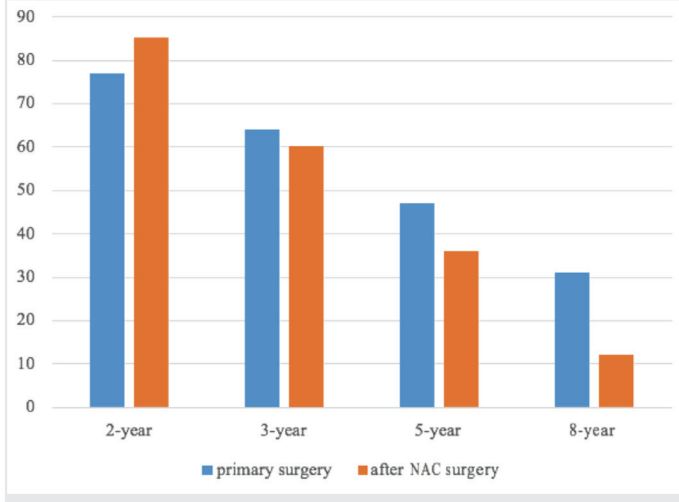

Figure 2. Comparison of overall survival rates (%) for IDS/PDS groups at 2, 3, 5 and 8th years

IDS: interval debulking surgery, PDS: primary debulking surgery

patients with PDS had better OS than with NAC-IDS (60 months vs. 48 months, p=0.039). However, complete cytoreduction rates in the PDS group were lower than in the NAC-IDS group (65.9% vs. 40.2%, p=0.001).

In another study, Rosen et al. (9) reported that optimal surgery rates in patients with PDS were lower than patients with NAC-IDS (64% vs. 79%). However, long-term OS rates were significantly higher (seven-year survival rate 8.6% vs. 41.1%; p<0.0001) in patients with PDS. In our study, 8-year OS rates were higher in the PDS group (31.8% vs. 12.7%) (Table 1). In this study, 2-year OS rate in IDS seems to be better (not statistically significant) and 3-year and later survival was higher in PDS. The number of patients who died in the postoperative period was higher in the primary surgery arm (5 vs. 0). This result causes the survival of the PDS to be short in the first year.

In a recent comparative study of two groups, May et al. (16) reported that 5-year survival was better for patients undergoing PDS than in patients who received NAC (39% vs. 27%; p=0.02). However, the gross residual tm (>1 cm) ratio in the PDS group was higher in their study (28% vs. 19%, p=0.02).

Many studies comparing the survival of the two groups are presented in Table 4. According to randomized controlled prospective trials, survival rates were similar in patients with advanced stage ovarian cancer who underwent NAC-IDS or PDS. Conversely, in retrospective studies, the survival of patients with PDS appears to be slightly better than that of patients with NAC-IDS (Table 4). However, optimal cytoreduction rates in PDS arms of randomized controlled trials were low. The reported rates were 42% in Vergote and 37.6% in Kehoe. This may be associated with low survival in the PDS group. Additionally, a patient eligible for PDS may have received NAC due to the randomization procedure. The main limitation in these randomized trials is that the selection process, which significantly biases the results, is usually not known.

In a recent meta-analysis, Qin et al. (17) and colleagues analyzed 22 retrospective observational studies and reported that OS was longer in the PDS group than that in the NAC group, irrespective of the degree of residual disease. Additionally, the authors stated that patients with FIGO stage 3 [HR=1.43, (95% CI: 1.05-1.95)] and 4 [HR=1.14, (95% CI: 1.06-1.23)] diseases had a better survival with PDS.

Regarding the adverse effect of NAC, some authors suggest that chemotherapeutics given may facilitate the emergence of chemotherapy-resistant cancer cell clones in NAC-IDS patients (18,19). Another hypothesis is that the tumor implants, which are shrinking due to chemotherapy, cannot be seen during laparotomy.

There are probably a limited number of patients who are eligible for surgery after NAC, and the criteria for this group need to be clarified. In fact, the main limitation in our study and in other studies comparing NAC and IDS is the uncertainty of patient selection criteria.

Conclusion

In conclusion, NAC followed by IDS appears to be worse than PDS in patients with stage 3 ovarian cancer. With NAC, tumor spread and surgical morbidity are reduced and optimal cytoreduction rates are increased. However, these positive improvements do not reflect positively on the OS of the patients.

Table 2. Analysis of overall survival of subgroups according to neoadjuvant chemotherapy and optimal surgery

Optimality	Surgery	Median overall survival duration (months)				p
		Estimate	Std. Error	95% CI		
				Lower bound	Upper bound	
Optimal	Primary surgery (n=124)	64.9	8.1	48.9	80.9	**0.008**
	Surgery after NAC (n=156)	44.6	3.9	36.9	52.2	
	Overall	56.8	4.4	48.0	65.5	
Suboptimal	Primary surgery (n=67)	41.6	7.6	26.7	56.5	**0.044**
	Surgery after NAC (n=31)	25.3	1.6	22.0	28.6	
	Overall	34.4	5.0	24.6	44.2	
Overall	Overall	49.7	3.2	43.3	56.0	

CI: confidence interval, STD: standard, NAC: neoadjuvant chemotherapy

Table 3. Survival related factors according to multivariate and univariate cox regression analysis

Reference variabl	Univariate analysis				Multivarite analysis			
	HR	95% CI		p	HR	95% CI		p
		Lower	Upper			Lower	Upper	
Age	1.017	1.006	1.027	**0.002**	1.013	1.002	1.024	**0.025**
Suboptimal surgery	1.317	1.032	1.681	**0.027**	1.606	1.184	2.177	**0.002**
Presence of tumor at upper-abdomen	1.433	1.110	1.849	**0.006**	1.495	1.113	2.006	**0.007**
Absance of lymphadenectomy	1.707	1.302	2.237	**0.001**	1.766	0.938	1.736	**0.121**
IDS	1.317	1.032	1.681	**0.027**	1.456	1.076	1.970	**0.015**

CI: confidence interval, HR: hazard ratio, IDS: interval debulking surgery

Table 4. Results of studies comparing primary debulking surgery with interval debulking surgery after neoadjuvant chemotherapy in ovarian cancer

Trials/year	Design	n	Superior	Overall survival (months) IDS vs PDS	p
Vergote et al. (EORTC/NCIC trial) 2010 (4)	Randomized controlled	670	-	29.0 vs. 30.0	NS
Kehoe S et al. (CHORUS) 2015 (20)	Randomized controlled	550	IDS	24.1 vs. 22.6	NS
Shimizu Y et al. 1993 (21)	Retrospective	165	IDS	31 vs. 21	<0.05
Peter E et al. 1999 (22)	Retrospective	265	PDS	12.8 vs. 26.1	NS
Walther Kuhn et al 2001 (23)	Prospective, nonrandomized	63	IDS	42 vs. 23	0.007
Kayıkcioglu F et al. 2001. (24)	Retrospective	205	PDS	34.1 vs. 37.9	NS
Morice et al. 2003 (25)	Retrospective	68	IDS	26 vs. 22	NS
Hegazy et al. 2005 (26)	Prospective cohort	59	PDS	25 vs. 28	NS
Loizzi V et al 2005 (27)	Retrospective	60	PDS	32 vs. 40	NS
Inciure et al. (28) 2006	Retrospective	574	PDS	23.7 vs. 25.4	NS
Steed et al. 2006 (29)	Retrospective	116	PDS	29 vs 44	0.03
Hou et al. 2007 (30)	Retrospective	172	PDS	46 vs 47	NS
McLean et al. 2010 (31)	Retrospective	175	PDS+	29 vs. 34	NS
Dennis S Chi et al. 2012 (32)	Retrospective	316	PDS	37 vs. 50	-
Alejandro et al. 2012 (33)	Retrospective	242	IDS++	33 vs. 29	NS
Michelle et al. 2013 (34)	Retrospective	104	PDS€	25 vs. 39	NS
Fagö-Olsen CL et al. 2014 (8)	Retrospective	1677	PDS	29.4 vs. 31.9	0.099
Rosen et al. 2014 (9)	Retrospective	326	PDS*	8.6% vs. 41.1%	<0.001
Ulas S et al. 2015 (35)	Retrospective	292	PDS	48.2 vs. 57.7	NS
Bian C. 2016 (36)	Retrospective	339	-	25 vs. 25	NS
Yanlin Luo et al. 2016 (19)	Retrospective	341	PDS	41 vs. 51	NS
Meyer et al. 2016 (13)	Multi-institutional observational	1538	PDS	33 vs. 43 (IIIC) 31 vs. 36 (IV)	>0.05 (in IIIC)
Kessous et al. 2017 (15)	Retrospective	263	PDS	48.8 vs. 60.2	0.039
May et al. 2017 (16)	Retrospective	303	PDS**	27% vs. 39%	0.02
Present study 2018	Retrospective	392	PDS	41 vs. 56	0.014

*The authors reported a 7-year overall survival rate in each group, **5-year survival, +only patients older than 65 years analyzed, ++only stage IV patients analyzed, €only patients older than 70 years analyzed, IDS: interval debulking surgery, PDS: primary debulking surgery

Ethics Committee Approval: The study included patients who underwent surgery for advanced stage ovarian, tubal, or peritoneal cancer at İstanbul University İstanbul Faculty of Medicine Hospital between 2001 and 2013 (decision number: 05, date: 19.03.2018).

Informed Consent: All patients signed an informed consent for the use of their clinical data.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.K., S.T., H.S., Y.S.; Design - A.K., S.T., H.S., Y.S.; Supervision - A.K., S.T., H.S., Y.S.; Resources - A.K., S.T., H.S., Y.S.; Materials - A.K., S.T., H.S., Y.S.; Data Collection and/or Processing - A.K., S.T., H.S., Y.S.; Analysis and/or Interpretation - A.K., S.T., H.S., Y.S.; Literature Search - A.K., S.T., H.S., Y.S.; Writing Manuscript - A.K., S.T., H.S., Y.S.; Critical Review - A.K., S.T., H.S., Y.S.

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Abdominal Wall Endometriosis: Analysis of 66 Patients at a Tertiary Center

Abdominal Duvar Endometriozis: Tersiyer Merkezde 66 Hastanın Analizi

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ABSTRACT

Introduction: The objective of this study was to review the patients' characteristics and surgical findings of surgically excised abdominal wall endometriosis (AWE) cases.

Methods: We retrospectively analyzed the medical records of patients diagnosed with AWE between 2005 and 2015. Descriptive data were collected and analyzed.

Results: Sixty-six patients with histopathological diagnosis of AWE were included in our study. The mean age was 32±6.8 years and all cases were multiparous. All patients had a history of previous abdominal surgery and 63 patients had a history of cesarean delivery. The primary symptom was a painful palpable mass. The excised mass was generally on the previous surgical scar. The excised mass location was observed as subcutaneous tissue, fat layer, fascia and muscle tissue. There was no statistical correlation depth of invasion and mass size with the number of previous surgeries.

Conclusion: Caesarean incision was considered as the most important predisposing factor for AWE. As caesarean rates are increasing, we believe that the incidence of AWE will increase in the future. For this reason, more prospective studies are needed for prognosis and prophylaxis of the disease.

Keywords: Abdominal wall endometriosis, extrapelvic endometriosis, incisional endometriosis, scar endometriosis

ÖZ

Amaç: Çalışmamızın amacı, cerrahi olarak eksize edilmiş abdominal duvar endometriozis olgularının hasta karakteristik özelliklerini ve cerrahi bulgularını değerlendirmektir.

Yöntemler: 2005-2015 yılları arasında histopatolojik olarak abdominal duvar endometriozis tanısı alan hastaların tıbbi kayıtlarını retrospektif olarak taradık ve tanımlayıcı dataları analiz ettik.

Bulgular: Çalışmamıza histopatolojik abdominal duvar endometriozis tanılı 66 hasta dahil edildi. Ortalama yaş 32,0±6,8 idi ve tüm olgular multipar idi. Tüm hastaların geçirilmiş abdominal cerrahi öyküsü mevcuttu. Üç olgu hariç, tüm hastaların geçirilmiş sezaryen öyküsü mevcuttu. Hastaların primer semptomu ağrı ve palpe edilen kitle idi. Eksize edilen kitle genellikle önceki cerrahi skar üzerindeydi. Eksize edilen kitle lokasyonu subkutan doku, yağ tabakası, fasya ve kas dokusu olarak izlendi. Abdominal duvara invazyon derinliği ve kitle boyutu ile geçirilmiş cerrahi sayısı arasında bir ilişki izlenmedi.

Sonuç: Sezaryen insizyonu, abdominal duvar endometriozis için en önemli predispozan faktör olarak değerlendirildi. Günümüzde sezaryen oranları arttığı için, gelecekte abdominal duvar endometriozis olgularının insidansının artacağına inanıyoruz. Bu nedenle hastalığın prognozu ve profilaksisi için daha çok prospektif çalışmaya gereksinim duyulmaktadır.

Anahtar Kelimeler: Abdominal duvar endometriozis, ekstrapelvik endometriozis, insizyonel endometriozis, skar endometriozis

Introduction

Endometriosis is defined as the presence of endometrial glands and stroma outside the lining of the uterine cavity (1). Endometriosis is often found in intrapelvic areas such as ovaries, posterior cul de sac, ligaments of uterus, pelvic periton, rectovaginal septum, but it may rarely be in extrapelvic regions such as urinary tract, gastrointestinal tract and thorax (2,3). The abdominal wall endometriosis (AWE) is an uncommon clinical entity with a reported incidence of 0.03-3.5% (4). This condition may develop spontaneously, however, the most important risk factor is previous surgeries (5,6).

The purpose of our study was to investigate the demographic characteristics, surgical history, symptoms, diagnostic methods and intraoperative findings of patients with AWE and to make proposals for implementation.

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Methods

This is a retrospective descriptive case study. We reached the records of patients between November 2005 and March 2015 who had definitive histopathological diagnosis of AWE or scar endometriosis after surgical resection. Age, gravidity, parity, surgical history and characteristics of patients, diagnostic methods, and characteristics of the masses (e.g. number, localization, associated anatomical structures) were recorded. The time interval between the previous surgery and the diagnosis of AWE was defined as the "recognition period". Patients with intraabdominal organ endometriosis were excluded from study.

This study has been approved by İstanbul Training and Research Hospital Ethics Committee. Every patient admitted to our clinic had signed informed consent for admission and we are allowed to investigate clinical data unless we use personal data.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows version 15.0. Descriptive statistics were reported as number and percentage for categorical data, and mean, standard deviation, minimum and maximum for numerical variables. The trend for rate increase was examined with Mantel-Haenszel linear-by-linear association in chi-square test. Statistical significance level was considered as $p<0.05$.

Results

Sixty-six patients with histopathological AWE were included in our study (Table 1). The mean age was 32±6.8 years. All cases were multiparous. The recognition period for AWE ranged from 2 to 24 years. Majority of the patients had a history of cesarean delivery. Almost all of the patients had Pfannenstiel incision scar. Major presenting symptoms were palpable mass and pain. Ultrasonography (US) (44%), magnetic resonance imaging (MRI) (12%), computed tomography (CT) (4.5%) and fine-needle aspiration (FNA) (20%) had been performed for preoperative diagnosis. Thirteen of the patients (20%) had no preoperative diagnostic procedure and the masses were detected incidentally. The masses were mostly located at the previous surgery scars. In five patients, the masses were at umbilicus and far from previous scar. Sixty-nine percent of the masses were located at the incision corners. The endometriotic masses were mostly located in the subcutaneous tissue (45.5%). The mean mass size was 28.7±10.4 mm. The masses were completely excised in all patients. Polypropylene mesh graft was used in one patient. There was no statistically significant relationship between mass location and number of cesarean sections (p=0.744) (Table 2). There was no significant relationship between endometriotic mass size and the number of cesarean sections (p=0.197) (Table 3).

Discussion

Iatrogenic implantation theory is the most widely accepted theory for AWE. According to this theory, it is suggested that endometrial cells are planted directly at the incision (7,8). The development of endometriotic implants/masses mostly in previous gynecologic scars (such as cesarean section, hysterotomy, hysterectomy) supports iatrogenic implantation theory (6,9). Metaplasia and migration theories are other accepted theories in the development of

Table 1. Characteristics of the patients

		Range	Mean ± SD
Age (year)		19-51	32.0±6.8
The recognition period (month)		2-24	5.6±4.1
		n	%
Surgery history	One cesarean section	32	48.5
	Two cesarean sections	23	34.8
	Three cesarean sections	8	12.1
	Ovarian cystectomy	2	3.0
	Hysterectomy	1	1.5
Shape of incision	Transvers (Pfannenstiel)	65	98.5
	Midline	1	1.5
Symptoms and findings	Palpable mass	43	65.2
	Pain	23	34.8
Preoperative imaging	US	29	43.9
	MRI	8	12.1
	CT	3	4.5
	FNA	13	19.7
	None	13	19.7
AWE mass	**Region**		
	Previous scar	61	92.4
	Umbilicus	5	7.6
	Site (Pfannenstiel)		
	Left corner	26	39.4
	Right corner	20	30.3
	Middle	15	22.7
	Location		
	Subcutaneous tissue	30	45.5
	Muscular	23	34.8
	Fascia	9	13.6
	Fat	4	6.1
		Range	**Mean ± SD**
	Number	1-2	1.0±0.1
	Size (mm)	11-55	28.7±10.4

SD: standard deviation, US: ultrasonography, MRI: magnetic resonance imaging, CT: computed tomography, FNA: fine needle aspiration, AWE: abdominal wall endometriosis

Table 2. The relationship between the number of cesarean sections and the mass localization

	Number of cesarean, n (%)		
Mass location	**One**	**Two**	**Three**
Subcutaneous tissue	18 (56.3)	9 (39.1)	3 (37.5)
Fat	1 (3.1)	1 (4.3)	1 (12.5)
Fascia	2 (6.3)	3 (13.0)	4 (50.0)
Muscular	11 (34.4)	10 (43.5)	0 (0.0)
p=0.744			

Table 3. The relationship between the number of cesarean sections and mass size

Cesarean number	Diameter of mass Mean ± SD (mm)
One	27.0±9.9
Two	29.9±11.6
Three	33.6±9.1

SD: Standard deviation, p=0.197

extrapelvic endometriosis (9,10). Metaplasia theory claims that the differentiation of primitive mesenchymal cells into endometrial cells in the scar tissue causes endometriosis. The migration theory claims lymphatic or vascular spread of endometrial cells to distant sites. The nodules in previously non-operated patients or nodules in distant locations can be explained by this theory. None of these theories can exactly explain the whole case. Therefore, some researchers claim that genetic and environmental factors together play a role in the etiology of endometriosis (11). Cesarean section is one of the most common causes of AWE (2,6). The incidence of AWE in cesarean scar has been reported to between 0.03-1.08%. In the studies of Khamechian et al. (2) and Ding and Zhu (6), all patients had a history of cesarean section.

AWE usually develops in women of reproductive age (10,12). Predominantly, the patients are multiparous. Palpable mass is seen in 63-100% and pain in 41-92.5% (2,6,9,13). The increase in mass size during menstruation is pathognomonic for scar endometriosis (9,14). In our study, most common finding was palpable mass (65%). In the differential diagnosis, hernia, suture granuloma, primary or metastatic tumors, sarcoma, cysts, nodular and proliferative fasciitis, fat necrosis, lipoma, abscess or hematoma of the abdominal wall should be considered (14,15). US, CT and MRI can be used in the diagnosis and US is the primary imaging method to be preferred. The endometriotic masses are mostly vascularized and hypoechoic sonographically. CT and MRI provide useful information about the anatomic location of the mass in the abdominal wall and its relation with neighboring structures for preoperative evaluation. However, imaging findings are not specific (12,16). Definitive diagnosis is possible only histopathologically (2,17). Some authors recommend FNA cytology before surgical excision. Observation of endometrial gland, stroma and hemosiderin-laden macrophages in cytology are considered diagnostic findings (15,18,19). On the other hand, there is no consensus for FNA, because there is some risk of planting endometrial cells to the puncture site (9,20).

Local wide surgical excision is the primary treatment for AWE. For both treatment and reducing the risk of lesion recurrence, the mass should be widely excised with at least 1 cm margin (6,21). After surgical excision, defect can be repaired by using autologous or synthetic graft according to the width of the defect and its anatomical localization (11,22). Postoperative adjuvant hormone therapy such as danazol, progesterone and GnRH analogs are recommended for patients with concomitant pelvic endometriosis or recurrent AWE (21,23).

Study Limitations

The major limitations of our study were retrospective nature and failure of post-treatment controls due to inability to reach the majority of patients.

Conclusion

Endometriosis should be considered in differential diagnosis of a painful mass in anterior abdominal wall, especially in women with a history of pelvic or obstetric surgery. According to our findings and the literature (2,4,6-14,24,25), previous cesarean section is the most well known risk factor in etiology. This suggests that the disease is highly caused by iatrogenic sowing. For this reason, the following recommendations will contribute to non-occurrence of AWE after cesarean sections; intraoperatively, a) rapid removal of the gauze used to clean uterine cavity and ensure no contact to the incision, b) replacement of gloves after uterine incision suturing, c) washing of the abdominal wall tissues with physiological saline after the uterus is closed, d) not using of remaining uterine suture materials elsewhere, e) irrigation of incision with physiological saline after the parietal peritoneum is closed. These recommendations can considerably reduce the incidence of AWE.

Ethics Committee Approval: This study has been approved by İstanbul Training and Research Hospital Ethics Committee.

Informed Consent: Every patient admitted to our clinic had signed informed consent for admission.

Peer-review: Externally and internally peer-reviewed.

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Assessment of Cervical Length by Transvaginal Ultrasound in Pregnant Women Between 24-34 Weeks

Gebelerde Transvajinal Ultrason ile 24-34 Hafta Arasında Servikal Uzunluğun Değerlendirilmesi

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ABSTRACT

Introduction: The purpose of this study was to assess the role of cervical length measurement by transvaginal ultrasound for predicting preterm delivery.

Methods: Cervical lengths were measured by transvaginal ultrasound in 73 pregnant women with 24-34 weeks of gestation. Cervical length measurements were analyzed for the predictability of preterm birth.

Results: Of the 73 pregnant women, 19 (26%) had preterm labor (<37 weeks) and 54 (74%) had term labor. For predicting preterm birth, cut-off values were determined using the Receive Operating Characteristic Curve curves and corresponding values. The cut-off value of the cervical length was 31.5 millimeters and sensitivity, specificity, positive predictive value and negative predictive value were 70.3%, 89.4%, 51.5% and 95%, respectively.

Conclusion: According to the study, the evaluation of cervical length by transvaginal ultrasound in pregnant women with 24-34 weeks of gestation may be useful as a screening test for preterm birth prediction. The risk of premature birth in pregnant women with a cervical length more than 31 mm is minimal.

Keywords: Cervical length, preterm birth, transvaginal ultrasound

ÖZ

Amaç: Bu çalışmanın amacı, erken doğumu öngörmede transvajinal ultrason ile servikal uzunluk ölçümünün rolünü değerlendirmektir.

Yöntemler: Yirmi dört-otuz dört haftalık gebeliği olan 73 kadında, transvajinal ultrasonografi ile servikal uzunluklar ölçüldü. Servikal uzunluk ölçümleri preterm doğum tahmin edilebilirliği açısından analiz edildi.

Bulgular: Yetmiş üç gebe kadından 19'u preterm (<37 hafta) (%26) ve 54'ü (%74) miadında doğum yaptı. Erken doğumu kestirmek için, kesme değerleri Receive Operating Characteristic Curve eğrileri ve karşılık gelen değerler kullanılarak belirlendi. Servikal uzunluğun kesme değeri 31,5 milimetre olarak belirlendi ve duyarlılık, özgüllük, pozitif prediktif değer ve negatif öngörü değeri sırasıyla %70,3, %89,4, %51,5 ve %95 idi.

Sonuç: Çalışmaya göre, gebe kadınlarda 24-34. haftalar arasında transvajinal ultrasonografi ile servikal uzunluğun değerlendirilmesi preterm doğum tahmini için tarama testi olarak faydalı olabilir. 31 mm'nin üzerinde servikal uzunluğa sahip gebelerin prematür doğum riski minimaldir.

Anahtar Kelimeler: Servikal uzunluk, erken doğum tahmini, transvajinal ultrason

Introduction

Preterm delivery is the birth that occurred before the completion of 37 weeks of gestation. The rate of preterm birth is different in reports and can be up to 15% (1-4). According to the literature, the incidence of preterm delivery has increased in recent years (5). Preterm delivery is one of the main causes of neonatal morbidity and mortality (5). The risk of mortality and serious acute morbidities such as respiratory distress syndrome, necrotizing enterocolitis and intraventricular hemorrhage are related with preterm birth (6, 7).

In recent years, cervical length measurement by cervical transvaginal ultrasound (US) has been proposed as an effective method for predicting preterm delivery (8-11). However, there is no consensus on the routine use of cervical length measurement for predicting preterm delivery (12-14).

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In this study, the relationship between cervical length measurement by transvaginal US and preterm delivery was investigated.

Methods

This study was performed in pregnant women between 24-34 weeks of pregnancy who applied to the obstetrics clinic for routine antenatal follow-up. İstanbul Gaziosmanpaşa Taksim Training and Research Local Ethics Committee approval was obtained for this study (decision number:16.01.2009). Informed consent form was obtained from all patients included in the study. Patients with vaginal bleeding, membranous rupture, pregnancies with >3 cm of cervical dilatation, mandatory birth due to fetal or maternal reasons were excluded. Pregnancy history was obtained, the last menstrual period (LMP) was recorded and gestational week was calculated. Gestational weeks were calculated according to the first trimester US of pregnant women who did not know the LMP. The first trimester US was used to determine gestational week if there was a significant difference (more than 7days) between the LMP and first trimester US. The pregnancies that did not have first trimester US and did not know LMP were not included in the study.

The vaginal US probe was prepared by attaching a condom to the tip. The cervix was assessed by transvaginal US. Cervical length measurement was performed visualizing the cervical internal ostium, external ostium and cervical channel on the same line.

A total of 80 pregnant women were included in the study. After the study was completed, seven pregnant women were excluded from the study due to missing data.

Those who gave birth at ≥37 gestational weeks were accepted as term delivery and <37 gestational weeks as preterm delivery.

Statistical Analysis

Statistical analysis was performed by SPSS. Mann-Whitney U test was used in the comparisons between independent groups. The chi-square test was used to compare expected and observed values.

Results

Of 73 pregnant women, 19 had preterm and 54 had term delivery. The results of these two groups were compared. There was no significant difference between the two groups regarding median gestational age at the time of examination (p=0.477). The mean birth age was 242±11 days in preterm delivery and 275±7 days in term delivery. The mean birth weight was 2371±292 grams at preterm delivery and 3302±430 grams at term delivery and the difference was statistically significant (p<0.001) (Table 1).

Cervical Length

The cut-off value of the cervical length was determined using the Receive Operating Characteristic (ROC) curve and the corresponding cervical length values, and the cut-off value was determined as 31.5 mm. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy rate were 70.3%, 89.4%, 51.5%, 95% and 75.3%, respectively (Table 2, Figure 1). Cervical length in 17 of 19 pregnant women who underwent preterm delivery was below the cut-off value of 31.5 mm (89.4%).

Discussion

The World Health Organization recognizes births that occur before the completion of 37 gestational weeks as premature births (4). Preterm delivery is a major cause of morbidity and mortality (15). Cervical length measurement by cervical transvaginal US is suggested as an effective screening method for premature birth (8, 9, 16). However, some studies suggest that it is not useful as a screening method (12, 13).

The cervical length can be measured in different ways by US. These are transabdominal, transperineal and transvaginal approaches. Transvaginal approach is considered to be the gold standard (17). In our study, cervical lengths were measured by transvaginal US in 73 women. The cervical length was shorter in women who gave birth before 37

Table 1. Characteristics of preterm and term groups

Features	Preterm (n=19)	Term (n=54)	p
Cervical length, (mm) mean ± SD	24±7	34±7	< 0.001
Gestational age during examination, median (95% CI)	32 (30-33)	32 (28-33)	0.477
Age of birth, (days) mean ± SD	242±11	275±7	< 0.001
Birth weight, (gr) mean ± SD	2371±292	3302±430	< 0.001

CI: confidence interval, SD: standard deviation

Table 2. Predictive values of cervical length with a cut-off value of 31.5 mm

	Preterm (n=19)	Term (n=54)	Total
Cervical length (≤ 31.5 mm)	51.5% (17)	48.5% (16)	33
Cervical length (> 31.5 mm)	5.0% (2)	95.0% (38)	40
Total	19	54	73

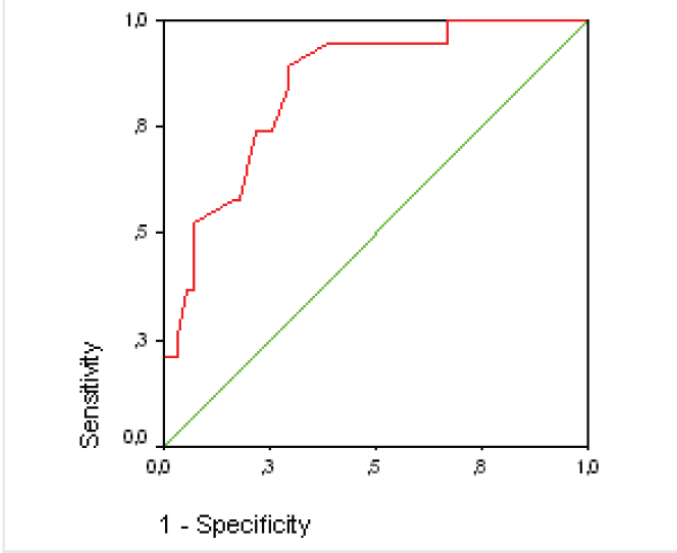

Figure 1. Receive Operating Characteristic Curve of cervical length (The area under the Receive Operating Characteristic Curve is 0.85)

weeks (defined as preterm labor) (24±7 mm vs. 34±7 mm, p<0.001). When the cut-off value was accepted as 31.5 mm, the negative predictive value was 95%. Of the 40 women whose cervical length measurements were above the cut-off value, only 2 had preterm labor (Table 2). The risk of preterm delivery was 51.5% if the cervical length was shorter than 31 mm.

According to Timothy and colleagues, 25 mm cervical length has the best predictive accuracy (8). If the cervical length is shortened and it is detected early in pregnancy, the risk of preterm birth increases.

According to the studies of Kuusela et al. (14), there was no significant association between cervical length (<25 mm) and spontaneous preterm delivery at <37 weeks. The authors reported a significant relationship between cervical length and spontaneous preterm birth at <34 weeks and reported that a larger study is needed to evaluate the prevalence of short cervical length and the possible association with preterm delivery before universal screening is recommended.

There are three main mechanisms associated with the development of a short cervical length (18). Firstly, the most accepted hypothesis is that of an internal weakness of a short cervical length. This cervical insufficiency is usually caused by traumatic or surgical injury or, more rarely, by a congenital disorder or connective tissue disease. Second, another hypothesis is that a short cervical length is due to an inflammatory or infectious process. In the other hypothesis, it is thought that shortening of cervical length is due to uterine contractions. Studies have shown that asymptomatic women with a cervical length less than 25 mm before 24 weeks have higher risk of preterm birth more than controls with a normal cervix (9).

Conclusion

This study showed that measurement of cervical length by transvaginal US might be useful as a screening test in predicting preterm birth. In this study, the cut-off value was found to be 31.5 mm and the probability of premature birth was lower in women with a cervical length above this value.

Ethics Committee Approval: İstanbul Gaziosmanpaşa Taksim Training and Research Local Ethics Committee approval was obtained for this study (decision number:16.01.2009).

Informed Consent: Informed consent form was obtained from all patients included in the study.

Peer-review: Externally peer-reviewed.

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

Conflict of Interest: No conflict of interest was declared by the authors.

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Diaphragm Thickness Measurement in Computed Tomography: Intra- and Inter-Observer Agreement

Bilgisayarlı Tomografide Diyafram Kalınlık Ölçümü: Gözlemci İçi ve Gözlemciler Arası Güvenilirlik

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ABSTRACT

Introduction: Diaphragm thickness (DT) measurement in computed tomography (CT) has become popular in recent years. Our aim was to assess the intra- and inter-observer agreement of DT measurement and to investigate the best points for DT assessment in CT based on the most reliable measurement.

Methods: Thoraco-abdominal CT angiography scans of 44 patients (23 males, mean age: 49.9+17.8 years) were retrospectively evaluated. All of the CT images were evaluated independently by four radiologists. Each observer evaluated images twice to assess intra-observer reproducibility. On both axial and coronal reconstructed CT images, the crura of 88 hemidiaphragms were measured at five different points. A p value less than 0.05 was considered to indicate statistical significance. Intra- and inter-observer agreement was evaluated by using intraclass correlation coefficient (ICC) scores with a 95% confidence interval.

Results: In intra-observer analysis, ICC scores demonstrated substantial to almost perfect agreement for all measurements (ICC score range: 0.758-1). When we analyzed the inter-observer agreement, there was a moderate to almost perfect agreement for each measurement point (ICC score range: 0.523-0.895). All axial measurements showed the highest inter-observer agreement (ICC scores were 0.926 and 0.886 for first and second measurements, respectively). The maximum inter- and intra-observer agreement for single point DT measurements were found in maximum DT at the level of the origin of the celiac artery and in anterior DT at the level of the upper part of the L1 vertebral body.

Conclusion: CT is a reliable tool DT measurement with excellent intra- and inter-observer agreement.

Keywords: Computed tomography, diaphragm thickness, measurement, reliability

ÖZ

Amaç: Çeşitli hastalıklarda bilgisayarlı tomografide (BT) diyafram kalınlığı (DK) ölçümü son yıllarda popüler hale gelmiştir. Amacımız, DK ölçümünün gözlemci içi ve gözlemciler arası anlaşmasını değerlendirmek ve en güvenilir ölçümlere dayanarak BT'de en iyi DK ölçümü yerini araştırmaktır.

Yöntemler: DK ölçümünde 44 hastanın (23 erkek, ortalama yaş; 49,9±17,8) torako-abdominal BT anjiyografisi retrospektif olarak değerlendirildi. Tüm BT görüntüleri dört radyolog tarafından bağımsız olarak değerlendirildi. Her gözlemci, gözlemciler arası tekrarlanabilirliği değerlendirmek için görüntüleri iki kez değerlendirdi. Hem aksiyal hem de koronal rekonstrüksiyon yapılmış BT görüntülerinde, 88 hemidiyaframın krusları beş farklı noktada ölçülmüştür. İstatistiksel anlamlılığı göstermek için 0,05'ten küçük bir p değeri göz önüne alınmıştır. Gözlemci içi ve gözlemciler arası anlaşma, %95 güven aralığında sınıf içi korelasyon katsayısı (ICC) skorları kullanılarak değerlendirildi.

Bulgular: Gözlemci içi arası analizde, ICC skorları, tüm ölçümler için iyi - neredeyse mükemmel bir anlaşma göstermiştir (ICC skorları aralığı; 0,758-1). Gözlemciler arası anlaşmayı incelediğimizde, her bir ölçüm noktası için orta - neredeyse mükemmel bir anlaşma vardı (ICC skoru aralığı, 0,523-0,895). Tüm aksiyal ölçüm değerleri en yüksek gözlemciler arası anlaşmayı gösterdi (ICC skorları sırasıyla birinci ve ikinci ölçümler için 0,926 ve 0,886 idi). Tek nokta DK ölçümleri için en iyi gözlemci içi ve gözlemciler arası anlaşma, çölyak arter çıkımı düzeyinde maksimum DK ve L1 vertebra gövdesinin üst kısmı seviyesinde anterior DK ölçülmesinde bulundu.

Sonuç: Bilgisayarlı tomografi, yüksek gözlemci içi ve gözlemciler arası uyum nedeniyle DK ölçümü için güvenilir bir araçtır.

Anahtar Kelimeler: Diyafram kalınlığı, ölçüm, bilgisayarlı tomografi, güvenilirlik

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Introduction

The diaphragm is the major inspiratory muscle with a dome-like shape and measurement of diaphragm thickness (DT) in various disorders has become popular in recent years. Decreased DT on ultrasound was shown to correlate with reduced myocyte cross-sectional area in a porcine model (1). Measurement of DT in computed tomography (CT) has been shown to be successful in the assessment of the success of diaphragm pacing system in amyotrophic lateral sclerosis (ALS) patients (2), detection of diaphragmatic thinning due to mechanical ventilator therapy and sepsis (3,4), and the diagnosis of unilateral diaphragm paralysis (5). In previous studies (2-5), DT measurement in CT was performed by single observers. The main limitation of CT in DT measurement is the absence of a consensus on reliable measurement locations (points). This may lead to variability in the performance of CT in DT measurements, which may weaken the reliability of CT measurements. To the best of our knowledge, no study has investigated the best points for DT measurement and agreement between observers.

Our aim was to assess the intra- and inter-observer agreement of DT measurement and to investigate the best points for DT assessment in CT based on the most reliable measurement.

Methods

This retrospective study started after our institutional Pamukkale University Local Ethics Committee approved letter of application (no: 60116787-20/85543). Informed consent was not obtained from the patients because of retrospective nature of the study.

Patients

Patients who underwent thoraco-abdominal CT angiography for suspected acute aortic syndrome between January 2016 and July 2017 were included the study. The exclusion criteria were as follows: pulmonary pathology that can affect DT measurement (such as lower lob atelectasis, mass or pleural effusion), focal or diffuse diaphragmatic crus defect and CT examinations with inadequate diagnostic quality due to motion artifacts. A total of 44 patients (23 males, mean age: 49.9+17.8 years, range: 18-85 years) were included in the study.

Computed Tomography Scanning Protocol

All thoraco-abdominal CT angiography scans were obtained in the supine position with maximum inspiration using a multi-detector CT scanner (Brilliance 16; Philips Healthcare, Best, Netherlands). The area between the thoracic inlet and the deep costophrenic sulcus was scanned. The scanning parameters were as follows: tube voltage, 120 kV; tube current, 100 mAs; collimation, 16x0.75 mm; field of view, 300 mm; matrix, 512 x 512; rotation time, 0.75 s; table speed, 15 mm/s and beam pitch, 0.94. All CT images were reconstructed in transverse and coronal planes at 1.5 mm slice thickness.

Radiological Evaluation

All CT images were evaluated independently by four radiologists with various experience (3, 9, 12 and 20 years) on the same workstation (Extended Brilliance Workspace, Philips Healthcare). Observers were blinded to measurements of each other. Each observer evaluated the images twice to assess intra-observer reproducibility. The second assessment was done at least three months after the first to prevent recall.

Five measurements were performed on both axial and coronal images for each hemidiaphragm (88 hemidiaphragms) thickness. CT images were evaluated in the mediastinal window (window center, 90 HU; window width, 350 HU) and magnification was freely modifiable. Measurements were performed as described by Sukkasem et al (5). On both axial and coronal reconstructed CT images, the crura of the hemidiaphragms were measured at the level of the origin of the celiac artery, and minimum and maximum DT were recorded. In addition, measurements were recorded for each crura at the level of the upper part of the L1 vertebral body along the anterior, middle and posterior aspects of the vertebral body on axial images and upper, middle and lower aspects of the vertebral body on coronal images (Figure 1).

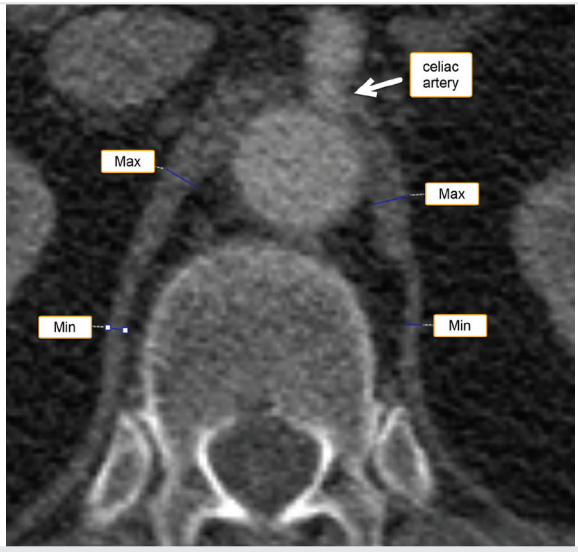

Figure 1. Points of diaphragm thickness measurements. a) Axial computed tomography scan at the celiac artery origin level (arrow) shows maximum and minimum diaphragm thickness measurements

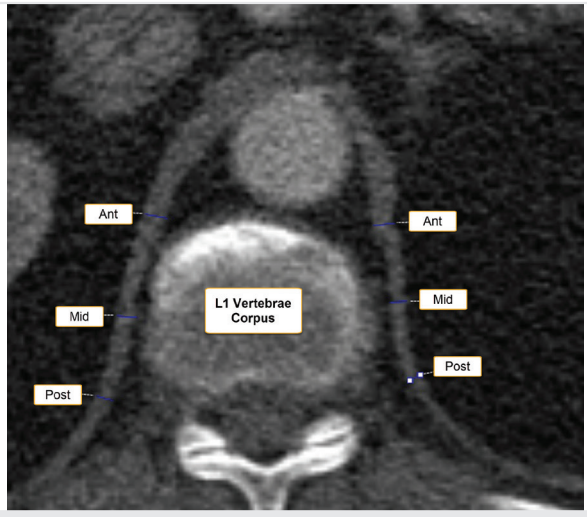

Figure 1. b) Axial computed tomography scan at the L1 vertebra corpus level shows anterior, mid and posterior diaphragm thickness measurements

Table 1. The diaphragm thickness measurement results of patients and intra-observer agreement scores for each measurement

	First evaluation Mean ± SD (mm)	Second evaluation Mean ± SD (mm)	Intraclass correlation coefficient	Lower bound (95% CI)	Upper bound (95% CI)
	Axial (observer 1)				
Max	7.3±1.9	7.7±1.8	0.951	0.911	0.995
Min	2.9±0.6	3±0.4	0.915	0.845	0.951
Ant	5.3±1.5	5.1±1.3	0.94	0.891	0.992
Mid	3.6±0.8	3.5±0.6	0.937	0.885	0.966
Post	3.1±0.8	3.2±0.5	0.895	0.808	0.943
	Coronal (observer 1)				
Max	6.2±1.8	6.9±1.9	0.912	0.866	0.986
Min	2.2±0.6	2.4±0.5	0.905	0.868	0.961
Low	2.5±0.6	2.9±1.1	0.88	0.872	0.905
Mid	2.9±1	3±0.7	0.924	0.860	0.958
Upp	4.6±1.7	4.1±1.4	0.774	0.659	0.899
	Axial (observer 2)				
Max	6.5±2.1	6.8±1.8	0.962	0.926	0.991
Min	2.8±0.6	3±0.4	0.948	0.904	0.972
Ant	5.1±1.3	5.1±1.3	1	1	1
Mid	3.7±1	3.5±0.8	0.966	0.937	0.981
Post	3.3±0.7	3±0.5	0.95	0.909	0.973
	Coronal (observer 2)				
Max	7.2±2.4	6.6±1.4	0.795	0.773	0.832
Min	2.2±0.5	2.3±0.4	0.885	0.813	0.951
Low	3±1.5	3.3±1.2	0.825	0.763	0.879
Mid	3.4±0.8	2.9±0.4	0.785	0.718	0.834
Upp	4.9±0.5	4.5±0.4	0.812	0.782	0.935
	Axial (observer 3)				
Max	7.3±2.4	7.1±2	0.972	0.947	0.990
Min	2.9±0.7	2.9±0.5	0.904	0.882	0.972
Ant	5.2±1.6	5.2±1.3	0.975	0.955	0.986
Mid	4±1.3	4.1±1.2	0.923	0.869	0.952
Post	3.6±0.9	3.7±0.6	0.913	0.840	0.952
	Coronal (observer 3)				
Max	7.2±2.4	7.1±1.8	0.947	0.903	0.971
Min	2.3±0.5	2.7±0.4	0.822	0.767	0.856
Low	3.2±1.4	4.1±1.2	0.758	0.659	0.888
Mid	3.5±1.1	3.5±0.9	0.949	0.913	0.963
Upp	4.7±0.8	4.2±0.7	0.767	0.712	0.835
	Axial (observer 4)				
Max	6.8±1.9	6.7±1.6	0.974	0.953	0.986
Min	2.6±0.5	2.6±0.3	0.951	0.910	0.973
Ant	4.9±1.5	4.5±1.1	0.952	0.912	0.974
Mid	3.8±1.1	3.7±0.7	0.939	0.888	0.967
Post	3.3±1.1	3.2±0.8	0.95	0.928	0.978
	Coronal plane (observer 4)				
Max	6.3±2.3	6.9±1.7	0.867	0.820	0.882
Min	2.2±0.6	2.5±0.4	0.882	0.817	0.936
Low	3.6±1.8	4.1±1.6	0.788	0.712	0.893

Table 1. Continued

	First evaluation Mean ± SD (mm)	Second evaluation Mean ± SD (mm)	Intraclass correlation coefficient	Lower bound (95% CI)	Upper bound (95% CI)
	Coronal plane (observer 4)				
Mid	3.3±0.9	3.7±0.7	0.83	0.782	0.874
Upp	4.1±0.8	4.8±0.6	0.768	0.638	0.826

Max: maximum diaphragm thickness at the level of the origin of the celiac artery, Min: minimum diaphragm thickness at the level of the origin of the celiac artery, Ant: anterior diaphragm thickness at the level of the upper part of the L1 vertebral body on axial images, Mid: mid diaphragm thickness at the level of the upper part of the L1 vertebral body, Post: posterior diaphragm thickness at the level of the upper part of the L1 vertebral body on axial images, Upp: diaphragm thickness at the upper aspects of the L1 vertebral body on coronal images, Low: diaphragm thickness at the lower aspects of the L1 vertebral body on coronal images, CI: confidence interval, SD: standard deviation

Table 2. The inter-observer agreement for the first and second measurements

	Intraclass correlation coefficient	Lower bound (95% CI)	Upper bound (95% CI)
	First measurements		
Axial			
Max	0.895	0.773	0.947
Min	0.564	0.349	0.660
Ant	0.823	0.727	0.900
Mid	0.753	0.649	0.873
Post	0.722	0.533	0.887
All	0.926	0.873	0.958
Coronal			
Max	0.753	0.610	0.853
Min	0.625	0.439	0.789
Low	0.742	0.607	0.854
Mid	0.614	0.453	0.792
Upp	0.705	0.523	0.822
All	0.790	0.684	0.870
	Second measurements		
Axial			
Max	0.817	0.765	0.909
Min	0.782	0.723	0.904
Ant	0.860	0.773	0.918
Mid	0.721	0.558	0.851
Post	0.736	0.591	0.860
All	0.886	0.832	0.926
Coronal			
Max	0.613	0.383	0.772
Min	0.523	0.252	0.707
Low	0.640	0.479	0.804
Mid	0.762	0.669	0.876
Upp	0.585	0.294	0.734
All	0.776	0.662	0.838

Max: maximum diaphragm thickness at the level of the origin of the celiac artery, Min: minimum diaphragm thickness at the level of the origin of the celiac artery, Ant: anterior diaphragm thickness at the level of the upper part of the L1 vertebral body on axial images, Mid: mid diaphragm thickness at the level of the upper part of the L1 vertebral body, Post: posterior diaphragm thickness at the level of the upper part of the L1 vertebral body on axial images, Upp: diaphragm thickness at the upper aspects of the L1 vertebral body on coronal images, Low: diaphragm thickness at the lower aspects of the L1 vertebral body on coronal images, CI: confidence interval

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) for Windows (Version 24.0, SPSS Inc. IBM Corp, Chicago, IL). The distribution of normality for each continuous variable group was calculated by Kolmogorov-Smirnov Z-test. Student's t-test was used for comparisons of paired samples. A p value less than 0.05 was considered to indicate statistical significance. Intra- and inter-observer agreement was evaluated by using intraclass correlation coefficient (ICC) scores with a 95% confidence interval (CI). Intra- and inter-observer agreement was categorized as follows: 0.01–0.20 as poor, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial and 0.81–1.00 as almost perfect.

Results

In all groups, DT values showed normal distribution. The results of DT measurements of 44 patients and intra-observer agreement scores for each measurement are shown in Table 1. The inter-observer agreement

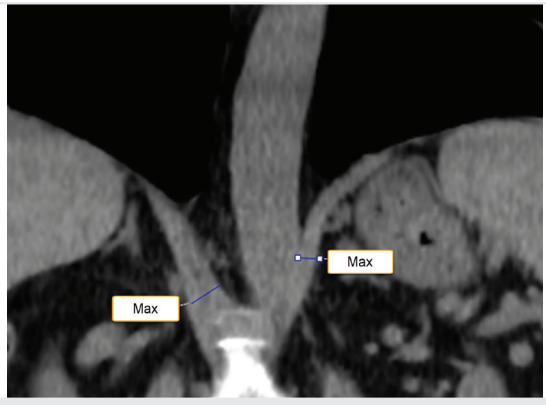

Figure 1. c) Coronal reformatted computed tomography images at the celiac artery level shows maximum and minimum diaphragm thickness measurements and

Table 3. Comparison of first and second measurements by different observers for all measurements

Second measurement	First measurement p value			
p value	OBS-1	OBS-2	OBS-3	OBS-4
OBS-1	0.465	0.212	0.589	0.674
OBS-2	0.355	0.273	0.740	0.688
OBS-3	0.289	0.068	0.688	0.723
OBS-4	0.448	0.045*	0.759	0.812

OBS: indicates observer
*Statistically significant value

for the first and second measurements is given in Table 2. There was a statistically significant difference between the measurements of observer 2 and observer 4 when all DT measurements were compared in the axial and coronal plane ($p = 0.045$) (Table 3).

In intra-observer analysis, ICC scores demonstrated substantial to almost perfect agreement for all measurements (ICC scores range=0.758 - 1) (Table 1). When we analyzed the inter-observer agreement, there was a moderate to almost perfect agreement for each measurement points (ICC score range=0.523 - 0.895). All axial measurement values showed the highest inter-observer agreement (ICC scores were 0.926 and 0.886 for first and second measurements, respectively). There was a substantial agreement between observers for all coronal measurement values with ICC scores of 0.790 (95% CI, 0.684 - 0.870) and 0.776 (95% CI, 0.662 - 0.838) for the first and second measurements, respectively (Table 2).

The maximum inter- and intra-observer agreement for single point DT measurements were found in maximum DT at the level of the origin of the celiac artery and in anterior DT at the level of the upper part of the L1 vertebral body. In the coronal plane, the intra- and inter-observer agreement for DT measurements varied widely for each measurement point (Tables 1 and 2).

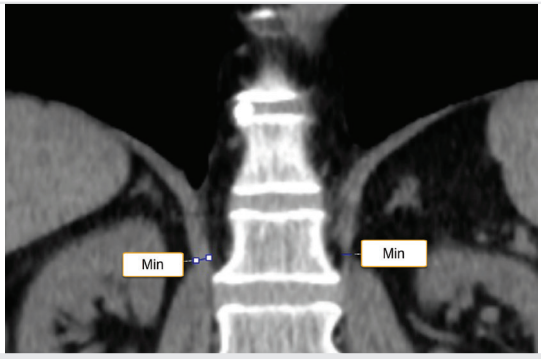

Figure 1. d) Coronal reformatted computed tomography images at the celiac artery level shows maximum and minimum diaphragm thickness measurements and

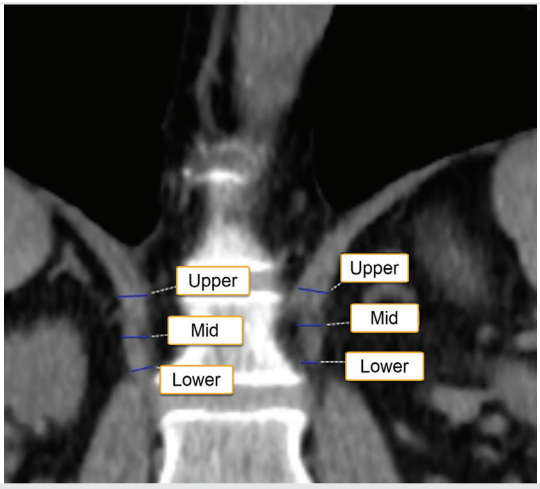

Figure 1. e) Coronal reformatted computed tomography image at the L1 vertebra corpus level shows upper, mid and lower diaphragm thickness measurements

Discussion

This study showed that the assessment of DT by CT has high intra and inter-observer reliability. All DT measurements showed the highest inter-observer agreement at five points (maximum, minimum thickness at the level of celiac artery origin, anterior, middle and posterior thickness at the level of L1 vertebral body) on axial CT images. There was substantial agreement between observers for all measurements on coronal CT images. The maximum inter- and intra-observer agreement for single point DT measurements were found in maximum DT at the level of the origin of the celiac artery and in anterior DT at the level of the upper part of the L1 vertebral body. In the coronal plane, the intra- and intra-observer agreement for DT measurements varied widely for each measurement point. Therefore, we suggest that if DT will be evaluated in the coronal plane, it would be appropriate to evaluate by measuring from all described 5 points.

Despite the increased use of CT for diaphragm evaluation, there is a lack of reference locations for DT measurement in CT. To the best of our knowledge, this is the first study that assessed the intra- and inter-observer agreement for DT measurement in CT and that investigated the best points for measurement in CT. The inter-observer variability in our study varied from moderate to almost perfect according to the measurement points and image plane. Therefore, we can say that the image plane (axial or coronal) and location is very important for DT measurement in CT. In our study, DT measurements were performed from the upper part L1 vertebra corpus level due to blurring of the diaphragm crus by psoas muscle in the middle and lower parts of the L1 vertebra corpus level. Unlike Sukkasem et al. (5), we did not measure DT at the level of superior mesenteric artery (SMA) origin, due to blurring of the diaphragm crus by psoas muscle at SMA origin level in many patients.

In mechanically ventilated patients and patients with paralyzed hemidiaphragm, diaphragmatic dysfunction is an important cause of complications, such as pulmonary atelectasis, infection and hypoxemia. These complications have been shown to correlate with mortality, poor prognosis and significantly higher health costs (6-9). In addition, weakness of the diaphragm is a major cause of difficult weaning from mechanical ventilation (10). Therefore, evaluation of DT and functions is very important. It has been shown that ultrasound (US) measurements of DT have a high degree of reproducibility and decreased DT on ultrasound has been shown to correlate with reduced myocyte volume (1,9-14). Experience is important when performing DT measurement by US. For an inexperienced observer, it may be difficult to accurately measure the DT by UA in incompatible patients (14). Compared to US, CT better depicts the anatomy of the diaphragm and also demonstrates associated lung and mediastinal pathologies (15-18). However, CT is not a suitable method for only assessing DT due to radiation exposure. Therefore, it is more appropriate to assess DT on CT images which were obtained to evaluate lung or mediastinal pathology.

There are only a few studies on DT evaluation in CT (2-5). Sanli et al. (2) found that DT is an important feature in patients with ALS in whom diaphragm pacing system implantation is planned. In their study, a single observer measured DT at the level of thoracic 11-12 vertebra

corpus on coronal images. The location specified for DT measurement is not a specific point and represents a very large area for DT measurement. In addition, they did not specify the CT slice thickness used in the study (2). Lee et al. (3) demonstrated that DT decreased in patients who underwent mechanical-ventilation therapy in CT. In that study, a radiologist measured the DT at the level of the celiac artery by using software on axial and coronal images. However, the number of patients included in the study was thirteen, which is quite small. Also, they did not specify the thickness of the CT slice used in the study (3). Jung and colleagues (4) found that diaphragm volume was decreased in patients with sepsis in CT. In their study, the diaphragm volumes were calculated semi-automatically by a single radiologist. However, in this study, it was not specified in which phase (inspiration-expiration) the CT images were obtained (4). Sukkasem et al. (5) found a high sensitivity and specificity in the differentiation of paralyzed and non-paralyzed hemidiaphragms when they assumed 2.5 mm as the threshold value of a minimum DT on axial images at the level of celiac artery in CT. In their study, all measurements were performed by one observer and the slice thickness of the CT was variable (range: 0.625 to 5 mm) (5). We used a standard 1.5 mm slice thickness in our study. Our results demonstrated a better inter-observer agreement for axial CT images than coronal CT images. This may be due to relatively thick CT slices or due to the natural shape of the diaphragm (the shape of the dome).

Our study also has some limitations. The relatively small sample size is the first one. However, this study was not intended to determine DT values in the population. The aim of this study was to determine the best DT measurement points in CT and the reliability of DT measurement in CT. The retrospective design of the study is the second one. However, these are acceptable limitations due to the lack of similar CT studies.

Conclusion

CT is a reliable tool for DT measurement with excellent intra and inter-observer reliability. This is the first study that reveals the best and reproducible measurement points and plane for DT measurements in CT. All DT measurement values at five identified points on axial CT images showed the highest inter-observer reliability. The most reliable single measurement point in the axial plane was maximum DT at the level of the celiac artery or anterior DT at the level of the upper part of the L1 vertebral body.

Ethics Committee Approval: This retrospective study started after our institutional Pamukkale University Local Ethics Committee approved letter of application (no: 60116787-20/85543).

Informed Consent: Informed consent was not obtained from the patients because of retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.U., P.Ç.; Design - F.U., P.Ç., D.H., E.S.; Supervision - F.U., A.B.Y.; Data Collection and/or Processing - F.U., P.Ç., D.H.,; Analysis and/or Interpretation - F.U., D.H., A.B.Y.; Literature Search – F.U., M.A., E.S.; Writing Manuscript – F.U., D.H., M.A.; Critical Review – D.H., A.B.Y.

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Vitamin D Deficiency Among Female University Students (18 to 25 years) in Spring

Kadın Üniversite Öğrencilerinde Hastalık Riski Düzeyinde Vitamin D Eksikliği

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ABSTRACT

Introduction: In this study, the laboratory results of female university students whose vitamin D levels were requested were reviewed. Thus, it was aimed to determine the levels of vitamin D, as well as to classify it as deficiency, insufficiency, normal and preferred.

Methods: The vitamin D levels of 92 female university students between the ages of 18 and 25 years who admitted to an outpatient clinic between April and May 2017 were retrospectively evaluated. Vitamin D levels were classified according to the criteria of the Endocrine Society. Vitamin D deficiency was accepted in individuals with vitamin D levels below 20 ng/mL. Spearman's correlation test was used for statistical analysis. $p<0.05$ was considered significant.

Results: The mean 25(OH)D level was 17.32±7.18 ng/mL. The frequency of deficiency, insufficiency, normal and desired 25(OH)D levels were 78.3% (72), 14.1% (13), 6.5% (6) and 1.1% (1), respectively.

Conclusion: In this retrospective study in female university students, vitamin D deficiency was found to be frequent. In addition to other trainings, awareness raising and education are compulsory to exclude possible risks of vitamin D deficiency. Additionally, the development of health policies for vitamin D supplementation without laboratory examination in this population would prevent possible skeletal and extra-skeletal problems.

Keywords: 25(OH)D vitamin, insufficiency, adolescents

ÖZ

Amaç: Bu araştırmada, vitamin D düzeyi istenen kadın üniversite öğrencilerinin laboratuvar sonuçları gözden geçirilmiştir. Böylece vitamin D düzeylerini belirlemek, ayrıca eksiklik, yetersizlik, normal ve tercih edilen düzey olarak sınıflandırmak amaçlanmıştır.

Yöntemler: Bu araştırmaya Nisan ve Mayıs 2017 tarihleri arasında polikliniğe başvuran 18-25 yaş arası 92 kadın üniversite öğrencilerinin vitamin D düzeyleri üzerinde retrospektif olarak yapıldı. Vitamin D düzeyleri Endokrin Topluluğu'nun önerilerine göre sınıflandırıldı. Vitamin D düzeyi 20 ng/mL'nin altında olan bireylerde vitamin D eksikliği varlığı kabul edildi. İstatistiksel analiz için Spearman korelasyon testi kullanıldı. $P<0,05$ anlamlı olarak kabul edildi.

Bulgular: 25(OH) D seviyesi ortalama 17,32±7,18 ng/mL idi. Eksik, yetersiz, normal ve arzu edilen vitamin D düzeyi oranları sırasıyla %78,3, %14,1, %6,5 ve %1,1 saptandı.

Sonuç: Kadın üniversite öğrencilerinde yürüttüğümüz bu retrospektif çalışmada; hastalık oluşturma riski düzeyinde olan vitamin D eksikliğinin sık olduğu görüldü. Diğer eğitimlerin yanı sıra D vitamini eksikliğinin olası risklerini dışlamak için bilinçlendirme ve eğitim zorunludur. Ayrıca, bu popülasyonda laboratuvar incelemesi olmaksızın gerekli D vitamini takviyesi için sağlık politikalarının geliştirilmesi olası iskelet ve iskelet dışı problemleri önleyecektir.

Anahtar Kelimeler: 25(OH)D vitamini, yetersizlik, gençler

Introduction

Vitamin D, a hormone called "Pro-survival Molecule" due to its role in the immune system and cell life, is also necessary for the prevention of type 2 diabetes and obesity, which are important problems of current era (1,2). Optimal levels of vitamin D are indispensable for substantial effects on many systems in sensitive populations such as pregnant women, nursing women, children, adolescents, and elder individuals as well as in all stages of human life (3,4). It contributes to the prevention of depression in adolescents and increase in cardiovascular capacity in young adults (5,6).

Vitamin D level below 20 ng/mL is defined as deficiency by Endocrine Society (ES). Its deficiency is associated with increased risk of cancer, especially colorectal (7,8). Hereditary or acquired diseases (e.g., tumor-induced osteomalacia, hyperparathyroidism, granulomatous diseases

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and lymphoma) and insufficiency in organs (e.g., liver, kidney and skin) may decrease vitamin D levels. In addition, using sun cream, pigmentation or aging on the skin affects the synthesis of vitamin D. Also, gastrointestinal diseases adversely effect vitamin D absorption and obesity leads to an increase in its deposition (9). The use of certain drugs such as immunosuppressants, steroids and anticonvulsants also leads to the destruction of vitamin D (10,11). However, there is no enough data on vitamin D status and recommendations for asymptomatic, adolescent female university students who do not have any disease or use drugs that affect vitamin D metabolism (12). While vitamin D deficiency is mainly considered to be a predisposing factor to many diseases, neither adolescent female nor male students are included in the risk group in terms of low vitamin D status and are evaluated in daily practice (12).

In this study, we aimed to determine and classify vitamin D levels as deficiency, insufficiency, normal and preferred in female university students.

Methods

This cross-sectional, retrospective and descriptive study was carried out with the approval of the local ethics committee of the Faculty of Medicine of Trakya University (TÜTF-BAEK 2017/335). Vitamin D levels of female university students between the ages of 18 and 25 years who admitted to Physical Medicine and Rehabilitation Department of Trakya University Hospital between April and May 2017 were examined. Data of students with no systemic or chronic disease, no drug use, and no history of disease that would affect vitamin D metabolism were included. Exclusion criteria were as follows: male gender, drug use, serum 25(OH) D level obtained by a method other than electrochemiluminescence method (Beckman Coulter UniCel DxI 600), and the presence of a known disease. Each student was contacted by phone and interviewed about the style of clothing. Written consent was obtained from each participant. The clothing style was recorded as veiled or unveiled. Serum 25(OH)D levels were classified as deficiency (below 20 ng/mL), insufficiency (21-29 ng/mL), normal (30-39 ng/mL) and preferred (40-60 ng/mL) levels according to most frequently used method by ES (13).

Statistical Analysis

Statistical evaluations were performed using IBM SPSS version 20.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistical methods (frequency, percentage, mean, standard deviation) were used to assess the study data. The relationships between variables were assessed using Spearman's rho correlation test. The significance limit for all statistics was selected as $p<0.05$. Kolmogorov Smirnov test was used to check whether the data were normally distributed. Mann-Whitney U test was used to compare the mean 25(OH)D levels between groups when the data were abnormally distributed. Two-sample Kolmogorov Smirnov Z test was used to make inter-group (unveiled vs. veiled) comparisons of 25(OH)D classifications.

Power Analysis

The post-hoc power of this study was calculated as 100% based on 25(OH)D levels between unveiled and veiled groups (18.25 vs. 13.19) with a standard deviation of 1.67, and with an alpha level of 5%.

Results

Data of 92 female university students were reached. Mean age, height, weight, and body mass index of the students were shown in Table 1. The mean 25(OH)D level was 17.32±7.18 ng/mL. According to ES, 25(OH) D levels were below the normal range in 92.4% (85) participants. The frequency of (all participants with) deficiency, insufficiency, normal and preferred 25(OH)D levels were 78.3% (72), 14.1% (13), 6.5% (6) and 1.1% (1), respectively. The distribution of participants according to clothing style (unveiled and veiled) were 81.5% (75) and 18.5% (17), respectively. There was no statistically significant difference in the distribution of the 25(OH)D Classification groups among the clothing style groups (Table 2). The mean 25(OH)D levels among unveiled and veiled participants were 18.25±0.80 and 13.19±1.67 ng/mL, respectively. There were a statistically significant difference between the groups in terms of mean 25(OH)D levels and negative correlation between 25(OH)D concentrations and veiled dressing style (r=-0,275, p=0,008) (Table 3). There was a statistically significant difference between the groups in terms of negative correlation between the 25 (OH) D levels and 25 (OH) D concentrations and the covered dressing style (r=-0.275, p=0.008) (Table 3).

Table 1. The descriptive statistics and 25(OH)D levels of participants

	n	Minimum	Maximum	Mean	Standard deviation
Age (years)	92	18	24	20.28	1.65
Weight (kg)	92	42.00	77.00	56.83	6.37
Height (m)	92	1.50	1.78	1.64	0.05
BMI (kg/m^2)	92	16.85	27.64	21.02	2.00
25(OH)D (ng/mL)	92	6.77	48.74	17.32	7.18

BMI: body mass index

Table 2. Distribution of 25(OH) D classifications among groups

Groups Unveiled n=75		n (% within groups) Veiled n=17	p value	Total n=92	
25 (OH) D classification	Deficiency	57 (76.0)	15 (88.2)	0.986	72 (78.3)
	Insufficiency	12 (16.0)	1 (5.9)		13 (14.1)
	Normal	5 (6.7)	1 (5.9)		6 (6.5)
	Preferred	1 (1.3)	0 (0)		1 (1.1)

Two-sample Kolmogorov Smirnov Z test

Table 3. 25 (OH) D levels (ng/mL) of participants according to clothing style

Clothing style	n	Minimum-maximum	Mean	Standard deviation	95% CI	p value
Unveiled	75	7.96-48.74	18.25	0.80	16.65-19.85	<0.001
Veiled	17	6.77-34.60	13.19	1.67	9.66-16.72	

CI: confidence interval, Mann-Whitney U test

Discussion

Although veiling is largely accepted as a predisposing factor for vitamin D insufficiency, both the unveiled females in our study and in countries with sufficient sunlight in previous studies did not have desired vitamin D levels (14,15).

The adverse effect of veiling on vitamin D status has led some researchers to assume the possibility of musculoskeletal complaints and low bone mineral density in veiled female with traditional Islamic type of dressing (16). Güzel et al. (16) reported significantly lower serum 25(OH)D levels with a mean of 33.1±16 ng/mL in the veiled women compared with the unveiled, but none of the veiled women had vitamin D insufficiency. Budak et al. (17) reported that there was a statistically significant difference between two groups of female students with different clothing style and the veiled group had vitamin D deficiency with a mean of 6.09±4.7 ng/mL. Tsur et al. (18) reported vitamin D deficiency in 50-100% of ultra-Orthodox young males who wore clothing which covers more then 90% of body. They also found that vitamin D deficiency was strongly associated with the degree of sun exposure. However, some researchers indicates that healthy females, even in countries with enough sunlight, are at risk for osteomalacia due to vitamin D deficiency (14,15). For all these reasons, the female gender in combination with veiling does not suffice for the possibility of vitamin D deficiency. Risks should be assessed comprehensively. In this study, 18.5% of females (17) had veiling, but 92.4% of all females (85) had low vitamin D. Faghih et el. (19) showed "alarmingly prevalent" vitamin D insufficiency and deficiency in Iranian students in a cross-sectional study including 126 female (51.2% and 44%) and 128 male (49.5% and 48%) university students. In our female population, we found that vitamin D deficiency was as high as 78.3%. The frequency of participants with normal and preferred vitamin D were 6.5% and 1.1%, respectively. Consistent with the literature, 25(OH)D levels were below 20 ng/mL in the majority of our participants. Data on vitamin D levels of young adults in our country are limited. The mean 25(OH)D level of 94 young individuals who applied to the hospital was 21.57±11.41 ng/mL by Uçar et al. (20). Hekimsoy et al. (21) reported that 74.9% of adults, especially females (78.7%), living in an urban, off-shore region have 25(OH)D deficiency. In this study, the reasons for mean 25 (OH) D levels below the normal are probably due to (a) in young adults, the lowest vitamin D levels are before summer onset. The data of our study group was obtained between April and May, when vitamin D levels are considered to be lowest. More significant differences between the veiled and unveiled female could possibly be shown if we had assessed data of these variables at a time of highest expected seasonal levels, but we have shown significant negative correlation between 25(OH)D concentrations and veiling even before the start of summer. (b) Edirne where our study was conducted is in the Marmara region of Turkey, latitudes 40°30-42°00 North and 26°00-27°00 East. The average maximum temperatures range between 6.5 °C in winter to 31.7 °C in summer, with annual average of 19.6 °C (22). (c) In our study, the data were assessed in a group of students with approximately 9-month training period, during which they resided in Edirne, which is a non-coastal living area. Therefore, we support the view that university students should be considered as a risky group for vitamin D deficiency regardless of their clothing style and gender,.

The mean 25(OH)D level was 17.32±7.18 ng/mL in our study. Serum vitamin D levels below 20 ng/mL affect skeletal health (8). Although the histopathological findings of osteomalacia in stage 1 are missing, intestinal calcium absorption decreases and loss of bone mineral density develops in this stage, named as subclinical osteomalacia. Indeed, the findings are observed when stage 2 is reached. Thus, no new bone loss occurs in stage 3, but instead histological and clinical findings are clearly identified. For all these reasons, the treatment in the stage with apparent findings does not prevent bone loss. The precautions should be focused in the asymptomatic first stage (23). However, many individuals with subclinical osteomalacia still remain without a laboratory confirmation and the lack of this knowledge leads to delay in taking precautions.

Vitamin D deficiency can contribute to patient burden caused by psychological reasons (depression, schizophrenia), and autoimmune disorders (type 1 diabetes, multiple sclerosis, rheumatoid arthritis), infections, asthma, type 2 diabetes, osteoporosis, osteomalacia and cancer (1,10). On the other hand, vitamin D supplementation is easy, safe and inexpensive (24). Unless vitamin D deficiency is eliminated, individuals are candidates for all these risks independent of deficiency, defined or undefined. However, supplementation is made only in the defined deficiencies. The missing aspect of our study is that we did not investigate parathyroid hormone levels, skin type and eating habits. However, our results are important to create awareness for optimal vitamin D requirements in this population.

Conclusion

In conclusion, our results indicate that vitamin D deficiency is frequently observed in female students. Awareness and training aimed at excluding the possible risks of vitamin D deficiency as well as other trainings are mandatory. Additionally, the development of health policies to provide the necessary vitamin D support in this population without laboratory examination would prevent possible skeletal and extra-skeletal problems.

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Ethics Committee Approval: University of Health Sciences, Trakya University Faculty of Medicine Local Ethics Committee (TÜFT-BAEK 2017/335).

Informed Consent: Retrospective study.

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The Relationship of Lumbar Multifidus Muscle Change to Disc Hernia and Low Back Pain: An Magnetic Resonance Imaging Study

Lomber Multifidus Kas Değişimiyle Disk Hernisi ve Bel Ağrısı Arasındaki İlişki: Bir Manyetik Rezonans Görüntüleme Çalışması

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ABSTRACT

Introduction: Our aim was to evaluate the relationship between lumbar multifidus (LM) muscle atrophy and lumbar disc herniation by magnetic resonance imaging (MRI) findings in patients with low back pain.

Methods: Lumbar MRI of 264 patients aged between 18 and 80 years who had a history of back pain for at least 6 months were evaluated retrospectively for LM muscle atrophy. LM muscle atrophy was evaluated at L4-5 and L5-S1 levels in axial T2-weighted images. The lumbar MRI of the patients were evaluated for LM muscle atrophy and lumbar intervertebral disc herniation. The relationship of LM muscle atrophy to lumbar intervertebral disc herniation and back pain was investigated statistically.

Results: Of 264 (147 female, 117 male) patients, 88 patients (33.3%) had grade 0 atrophy, 135 (51.1%) had grade 1 atrophy and 41 (15.5%) had grade 2 atrophy. The prevalence of LM muscle atrophy was 73.5% in females and 49.8% in males. In 210 of 264 patients, intervertebral disc herniation was detected at any level in the lumbar spine. Of these 210 patients, 150 (71%) had grade 1 and 2 LM muscle atrophy. Spinal canal stenosis, intervertebral disc herniation and nerve root compression were not detected in 54 of 264 patients. Of these 54 patients, 28 had grade 0 atrophy, 23 had grade 1 atrophy and 3 had grade 2 atrophy.

Conclusion: In our study, 9.8% of patients with low back pain had grade 1 and 2 LM muscle atrophy without accompanying spinal canal stenosis, intervertebral disc herniation or nerve root compression. LM muscle atrophy alone may be the cause of low back pain in patients with normal MRI.

Keywords: Low back pain, lumbar disc herniation, magnetic resonance imaging, multifidus muscle

ÖZ

Amaç: Bizim buradaki amacımız kronik bel ağrısı ile lomber multifidus (LM) kas atrofisi arasındaki ilişkiyi manyetik rezonans görüntüleme (MRG) bulguları ile birlikte değerlendirmektir.

Yöntemler: En az 6 aydır sırt ağrısı şikayeti bulunan yaşları 18 ile 80 arasında değişen 264 hastanın lomber MRG'si retrospektif olarak LM kas atrofisi açısından değerlendirildi. LM kas atrofisi aksiyal T2 görüntülemelerde L4-5 ve L5-S1 düzeylerinden değerlendirildi. Hastaların lomber MRG'si LM kas atrofisi ve lomber intervertebral disk herniasyounu açısından değerlendirildi. LM atrofisinin lomber intervertebral disk herniasyounu ve bel ağrısı ile olan ilişkisi istatistiksel olarak araştırıldı.

Bulgular: İki yüz altmış dört (147 kadın, 117 erkek) hastanın lomber MRG'sinde 88 hastada (%33,3) evre 0 atrofi, 135 hastada (%51,1) evre 1 atrofi ve 41 hastada (%15,5) evre 2 atrofi saptandı. Kadınlarda LM atrofisinin sıklığı %73,5 olup erkeklerde %49,8'dir. İki yüz altmış dört hastanın 210'unda lomber vertebralarda herhangi bir seviyede intervertebral disk hernisi saptandı. İki yüz on hastanın 150'sinde (%71) LM kasında evre 1 ve 2 atrofi saptandı. 264 hastanın 54'ünde herhangi bir seviyede intervertebral disk herniasyounu, spinal kanal darlığı ve sinir kökü basısı saptanmadı. Bu 54 hastanın 28'inde evre 0, 23'ünde evre 1 ve 3'ünde evre 2 atrofi saptandı.

Sonuç: Bizim yapmış olduğumuz çalışmada lomber intervertebral disk herniasyonu, spinal kanal stenozu ve sinir kökü basısı mevcut olmayan tek şikayeti bel ağrısı olan %9,8 olguda LM kasında evre 1 ve 2 atrofi saptanmıştır. Tamamen normal MRG'si olan olgularda LM kas atrofisi tek başına bel ağrısının nedeni olabilir.

Anahtar Kelimeler: Bel ağrısı, lomber disk hernisi, manyetik rezonans görüntüleme, multifidus kası

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Introduction

Low back pain (LBP) is a common and often recurrent health problem. Approximately 80% of people have at least one case of LBP during their lifetime. Paraspinal muscles play a significant role in the stability and functional movements of the lumbar spine (1). The lumbar multifidus (LM) muscle is the main stabilizer of the lumbar spine, and is important for spinal motion and stability (2,3). Dysfunction of the LM muscle has been found to be important in chronic and recurrent LBP (4). Chronic diseases and long-term neurological inhibition after trauma may cause muscle atrophy and may lead to the replacement of healthy LM muscle fibrils with adipose tissue (5). Morphological changes of LM muscles in patients with lumbosacral disc herniation have been reported in literature (6-9). Kim et al. (7) demonstrated that the cross-sectional areas of the LM muscle were reduced when the symptom duration was 6 months or longer in case of lumbar disc herniation. In addition, studies in the literature have shown that LBP and paraspinal muscle atrophy have a relationship (3-5). In this study, we evaluated the relationship between lumbar disc herniation and LM muscle atrophy in patients with LBP by using magnetic resonance imaging (MRI).

Methods

The University of Health Sciences, Samsun Training and Research Hospital Ethics Committee approved this study (date: 28.11.2017) and written informed consent was obtained from the participants. In total, 264 patients (range: 18-80 years) who suffered from LBP for six months or longer were retrospectively evaluated. Patients with spinal fractures, malignancy, intraspinal mass, spondylitis, previous surgery or structural deformity were not included the study.

Radiological Protocol and Imaging

The MRI images were obtained with a 1.5 Tesla MAGNETOM Aera® MRI device (Siemens Healthcare, Erlangen, Germany) with a body surface coil. The sequences included sagittal T1-weighted fast spin-echo (FSE) (TR/TE: 475/9.3), T2-weighted FSE (TR/TE: 3790/97) and axial T2-weighted FSE (TR/TE: 4271/108), 280 mm field of view, 180×256 matrix, and 4 mm section thickness, NEX 2.

LM muscle atrophy was assessed at L4-L5 and L5-S1 levels in all patients. LM muscle was evaluated in three grades according to fatty atrophic changes, as grade 0 (fatty atrophy less than 10%), grade 1 (fatty atrophy between 10% and 50%) and grade 2 (fatty atrophy greater than 50%) (Figures 1a, 1b, and 1c) (10,11). Evaluation of the fatty atrophic changes in the LM muscle was performed visually and it was conducted by a single researcher. The fatty infiltration percentages were bilaterally identical in all study groups.

Statistical Analysis

Statistical analysis was performed with SPSS software version 21 (IBM Corporation, Armonk, USA). Kolmogorov-Smirnov test was used to test the normal distribution of data. The results were presented as mean, standard deviation, minimum, maximum, frequency and percentage according to characteristics.

Independent Samples t test or univariate analysis of variance were used for intergroup comparisons. Chi-square test was used for the comparison of nominal variables. $P<0.05$ was considered significant.

Results

Patients

One hundred and forty-seven women (62.3%) and 117 men (37.7%) with LBP were included in the study. The mean age was 47.6±14.0 years (range=18-80 years). The mean age of the patients with and without lumbar intervertebral disc herniation at any level is shown Table 1.

Imaging Results

Two hundred and ten (115 female, 95 male) (79.5%) patients were diagnosed as having lumbar intervertebral disc herniation at any level by MRI. Intervertebral disc herniation was not detected in 54 (32 female, 22 male) of 264 patients. The mean age of the patients with and without lumbar intervertebral disc herniation is shown in Table 1. Of 264 patients, 88 (33.3%) had grade 0 atrophy, 135 (51.1%) had grade 1 atrophy and 41 (15.5%) had grade 2 atrophy. **LM muscle atrophy was 73.5% in women and 49.8% in men (p=0.01).** In addition, LM muscle atrophy was more common in both male and female patients older than 40 years of age (Table 2). All LM muscles were bilaterally atrophic.

Table 1. The mean age of the patients with and without lumbar intervertebral disc herniation

Intervertebral disc herniation at any level	Grade	Female	Male	p
With herniation (n=210)	0 (n=60)	39.7±9.2 (n=26)	37.8±12.1 (n=34)	0.12
	1 (n= 112)	50.1±9.3 (n=62)	49.8±10.6 (n=50)	0.70
	2 (n=38)	64.7±6.6 (n=27)	64±15.7 (n=11)	0.83
Without herniation (n=54)	0 (n=28)	34.1±10.1 (n=13)	32.8±11.1 (n=15)	0.75
	1 (n=23)	43.6±13.3 (n=16)	53.7±14.5 (n=7)	0.19
	2 (n=3)	(n=3)	(n=0)	*

Grade 0 atrophy: fatty infiltration <10%, Grade 1 atrophy: fatty infiltration 10%-50%, Grade 2 atrophy: fatty infiltration >50%

*Comparison cannot be made because there were no male patients in this group

Table 2. Assessment of lumbar multifidus muscle atrophy according to age and sex

LM muscle atrophy					
	<40 years		>40 years		p
Male	Grade 0	31 (75.6%)	Grade 0	18 (23.6%)	<0.001
	Grade 1+2	10 (24.4%)	Grade 1+2	58 (76.4%)	
Female	Grade 0	25 (60.9%)	Grade 0	14 (13.2%)	<0.001
	Grade 1+2	16 (39.1%)	Grade 1+2	92 (86.8%)	

LM: lomber multifidus, grade 0: fatty infiltration <10%, Grade 1: fatty infiltration 10%-50%, Grade 2: fatty infiltration >50%

Disc herniation and LM muscle atrophy at L4-L5 level was significantly associated with age (p=0.001 and p<0.001, respectively), and disc herniation at L5-S1 level was not significantly associated with age (p=0.49). The coexistence of LM muscle atrophy and disc hernia at both levels (LM muscle atrophy and disc herniation at L4-L5 level, p=0.58, LM muscle atrophy and disc herniation at L5-S1 level, p=0.87) and disc herniation at L4-L5 and L5-S1 levels (p=0.36) were not associated with age.

The mean age of patients according to the grade of LM muscle atrophy is given in Table 3. There was a significant difference in the mean age of the patients with respect to different grades of LM muscle atrophy (p<0.01). LM muscle atrophy was found to increase with age.

Of 54 patients without lumbar intervertebral disc herniation, 28 had grade 0 atrophy, 23 had grade 1 atrophy (Figures 2a, b), and 3 had grade 2 atrophy. In addition, there was no spinal stenosis or nerve root compression in MRI of 25 patients with grade 1 or 2 LM muscle atrophy to explain the LBP. Moreover, 9.8% of our patients with LBP had normal MRI except for those with LM muscle atrophy.

Discussion

The LM muscle is an important local stabilizer of the lumbar spine. It can be divided into superficial and deep fibers, each with different functions. Because the superficial and deep parts of the muscle are near the center of lumbar joint rotation, the deep fibers can control intervertebral movement and the superficial fibers are well-suited to control spine orientation (4). Increased fat infiltration of the LM muscle may lead to lumbar dysfunction and this may cause LBP (9,12). Eating

Table 3. The mean age of patients according to the grade of LM muscle atrophy, excluding the patients with disc herniation

LM muscle atrophy	Number of patients	Age (years)	p
Grade 0	28	19.6±10.5	<0.001
Grade 1	23	33.9±14.1	
Grade 2	3	52.6±3.6	

LM: lomber multifidus, Grade 0: fatty atrophy <10%, Grade 1: fatty infiltration 10%-50%, Grade 2: fatty infiltration >50%

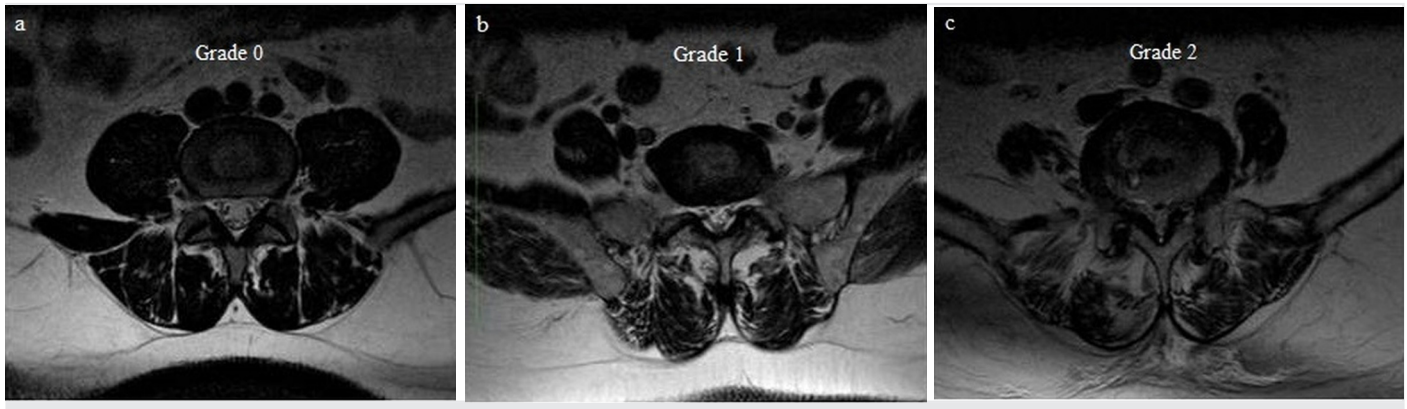

Figure 1. Axial T2-weighted images (WI) showing examples of LM muscle atrophy. Panel (a) shows grade 0 atrophy: fatty infiltration <10%; panel (b) shows grade 1 atrophy: fatty infiltration 10%-50%; and panel (c) shows grade 2 atrophy: fatty infiltration >50%

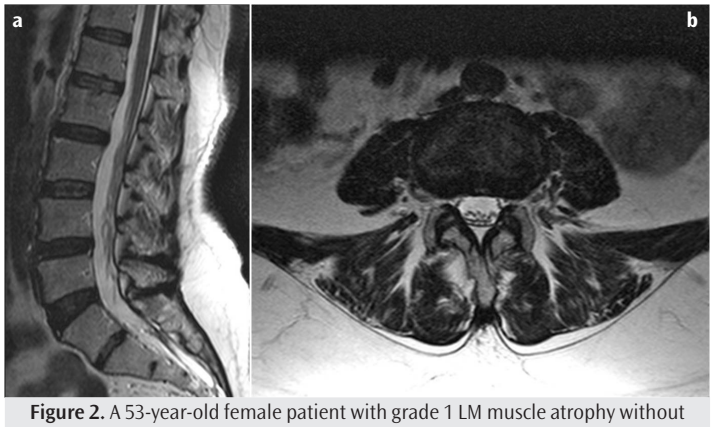

Figure 2. A 53-year-old female patient with grade 1 LM muscle atrophy without disc herniation. Mid-sagittal image (a) showing normal L4-L5 and L5-S1 discs, no significant loss of height or disc herniation. Axial T2-WI (b) showing grade 1 LM muscle atrophy at L4-5 level

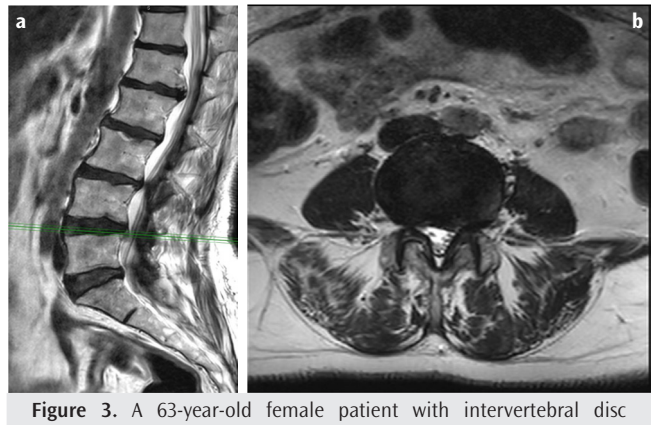

Figure 3. A 63-year-old female patient with intervertebral disc herniation. Mid-sagittal T2-WI (a) showing dehydration and bulging in the discs. Axial T2-WI (b) at L4-L5 level showing left paracentral herniation. Grade 2 atrophy is seen in lomber multifidus muscle

disorders, inactivity, and chronic diseases can cause muscle atrophy. LM muscle atrophy is more frequent in women. In our study, LM muscle atrophy was also found to be more common in women (73.5%). There is decline in muscle mass (approximately 8% for every ten years) after 40 years of age (5). In this study, LM muscle atrophy was found to be more common in females and males older than 40 years ($p<0.001$).

Morphological changes of the LM muscle can be detected by ultrasonography (US), computed tomography (CT) and MRI (4). US is not preferred for LM muscle assessment due to low tissue contrast and limited field of vision. CT can be used to assess LM muscle changes. However, it requires moderate to high radiation and provides less tissue contrast than MRI. MRI is quite successful in showing changes in LM muscle and additional pathologies in patients with LBP. In addition, MRI provides better soft tissue contrast than CT. MRI does not use ionizing radiation or any other type of radiation (4). LM muscle fatty atrophy is visualized as high intensity areas on T2-weighted sequences. Most of the mobility in the lumbar region emerges from L5-S1 and L4-L5 levels (11). Hence, we evaluated these levels to associate LM muscle with LBP.

Patients with LM muscle atrophy have more lumbar disc herniation than patients without atrophy. In our study, we found grade 1 (53.3%) LM muscle atrophy in 112 of the 210 patients and grade 2 (18%) atrophy in 38 patients with lumbar intervertebral disc herniation at any level (Figures 3a, b). We also found that coexistence of disc herniation and LM muscle atrophy at L4-5 levels was associated with age ($p<0.05$). However, coexistence of disc herniation and LM muscle atrophy at L5-S1 level was not associated with age.

Ekin et al. (5) reported that 13% of patients with LBP had LM muscle atrophy without disc herniation. In our study, 23 (42.5 %) of 54 patients had grade 1 LM muscle atrophy and 3 patients (5.5%) had grade 2 atrophy with LBP without lumbar intervertebral disc herniation. In 26 patients (9.8%) with grade 1 and grade 2 LM muscle atrophy, lumbar MRI was normal. We could not find any explanation of the causes for LBP radiologically, except for LM muscle atrophy. We thought that LM muscle atrophy may be the only finding in patients with LBP.

Woodham et al. (4) reported that spinal manipulative therapy in combination with LM muscle stabilization exercises could reduce LM muscle atrophy. In addition, there is evidence that specific exercise protocols, including multifidus activation, reverse the atrophy of the LM muscle and that these exercises can reduce LBP (13).

MRI is a useful imaging method for the detection of LBP etiology. Malignancy, inflammatory diseases, and infectious processes should be considered in patients with LBP (5). It should be noted that LM muscle atrophy could cause LBP in patients, even those with normal lumbar MRI findings. In our study, 9.8% of patients with LBP had grade 1 or 2 LM muscle atrophy without lumbar intervertebral disc herniation, spinal stenosis, or nerve root compression.

Conclusion

The LM muscle is the main stabilizer of the lumbar spine and LM muscle atrophy is closely associated with LBP. In our study, 9.8% of patients with LBP had grade 1 or 2 LM muscle atrophy without intervertebral disc pathologies or nerve root compression. We believe that LM muscle atrophy can be the only finding in patients with LBP.

The University of Health Sciences, Samsun Training and Research Hospital Ethics Committee approved this study (date: 28.11.2017) and

Ethics Committee Approval: The University of Health Sciences, Samsun Training and Research Hospital Ethics Committee approval was received for this study from the ethics committee of the hospital (2017/24).

Informed Consent: Written informed consent was obtained from the participants.

Peer-review: Externally and internally peer-reviewed.

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

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Use of Liquid Phenol for Management of Pilonidal Disease

Pilonidal Hastalığın Tedavisinde Sıvı Fenol Kullanımı

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ABSTRACT

Objective: This study describes the treatment of pilonidal sinus with liquid phenol and reports its short-term results.

Methods: Patients with pilonidal disease were operated under local anesthesia. Primary and secondary pits were excised. Pilonidal cyst cavity was cleaned with brushing, curettage and irrigation. Wounds were left open. Chemical destruction of sinus wall was performed by liquid phenol.

Results: A total of 67 patients with pilonidal sinus were enrolled in this study. The mean duration of surgery was 14.7 minutes. The mean follow-up period was 27.3 months. There were no systemic complications. Two patients had hemorrhage and three patients had wound infection. The wound healing time was 3-6 weeks. Three cases of recurrence were observed in the follow-up period (4.47 %).

Conclusion: Minimally-invasive surgical technique with liquid phenol is a safe and effective outpatient procedure that can be performed under local anesthesia. It has low recurrence and postoperative morbidity rates.

Keywords: Phenol, pilonidal sinus, wound healing

ÖZ

Amaç: Bu çalışma, pilonidal sinüsün sıvı fenol ile tedavisini tanımlayıp kısa dönemdeki sonuçlarını bildirmektedir.

Yöntemler: Pilonidal sinüslü hastalar lokal anestezi altında ameliyat edildiler. Primer ve sekonder delikler eksize edildi. Pilonidal sinüs kavitesi fırçayla temizlendi, kürete edildi ve yıkandı. Yaralar açık bırakıldı. Sinüs duvarı sıvı fenol kullanılarak kimyasal olarak tahrip edildi.

Bulgular: Bu çalışmaya pilonidal sinüsü olan toplam 67 hasta alındı. Ortalama ameliyat süresi 14,7 dakika idi. Ortalama takip süresi 27,3 ay idi. Sistemik komplikasyon görülmedi. İki hastada kanama ve üç hastada yara enfeksiyonu gelişti. Yara iyileşme süresi 3-6 hafta idi. Takip süresinde üç hastada (%4,47) nüks görüldü.

Sonuç: Sıvı fenol ile minimal invaziv cerrahi yöntem, lokal anestezi ile uygulanabilen güvenli ve etkili bir işlemdir. Bu işleminin nüks ve morbidite oranları düşüktür.

Anahtar Kelimeler: Fenol, pilonidal sinüs, yara iyileşmesi

Introduction

Pilonidal disease lesions are usually located beneath the skin in the sacrococcygeal region. Since its first definition, there are discussions about the treatment of pilonidal disease. Surgeons prefer to operate pilonidal diseases with wide excision extending to sacral tissue. Some surgeons leave the wound to secondary healing, some suture midline wounds for primary closure, and others use more complicated procedures, such as different kind of skin flaps designed to protect the incision away from the midline or flatten the natal cleft. Most commonly, such a complicated procedure requires general anesthesia and hospitalization. In addition, antibiotic treatment, drainage and variable use of sutures are also needed. Pilonidal sinus surgeries are notorious for their associated morbidity, recurrence rates, poor cosmetic results and costs (1). This study describes outpatient liquid phenol treatment of pilonidal disease with local anesthesia and reports short-term results of the technique.

Methods

Study Design

From February 2011 to March 2014, a total of 67 patients with symptomatic pilonidal disease were treated in our hospital. The surgeries included acute/ chronic or primary/ recurrent pilonidal diseases. Patients did not receive any premedication or antibiotics, with the exception of medical management in five patients with infected pilonidal disease. Clinical, operative and follow-up data were recorded prospectively. No patients were excluded. The patients were followed-up on a monthly basis and disease recurrence was assessed by office interview and

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physical examination. The interviews were held between September 2012 and December 2014. Recurrence was defined as the return of the symptoms after a recovery period. All patients signed a written informed consent form. The study was performed with the approval of the Ethics Committee of the Hospital (date: 22.11.2010).

Surgical Technique

We performed the same surgical technique in all patients regardless of the forms of the disease. Except for three patients, all participants had many primary and secondary pits and had advanced stage pilonidal disease (Pit is the tissue including the external orifice and the intradermal part of pilonidal disease). Local infiltrative anesthesia with 2 to 6 mL of bupivacaine (Marcaine 0.5%; AstraZeneca Turkey, İstanbul, Turkey) was usually sufficient for pain control regardless of the extent of disease or coexistence of infection. Local anesthesia was performed in all patients who underwent surgery, except six patients who asked for spinal anesthesia. Four of these six patients had an infected pilonidal disease.

Patients were placed in a prone or proctologic position. The buttocks were retracted with adhesive tape. The sacral region was completely shaved and disinfected with povidone iodine solution. The sinus was explored with a metal probe and marked with a marker pen. No blue dye or similar substance was used for demonstration of sinus tracts.

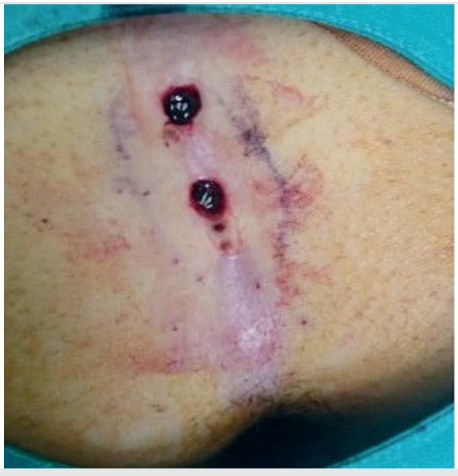

Figure 1. Destruction of sinus wall by liquid phenol

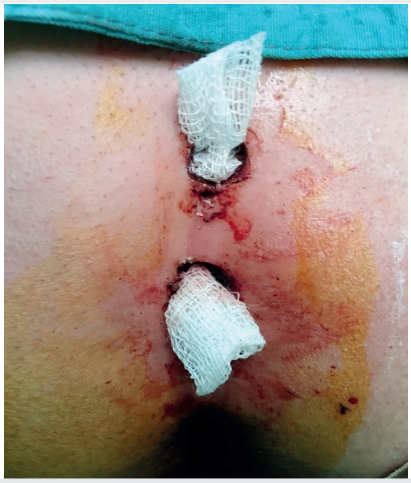

Figure 2. Packing sinus cavity

We made a minimum of two holes by excision of primary or secondary pits. If there were more than two pits, we performed deconstruction with a round cautery blade. Using surgical forceps, aspirator, curette or brush, we cleaned the entire contents of each sinus with debridement. We injected or dripped 3 to 5 mL of 80% liquid phenol into the sinus cavity, waited for 3 to 5 minutes and aspirated and irrigated the cavity with saline solution. The sinus wall was destroyed with this application (Figure 1). The phenol application was repeated if necessary. After careful hemostatic control, we packed the sinus cavity with a thin rolled wet gauze (Figure 2).

Postoperative Care and Follow-up

There was a relatively short period of postoperative follow-up (15 minutes to 2 hours for local anesthesia) before discharge. While antibiotics and analgesics were prescribed for patients with infected pilonidal disease, only analgesics were given to patients with non-infected pilonidal disease. There was no activity restriction such as driving, sitting or walking.

On the first or second postoperative day, we checked the patients for bleeding and other morbidities and instructed relatives of the patients about wound care. Patients were followed weekly until complete wound healing and then re-checked at 6 months (Figure 3).

Statistical Analysis

We evaluated our results in Excel program as percentage and ratio. We did not use any statistical program.

Results

A total of 67 patients with pilonidal sinus were treated by two surgeons between February 2011 and March 2014. Forty-eight patients (71.6%) were male and 19 (28.4%) were female. Male to female ratio was 2.5. The mean age of the patients was 26.8 years (range=16-52). The mean duration of symptoms was 3.8 years (range=2 months-10 years). Forty-six patients had a primary pit in the midline. Of these, 28 had a single

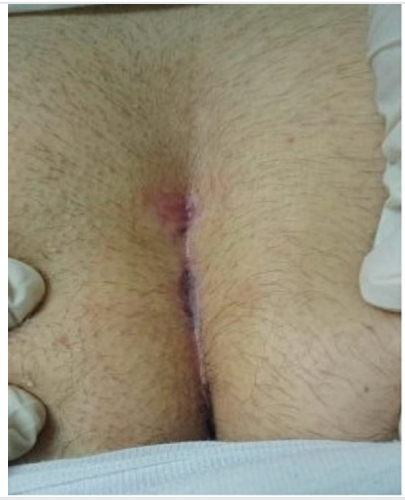

Figure 3. Complete wound healing

pit and 18 had multiple pits. Twenty-one patients had one or more pits extending in the midline. Eight of 67 patients were recurrent pilonidal disease. In our series, 11 patients had acute (infection or abscess) pilonidal disease.

The mean duration of surgery was 14.7 minutes (range=10-22 min), excluding the waiting time of the local anesthesia effect. Local anesthesia prevented pain for 3 to 4 hours after surgery. Three patients required parenteral analgesia in the postoperative period. The time required for wound healing was 3 to 6 weeks (mean 38 days). The mean follow-up was 27.3 months (range=6-37 months). The characteristics and operative findings of patients are shown in Table 1.

There were no systemic complications. Local complications included hemorrhage in two patients (one on the first postoperative day and one on the fourth postoperative day) that were both treated with blood stopper solution (Ankaferd, Immun Pharmaceutical Cosmetics, Ankara, Turkey) and infectious, foul-smelling, yellow-green discharge in three patients which were treated locally with antibiotic solution (Rifocin 125 mg/1.5 mL ampoule, Sanofi Turkey, İstanbul, Turkey). In 22 patients, we used a silver nitrate stick to permanently destroy unwanted granulation tissue.

There were three recurrences (4.4%) during follow-up. All three patients were treated with the same technique. Patient outcomes with liquid phenol treatment are summarized in Table 2.

Table 1. Characteristics and operative findings of patients (n=67)

Age	**16-52 years (mean=26.8)**
Gender	
Male	48 (71.6%)
Female	19 (28.4%)
Duration of symptoms	2 month-10 years (mean=3.8 years)
Presentation of disease	
Acute	11 (16.4%)
Chronic	56 (85.6%)
Previous surgery	8 (11.9%)
Location of pits	
Only midline	46
Midline and lateral	21
Anesthesia	
Local	62
Spinal	5
Mean operative time	14.7 minutes (range=10-27)

Table 2. Outcome of the patients

Follow-up	**27.3 months**
Additional parenteral analgesic requirement	3
Complication	
Infection	3
Bleeding	2
Recurrence	3 (4.4%)
Mean recovery time	38 days

Discussion

Many treatment methods have been reported for pilonidal sinus, but few treatments provide perfect long-term results. There are many stages and clinical presentations of pilonidal disease. Therefore, surgeons should know all available techniques and select the proper treatment according to the extent and severity of the disease and patient preference. Scientific data demonstrate that both open and closed surgical approaches have similar complication rates (2). In addition, both extensive and conservative surgical approaches in pilonidal sinus treatment are associated with similar recurrence rates (3).

Commonly, approximate hospital stay is between 5 and 14 days, and recovery period is between 6 and 10 weeks after total excision and open healing of pilonidal sinuses. In addition, the recurrence rate after surgery is 8% to 21%. Following years, instead of traditional methods, different types of primary closure procedures reduced the recovery time by less than 2 weeks, but hospital stay remained between 7 and 10 days and the recurrence rates ranged from 8% to 30%. These results dominate the use of primary closure procedures. However, one report demonstrated that this group had a recurrence rate of 23% compared to 12% in patients treated with excision and packing procedures (4).

There are still many therapeutic challenges in the treatment of pilonidal disease. Many surgical and non-surgical (conservative) modalities have been proposed. The vast majority of cases are treated surgically. However, there is no consensus on the “ideal” surgical technique. In order to determine an ideal surgical technique, we must first define the ideal management principles. According to accepted principles, some authors have suggested minimally invasive surgery (or non-excisional surgery) for pilonidal disease treatment. Support is growing for this treatment modality.

Phenol-based treatment of pilonidal disease is one of the minimally invasive or non-excisional surgery methods. Khanna and Rombeau (5) classified various treatment strategies for pilonidal disease and described phenol application as an “experimental treatment”. However, according to us and based on other studies, this method is suitable following conservative (non-surgical) treatment (6). Some authors stated that non-excisional therapies, such as phenol application, could result in a high rate of recurrence, especially when patients were not followed up closely (7). Crystalline phenol has been shown to be a successful treatment modality for pilonidal sinus disease, with similar results to other surgical treatments (8). Simple treatment methods for pilonidal disease such as minimally invasive surgery or non-excisional treatments have been associated with less morbidity and low recurrence rates (9-13).

Based on the pathogenesis of acquired foreign body, we described a novel surgical treatment for pilonidal disease that integrates the principles of a minimally invasive operative approach. Our method consists of easy excision of primary and secondary pilonidal pits only, with debridement, sinus cavity cleaning, and chemical cauterization of the sinus cavity and sinus wall with liquid phenol.

The results of surgical treatment for pilonidal disease differ substantially between studies, even among those describing similar techniques.

Postoperative infection and recurrence rates vary between nil and 40% or higher (14,15). In general, the recurrence time for pilonidal disease after surgery is 5 years, but recurrence can be seen in ten years after surgery (16).

Because of the small number of patients in this study and the short follow-up period, definitive conclusions cannot be made. However, our study describes a method of minimally invasive pilonidal disease surgery that resulted in no systemic complications. Three patients had recurrence during the follow-up period. We believe that the cause of recurrence was secondary infection.

Conclusion

Application of liquid phenol application is a simple, safe, and effective outpatient procedure for treating pilonidal sinus disease. It is performed by local anesthesia and can achieve good aesthetic outcomes for both chronic and acute infectious pilonidal disease. In case of recurrence, the same treatment can be repeated without hesitation.

Ethics Committee Approval: The study was performed with the approval of the ethics committee of the hospital.

Informed Consent: All patients signed a written informed consent form.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.Ö., Y.K.; Design - A.Ö., Y.K.; Supervision - A.Ö., Y.K.; Resources - V A.Ö., Y.K.; Data Collection and/or Processing - A.Ö., Y.K.; Analysis and/or Interpretation - A.Ö., Y.K.; Literature Search - A.Ö., Y.K.; Writing Manuscript - A.Ö., Y.K.; Critical Review - A.Ö.

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

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The Effect of Different Hemostatic Systems on the Injury of the External Branch of the Superior Laryngeal Nerve in Thyroidectomy

Tiroidektomi Ameliyatında Kullanılan Farklı Damar Kapama Sistemlerinin Süperior Laringeal Sinirin Eksternal Dalı Yaralanması Üzerine Etkisi

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ABSTRACT

Introduction: Vessel-sealing and ultrasonic coagulation systems that provide rapid and effective hemostasis are widely used in thyroid surgery. An important disadvantage of these systems is injury to the neighboring anatomical structures by thermal damage. However, data on injury to the external branch of the superior laryngeal nerve is limited. The aim of this study was to evaluate the effect of different vascular closure systems on this nerve injury in thyroidectomy.

Methods: A total of 45 patients who underwent thyroidectomy for benign thyroid disease between October 2008 and February 2009 were included in the study. Patients were randomized and divided into three groups, each consisting of 15 patients. Systems used were vessel-sealer in the first group, harmonic scalpel in the second group and conventional suture ligation technique in the third group. Laryngeal electromyography findings and voice complaints were compared.

Results: There were 37 female (82%) and 8 male patients. The mean age was 47.9±11.1 years. Demographic features and surgical procedures were statistically similar in all groups ($p>0.05$). The control electromyography of 84 nerves with preoperatively confirmed normal findings showed that three (10.7%) of the 28 nerves in the vessel sealer group, two (7.1%) of the 28 nerves in the harmonic scalpel group, and two (7.1%) of the 28 nerves in the suture ligation group had complete or partial nerve injury ($p>0.05$). No significant difference was found between the groups in terms of voice complaints ($p>0.05$).

Conclusion: Compared to the conventional suture ligation technique, the use of vascular closure devices does not increase the risk of injury to the external branch of the superior laryngeal nerve.

Keywords: Electromyography, external branch of the superior laryngeal nerve, nerve injury, thyroidectomy, vascular closure systems

ÖZ

Amaç: Hızlı ve etkin bir şekilde hemostaz sağlayan damar mühürleyici ve ultrasonik koagülasyon sistemleri tiroid cerrahisinde yaygın bir şekilde kullanılmaktadır. Bu sistemlerin bir dezavantajı termal hasar yolu ile komşu anatomik yapılara zarar verebilmesidir. Ancak süperior laringeal sinirin eksternal dalının yaralanması ile ilgili veriler sınırlıdır. Bu çalışmanın amacı tiroidektomi ameliyatında kullanılan farklı damar kapama sistemlerinin bu sinir yaralanması üzerine olan etkisini değerlendirmektir.

Yöntemler: Çalışmaya Ekim 2008 ile Şubat 2009 tarihleri arasında selim tiroid hastalığı nedeni ile tiroidektomi ameliyatı yapılan toplam 45 hasta dahil edildi. Hastalar randomize edilerek her biri 15'er hastadan oluşan toplam üç gruba ayrıldı. Ameliyatta ilk grupta damar mühürleyici, ikinci grupta harmonik kesici ve üçüncü grupta klasik sütür ile bağlama tekniği kullanıldı. Hastaların laringeal elektromiyografi bulguları ve ses şikayetleri karşılaştırıldı.

Bulgular: Hastaların 37'si kadın (%82), 8'i erkek ve yaş ortalaması 47,9±11,1 yıl idi. Demografik özellikler ve cerrahi işlemler tüm gruplarda istatistiksel olarak benzer bulundu ($p>0,05$). Ameliyat öncesi elektromiyografi bulguları normal olan 84 adet sinirin kontrol incelemesinde damar mühürleyici grubunda 28 sinirin 3'ünde (%10,7), harmonik kesici grubunda 28 sinirin 2'sinde (%7,1) ve klasik sütür ile bağlama grubunda 28 sinirin 2'sinde (%7,1) tam veya parsiyel sinir yaralanması mevcuttu ($p>0,05$). Ses şikayetleri açısından gruplar arasında anlamlı fark saptanmadı ($p>0,05$).

Sonuç: Damar kapama cihazlarının kullanımı klasik sütür bağlama tekniği ile karşılaştırıldığında, süperior laringeal sinirin eksternal dalı yaralanması riskini artırmadığı görülmektedir.

Anahtar Kelimeler: Elektromiyografi, süperior laringeal sinirin eksternal dalı, sinir yaralanması, tiroidektomi, damar kapama sistemleri

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Introduction

Thyroidectomy requires good anatomic exposure, careful dissection and adequate hemostasis. The principles of safe and effective thyroid surgery were standardized by Emil Theodor Kocher and Theodor Billroth between 1873-1883, and the mortality rate decreased to less than 5% thanks to this technique that reduces bleeding with the ligation of the arteries of the thyroid gland (1). Although this principle is still valid, morbidity rates have decreased with the increase in experience and the use of modern techniques.

In recent years, alternatives to electrocoagulation have been developed and been widely used in thyroid surgery, such as bipolar vessel sealer and ultrasonic cutter, which provide rapid and effective hemostasis (2-4). However, a disadvantage of these systems is that they can damage adjacent anatomical structures by direct or lateral thermal spread (5-7). These adjacent structures include the external branch of the superior laryngeal nerve (EBSLN), and in particular, injury to the nerve occurs during the dissection of the upper pole of the thyroid gland (8,9). EBSLN is the only nerve that innervates the cricothyroid muscle, which is the tensor of the vocal cords, and its injury may lead to hoarseness, loss of strength of the voice, vocal fatigue and inability to achieve high pitch tasks (10,11).

Although there are many studies in the literature on the effect of vascular closure systems on postoperative complications in thyroid surgery, there is little data on EBSLN injury (12). Therefore, in this study, we aimed to evaluate the effect of different vascular closure systems on iatrogenic EBSLN injury in patients undergoing thyroidectomy.

Methods

For the study, ethics committee approval was obtained from İstanbul Cerrahpaşa Faculty of Medicine Ethics Committee of Medical, Surgical and Pharmaceutical Research (numbered 35792). A total of 45 patients who underwent thyroidectomy at the Endocrine Surgery Service of İstanbul Cerrahpaşa Faculty of Medicine between October 2008 and February 2009 were included in the study. Patients who had undergone thyroid surgery, patients with recurrent disease or thyroid cancer, and patients with voice complaints prior to surgery were excluded from the study. All patients were informed about the procedures and written informed consent was obtained.

The patients were randomized by computer program and divided into three equal groups, each consisting of 15 patients. All patients underwent thyroid function tests, thyroid ultrasonography, scintigraphy or fine needle aspiration biopsy for preoperative diagnosis. Standard bilateral thyroidectomy (total, near-total or subtotal) was performed. All patients were operated by the same surgical team. LigaSure Precise® (Valleylab Corp., Tyco Healthcare Group LP, Colorado, US) was used for vascular ligation in the first group (LigaSure group) (Figure 1), Ultracision® harmonic scalpel (Ethicon Endo-Surgery, Ohio, US) in the second group (Ultracision group) (Figure 2), and conventional suture ligation technique in the third group (suture group) (Figure 3).

Under general anesthesia, the patient is placed in a supine position with the neck extended. After proper skin cleansing, Kocher's collar incision was made, and upper and lower skin flaps are developed. Thyrohyoid and sternohyoid muscles are divided vertically in the midline, and surgical field was entered. The right lobe of the thyroid is dissected free from the middle thyroid vein. The superior parathyroid gland is identified and preserved. The superior thyroid artery and vein were dissected and ligated from the level close to the thyroid capsule. In the

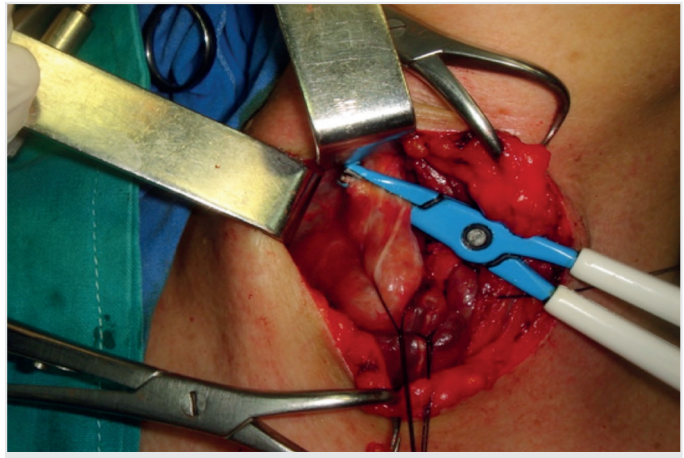

Figure 1. Release of the upper pole of the right thyroid gland with LigaSure Precise®

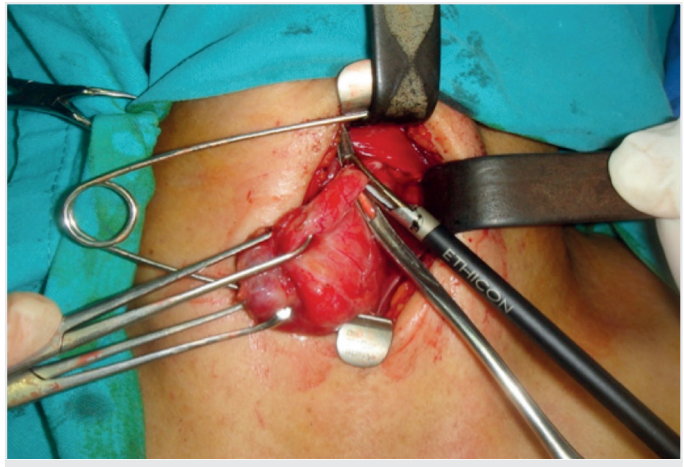

Figure 2. Release of the upper pole of the left thyroid gland with Ultracision®

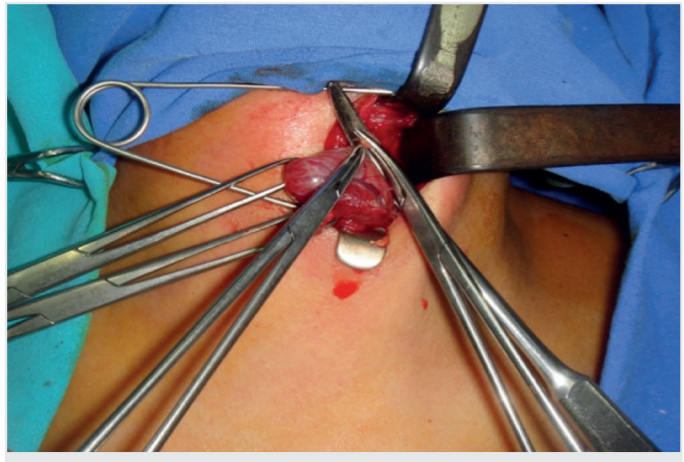

Figure 3. Release of the upper pole of the left thyroid gland with conventional suture ligation technique

meantime, no dissection was performed to reveal the EBSLN. The right recurrent laryngeal nerve was preserved in the anterolateral tracheal area. Subsequently, the inferior pole vessels were ligated by preserving inferior parathyroid gland. The contralateral thyroid lobe is removed in a similar manner. Thyroidectomy procedure is completed with removal of the specimen along with isthmus. Following hemostasis, a drain is placed. The midline muscles and skin are closed and the operation is terminated.

The function of EBSLN was evaluated by laryngeal electromyography (EMG). Recordings were performed before and after surgery in all patients, and bilateral cricothyroid muscles were examined. Preoperative muscular pathologies were investigated and repeated after one month because of abnormal spontaneous discharges. Before the control EMG, the patients were questioned in terms of phonation disorders (hoarseness, loss of strength of the voice, vocal fatigue and inability to achieve high pitch tasks). Neuropack MEB-9102K (Nihon Kohden, Tokyo, Japan) device was used for laryngeal EMG. Recordings were performed with concentric bipolar needle electrodes (size: 50x45 mm) (Myoline, Spes Medica, Italy). The ground electrode was placed in the neck area far from the needle entrance site and the patient was placed in the supine position. Local anesthetic agent or premedication was not performed because the procedure was relatively painless and anesthetic agents could cause artifact in action potentials in the cricothyroid muscle. A needle electrode was inserted into the cricothyroid muscle to evaluate the function of EBSLN. For this purpose, the neck of the patient was extended and the needle electrode was inserted into the cricothyroid membrane in the midline and directed 30-45 degrees laterally (Figure 4). After making sure that the tip of the electrode was in the muscle by phonation, the input activity of the needle, the presence of spontaneous activity at rest, the shape, duration and amplitudes of the motor unit action potentials during active contraction of the muscle were recorded via an audiomonitor and oscilloscope. Wave morphology was evaluated by the same neurologist in terms of EBSLN injury.

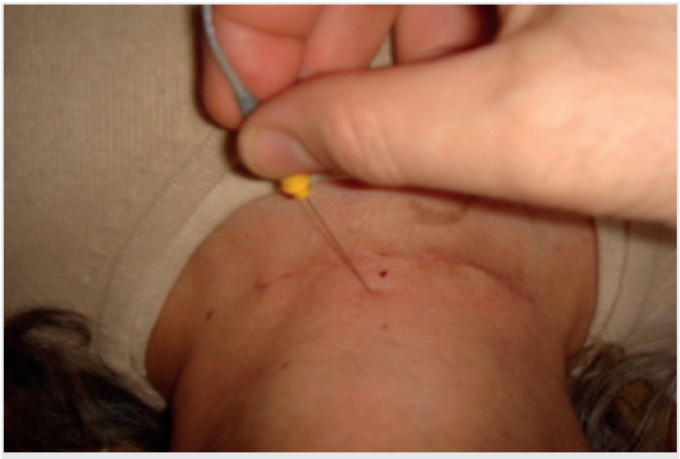

Figure 4. Insertion of the needle electrode into the cricothyroid muscle for the evaluation of superior laryngeal nerve function in a patient who underwent postoperative electromyography

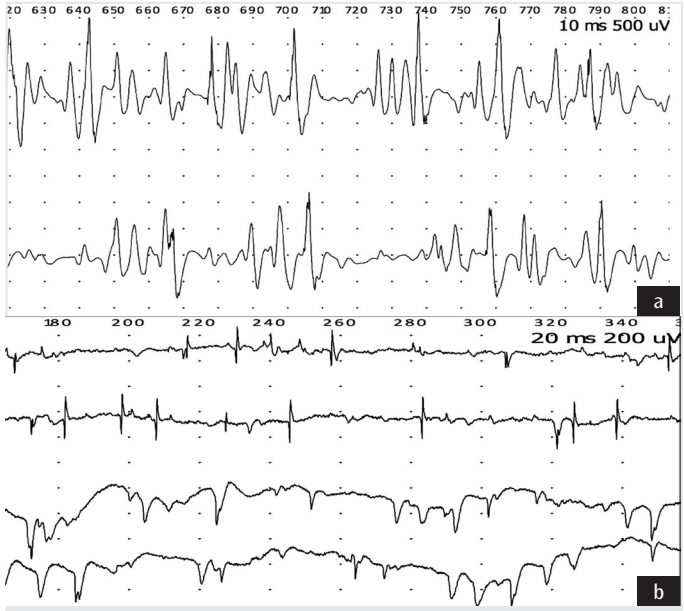

Figure 5. (a) Normal motor unit action potential pattern and (b) denervation pattern in laryngeal cricothyroid muscle electromyography

Demographic data, pathological diagnoses, surgical procedure, EMG findings and vocal complaints that occurred within one month after surgery were recorded in the follow up forms prepared for each patient.

Statistical Analysis

Data were analyzed by using SPSS 11 (SPSS Inc., Chicago, IL, USA), and comparisons between groups were performed using ANOVA post hoc Tukey and chi-square tests. Values were given as mean ± standard deviation. $p<0.05$ was considered statistically significant.

Results

Of the 45 patients included in the study, 37 were female (82%) and 8 were male (18%). The mean age of the patients was 47.9±11 (range: 21-68) years. Demographic data and clinical findings of the patients are presented in Table 1. The rate of female patients was 87% in the LigaSure group and 80% in the Ultracision and suture groups. Histopathological examination revealed no malignancy. There was no statistically significant difference between the demographic data and the surgeries performed ($p>0.05$).

The distribution of preoperative and postoperative EMG findings of groups is given in Table 2. When all groups were taken into account, a total of five EBSLN had pathologic EMG findings in the preoperative period. These were unilateral weak activity in one patient and unilateral activity loss in one patient in the LigaSure group, unilateral activity loss in one patient and unilateral neurogenic involvement in one patient in the Ultracision group, and unilateral weak activity in one patient in the suture group. In addition, unilateral EBSLN function could not be evaluated in one patient in the suture group because of postoperative technical failure. As a result, a total of 84 nerves were included in the statistical analysis, except for one nerve that could not be evaluated due to technical failure and five nerves with preoperative pathology in the EMG.

While EMG findings were normal in the preoperative period, one patient (6.7%) in the LigaSure group and one patient (6.7%) in the suture group had a unilateral cricothyroid muscle denervation pattern

in the postoperative period (Figure 5). In addition, two patients (13.3%) in the LigaSure group, two patients (13.3%) in the Ultracision group and one patient (6.7%) in the suture group developed unilateral weak action potential patterns in the postoperative period despite normal preoperative EMG findings. Denervation and weak action potential patterns were consistent with EBSLN injury (Table 2).

In the postoperative control EMG of 84 EBSLNs with preoperative normal EMG findings, pathology was detected in three of the 28 EBSLN in the LigaSure group, two of the 28 EBSLN in the Ultracision group, and two of the 28 EBSLN in the suture group. There was no statistical difference between the groups (p=0.61) (Table 3).

Postoperative vocal complaints were present in three patients in the LigaSure group, three patients in the Ultracision group and two patients in the suture group. No significant difference was found between groups in terms of vocal complaints (p=0.60) (Table 3).

Discussion

Thyroidectomy is one of the common surgeries in general surgery clinics. Although the principles of surgery have not changed much, new devices have been put into use with developing technology in order to make hemostasis faster and safer. LigaSure®, also known as electrothermal vessel sealing system, is a dissection and coagulation device developed in recent years. Ultracision® provides simultaneous coagulation and cutting with ultrasonic energy, and also has achieved a place in thyroid surgery in a short time (2-4). However, a significant disadvantage of these systems is that they may cause nerve injuries in thyroid surgery depending on the energy used (5-7). The results obtained in this study that specifically analyzed EBSLN injury showed that the use of these vascular closure systems in thyroidectomy surgery did not increase this complication compared to the classical suture ligation technique.

In the studies comparing vascular closure systems and conventional suture technique in the literature, complications such as postoperative

Table 1. The distribution of demographic characteristics and surgical procedures according to groups

	LigaSure group	Ultracision group	Suture group	p
Age, years ± SD	44.4±11	46.6±12	50.8±11	0.4
Female/male, n (%)	13/2 (87)	12/3 (80)	12/3 (80)	0.6
Surgery, n (%)				0.3
Total thyroidectomy	10 (67)	7 (47)	10 (67)	-
Near-total/subtotal thyroidectomy	5 (33)	8 (53)	5 (33)	-

SD: standard deviation

Table 2. Distribution of electromyography findings according to groups

	LigaSure group		Ultracision group		Suture group	
	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative
EMG findings, n (%)*						
Bilaterally normal	13 (87)	11 (73)	13 (87)	12 (80)	14 (93)	11 (73)
Unilateral weak activity	1 (7)	3 (20)	0 (0)	2 (13)	1 (7)	2 (13)
Unilateral activity loss	1 (7)	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)
Unilateral neurogenic involvement	0 (0)	0 (0)	1 (7)	1 (7)	0 (0)	0 (0)
Unilateral denervation	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	1 (7)
Technical failure	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)
EMG findings, n (%)**		26 (87)		27 (90)		
Normal	28 (93)	4 (13)	28 (93)	3 (10)	29 (97)	26 (87)***
Pathologic	2 (7)		2 (7)		1 (3)	3 (10)

EMG: electromyography, *numbers and percentages refer to the number of patients, **numbers and percentages refer to the number of nerves, ***since the nerve could not be found on one side due to technical failure, it was not taken into consideration

Table 3. Comparison of superior laryngeal nerve injury and postoperative phonation disorders among groups

	LigaSure group	Ultracision group	Suture group	p
Surgical SLN injury, SLN number (%)	3/28 (10.7)	2/28 (7.1)	2/28 (7.1)	0.6
Phonation disorder, number of patients	2	2	2	0.6

SLN: superior laryngeal nerve, SD: standard deviation

hemorrhage, recurrence laryngeal nerve injury and hypoparathyroidism were evaluated in the morbidity parameters (3,4,6,7), and data on EBSLN injury were insufficient. The only study in this regard is a prospective randomized study by Arslan et al (12). that compares the harmonic scalpel with conventional suture ligation technique in thyroidectomy. A total of 206 patients were included in this study, and temporary and permanent EBSLN injuries were detected in four (4%) and three (%) patients in the harmonic scalpel group and in two (1.9%) and two patients (1.9%) in the other group, respectively. No significant difference was found between the groups. The authors concluded that the use of a harmonic scalpel was safe for EBSLN injury.

The superior laryngeal nerve is separated from the vagus around the skull base; it descends from the medial of the carotid vessels and is divided into two branches as internal and external at the level of hyoid bone. The internal branch provides the sensation of epiglottis and larynx. EBSLN runs with superior thyroid vessels, and provides motor innervation of the cricothyroid muscle and determines the style of the voice by tensing the vocal cords (8,10,11). As a result of trauma to the nerve, the vocal cord in that side becomes flask and this creates difficulty in phonation. This is especially important for those who practice their profession using their voice continuously (teacher, announcer, singer, etc.) (8,11).

Vocal changes related to EBSLN injury were first described by Moran and Castro (13) in 1951, and later Cernea et al. (14) reported the anatomical classification of the different localizations of the nerve and reported high-risk location for surgical injury. According to this classification, EBSLN has a high-risk of injury during the release of thyroid upper pole. Later, Selvan et al. (15) described a new classification system on the anatomical localization of the nerve accompanied by EMG findings by performing EBSLN monitoring. According to this classification, the area with the highest risk of injury is defined as the area 1 cm superior-posterior of the artery before entering the thyroid gland. In the light of this anatomical information, some authors stated that the EBSLN should be explored directly or by intraoperative nerve monitoring before ligation of the artery (16-18), while others stated that even careful dissection in this area could damage the nerve (15,19). In our study, EBSLN was not visualized in none of the patients as it was thought to increase the risk of nerve injury and dissection was performed close to the capsule of the thyroid gland.

The fact that the vocal change due to EBSLN injury in thyroid surgery is not noticed by both the patient and the surgeon, or the requirement of detailed analyzes in order to reveal the pathology even if it is noticed shows why less attention is given to this nerve than the recurrent laryngeal nerve. Recurrent laryngeal nerve injury can be detected by simple diagnostic methods such as indirect laryngoscopy or fiberoptic examination, EBSLN injury requires the use of more advanced techniques such as laryngeal videostroboscopy, spectrographic analysis and laryngeal EMG. Among these techniques, the more invasive and time-consuming cricothyroid muscle EMG is the most accurate diagnostic method (9,20). The risk of iatrogenic partial or complete EBSLN injury varies between 0% and 6% after thyroidectomy and this rate increases up to 60% when EMG is performed (12,14,18,21).

In our study, the muscle denervation pattern detected in one patient in the LigaSure group and one patient in the suture group in the postoperative period is the most objective finding indicating complete nerve injury. This finding was not observed in any patient in the Ultracision group. In addition, weak action potentials detected in two patients in the LigaSure and Ultracision groups and one patient in the suture group indicate a mild axonal injury, namely partial nerve injury. There was no difference in EBSLN injury when all groups were compared.

Although surgical iatrogenic injuries are the most frequent, viral infectious diseases, trauma, peripheral neuropathies and some motor neuron diseases may cause loss of function in EBSLN and clinical symptoms may be subclinical (22). In our study, preoperative EMG was performed in all patients in order to determine if the postoperative nerve damage was iatrogenic or was an already existing pathological condition. When all study groups were considered, five patients had pathologic EMG findings in the preoperative period. If EMG is not performed in the preoperative period in such patients, the pathological EMG findings that may develop after surgery may lead to misinterpretations in terms of nerve damage. Similarly, the phonation disorders that can occur in patients with no obtained cricothyroid muscle activity in preoperative EMG, but with normal postoperative findings cannot be attributed to EBSLN injury. This suggests that the anatomical localization of the muscle may have changed due to the enlarged thyroid tissue. In our study, the right cricothyroid muscle could not be localized in one patient in the suture group. An additional interpretation could not be made for this muscle, which suggests that anatomical localization is impaired due to the displacement secondary to surgery.

Study Limitations

Lack of EMG control in the long term after surgery is an important limitation of our study. In laryngeal nerve paralysis, EMG findings may vary according to the severity and duration of nerve damage. In neuropraxia, neurogenic involvement that improves in a few weeks and decreased activity are observed in cricothyroid muscle. While denervation and reinnervation are seen in axonotmesis, denervation and loss of motor unit as well as inability to reinnervarte are observed in neurotmesis (23). For this reason, EMG should be repeated after 6 or 12 months in order to monitor the course of axon damage in the nerve and to follow up the reinnervation in cases with mild nerve damage and denervation. In addition, the lack of evaluation of the vocal cords by laryngoscopic examination in order to reveal whether the cause of vocal complaints is EBSLN injury or any recurrent laryngeal nerve injury is another limitation of the study.

Conclusion

In this study, it was found that hemostatic vascular closure systems did not increase the risk of EBSLN injury in thyroid surgery compared to the conventional suture ligation technique. The choice of the device to be used should be made by considering factors such as experience and cost.

Ethics Committee Approval: For the study, ethics committee approval was obtained from İstanbul Cerrahpaşa Faculty of Medicine

Ethics Committee of Medical, Surgical and Pharmaceutical Research (numbered 35792).

Informed Consent: All patients were informed about the procedures and written informed consent was obtained.

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Effects of Systemic Inflammatory Parameters on Mortality in Elderly Patients Admitted to Emergency Department with Abdominal Pain

Acil Servise Karın Ağrısı ile Başvuran Yaşlı Hastalarda Sistemik Enflamatuvar Parametrelerin Mortalite Üzerine Etkisi

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ABSTRACT

Introduction: The aim of this study was to evaluate the prognostic value of systemic inflammatory markers, especially neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) in geriatric patients presenting to the emergency department with abdominal pain.

Methods: This retrospective study was conducted in the Emergency Department of a Training and Research Hospital between 01.08.2016 and 31.12.2016. All patients over 65 years who presented with abdominal pain were included in the study. The demographic data, complete blood count parameters, diagnosis, surgical procedures, [American Society of anesthesiologists (ASA)] scores, length of hospital stay and hospital outcomes were evaluated.

Results: Six hundred and eighty-eight patients were included in the study. Surgery was performed in 77 patients (12%). The most frequent diagnosis was bowel obstruction (n=57, 8.3%). There were statistically significant differences between non-survivors (n=91) and survivors according to 30-day mortality in terms of age, ASA score, lymphocyte count, NLR and PLR ($p<0.001$, $p=0.03$, $p<0.001$, $p<0.001$, 40 $p>0.001$, respectively). There were also statistically significant differences between non-survivors (n=189) and survivors according to 365-day mortality in terms of age, surgery type, lymphocyte count, NLR and PLR ($p<0.001$, $p<0.001$, $p=0.009$, $p=0.01$, $p<0.001$, $p<0.001$ respectively). In the multivariate regression analysis, the clinical feasibility of the laboratory parameters was not significant for both 30 day and 365-day mortality ($p>0.05$).

Conclusion: According to the results of our study, we believe that NLR and PLR values do not have clinical utility as prognostic markers in determining 30-day and 365-day mortality in geriatric patients presenting with abdominal pain.

Keywords: Abdominal pain, elderly, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio

ÖZ

Amaç: Bu çalışmada acil servise karın ağrısı ile başvuran geriatrik hastalarda sistemik Enflamatuvar parametrelerin, özellikle nötrofil-lenfosit oranı (NLO) ve platelet-lenfosit oranlarının (PLO) prognostik değerlerinin değerlendirilmesi amaçlanmıştır.

Yöntemler: Çalışma retrospektif bir çalışma olup, 01.08.2016-31.12.2016 tarihleri arasında bir eğitim ve araştırma hastanesi acil tıp kliniğinde yapıldı. Karın ağrısı şikayeti ile başvuran 65 yaş ve üzeri tüm hastalar çalışmaya dahil edildi. Hastaların demografik verileri, başvuru anında alınan tam kan sayımı parametreleri beyaz kan hücresi sayımı, tanıları, uygulanan cerrahi yöntemler, American Society of Anaesthesiologists (ASA) skorları, hastanede kalış süreleri ve hastane sonlanımları değerlendirildi.

Bulgular: Çalışmaya 688 hasta alındı. Hastaların 77'sine (%12) cerrahi operasyon yapılmıştı. Barsak obstrüksiyonu en sık konulan tanıydı (n=57, %8,3). Yaş, ASA skoru, lenfosit, NLO ve PLO arasında ölen (n=91) ve yaşayan hastalar arasında 30 günlük mortaliteye göre istatistiksel olarak anlamlı fark vardı (sırasıyla $p<0,001$, $p=0,03$, $p<0,001$, $p<0,001$, $p>0,001$). Ayrıca yaş, lenfosit, platelet, ASA skoru, NLO ve PLO arasında ölen (n=189) ve yaşayan hastalar arasında 365 günlük mortaliteye göre istatistiksel olarak anlamlı farklılıklar vardı (sırasıyla $p<0,001$, $p<0,001$, $p=0,009$, $p=0,01$, $p<0,001$, $p<0,001$). Çok değişkenli regresyon analizinde ise, incelenen laboratuvar parametrelerinin klinik uygulanabilirliği, hem 30 günlük hem de 365 günlük mortalite için anlamlı bulunmadı ($p>0,05$).

Sonuç: Çalışmamızın sonuçlarına göre, karın ağrısı ile başvuran geriatrik hastalarda 30 günlük ve 365 günlük mortaliteyi belirlemede, NLO ve PLO değerlerinin prognostik belirteçler olarak klinik faydası olmadığını düşünüyoruz.

Anahtar Kelimeler: Abdominal ağrı, yaşlılık, nötrofil-lenfosit oranı, platelet-lenfosit oranı

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Introduction

Abdominal pain is one of the first most common causes emergency department admissions for the elderly. In emergency cases, the frequency of abdominal pain in the elderly population was found to be between 3% and 13% (1). While two-thirds of elderly patients with abdominal pain are admitted to the hospital, one-fifth of the patients in this group are surgically treated (2). Surgical intervention was found to be twice as high in geriatric patients with abdominal pain compared to younger patients. In addition, in geriatric patients with abdominal pain, the mortality rate is 6 to 8 times higher than other age groups (1). Physical examination findings in patients over 65 years of age who presented to the emergency department with abdominal pain differ from the findings of the young patients. Loss of neural functions in the feeling and assessment of pain, additional diseases, regular or multiple drug use, muscle atrophy are among the causes of this condition (3).

White blood cells (WBC) are regarded as a well-defined inflammatory marker and/or stress indicator. Furthermore, the neutrophil-lymphocyte ratio (NLR) calculated by dividing the absolute neutrophil count by absolute lymphocyte count was introduced as a new indicator for inflammatory response. In terms of mortality, a significant relation is observed between NLR and acute coronary syndrome, non-ST myocardial infarction, ischemic or hemorrhagic strokes, pulmonary embolism, various cancer types. On the other hand, it has been suggested that platelet-lymphocyte ratio (PLR) can be used as a potential indicator for the detection of thrombotic activity or inflammation in various oncological and cardiac diseases (4, 5).

There are a limited number of publications in the literature showing the relationship between subtypes of WBC count (especially NLR) and mortality under severe clinical conditions and major surgical interventions. All these parameters can be examined by a complete blood count, which is common, easy and cost-effective.

In our study, we aimed to investigate the prognostic value of these parameters in the abdominal pain of the geriatric age group with high early and late mortality rates.

Methods

The study was conducted retrospectively between 01.08.2016 and 31.12.2016 following the approval from Ethics Committee of Ankara Keçiören Training and Research Hospital (dated 27.07.2016 and numbered 1193). The study was conducted in accordance with World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013). The study was a retrospective study and the consent was not obtained from the patients.

Patient Selection

The International Classification of Disease-10 codes R10.4 (other and unspecified abdominal pain), K35.9 (acute appendicitis, unspecified), K81.0 (acute cholecystitis), R10.0 (acute abdomen), K56.7 (Ileus, unspecified), K52.8 (other specified non-infective gastroenteritis and colitis) were screened from the hospital automation system (Akgün Health Information Systems®) and the study population consisted of patients who met the inclusion criteria.

The demographic data, the complete blood count parameters such as hemoglobin, platelet count, WBC, NLR, Red Cell Distribution Width, PLR on admission, diagnosis, surgical methods, American Society of anesthesiologists (ASA) score, length of hospital stay, comorbidities, clinical outcomes (discharge or death) were obtained from automation system and patient files. In addition to these data, information about the survival status of the patients were obtained from Mortality Notification System of the Institute of Public Health, the Ministry of Health and recorded. Patients with trauma, history of hematologic disease, myocardial infarction within 30-days, liver failure, immunosuppressive status, and patients under the age of 65 and patients with missing data were excluded from the study.

Laboratory Parameters

Complete blood count is carried out with Abbott Cell-Dyn 3700 (Abbott Laboratories, Illinois, US). NLR was calculated as the ratio of neutrophil count to lymphocyte count, whereas, PLR was calculated as the ratio of platelet count to lymphocyte count.

Statistical Analysis

Data were analyzed using SPSS for Windows 16 package program. Kolmogorov-Smirnov test was performed to examine whether the distribution of discrete or continuous numerical variables complies with normal distribution. Descriptive statistics were shown as median IQR (25-75) for discrete and continuous numeric variables and as number of observations and percentages (%) for quantitative data. Categorical variables were assessed with chi-square test and continuous variables were assessed with Mann-Whitney U test. Multivariate Binary Logistic Regression analysis was used to determine adjusted odds ratio (OR) for 30-day and 1-year mortalities. The OR was presented at the confidence interval of 95% [95% confidence intervals (CI)]. $p<0.05$ was accepted as statistically significant.

Results

Eight hundred and seventy-six patients were included in this study. After excluding 188 patients who met the exclusion criteria or with missing data, 688 patients were included in the study. Of the included patients, 381 (55.4%) were female and 307 (44.6%) were male. The median age was 76 (IQR 70-82) years. The demographic data of the patients are given in Table 1.

Statistical analyzes comparing the demographic and clinical characteristics of non-survivors and survivors according to 30-day mortality are shown in Table 2. There was a statistically significant difference in terms of age, ASA score, lymphocyte count, NLR and PLR. Statistical analyzes comparing the demographic and clinical characteristics of non-survivors and survivors according to 365-day mortality are shown in Table 3. There was a statistically significant difference in terms of age, lymphocyte count, platelet count, ASA score, NLR and PLR.

The multivariate logistic regression analysis was performed with various variables to determine 30-day mortality. Age, NLR, PLR and lymphocyte

count were included into the established multivariate model that was found acceptable by Hosmer-Lemeshow test, it was noted that it would not be clinically feasible to determine 30-day mortality in consideration of these parameters. It was also considered that the age variable had no effect when the width of CI was evaluated independently from the significance on the table (p<0.001, OR=1.1 95% CI: 1.06-1.14) (Table 4).

The multivariate logistic regression analysis was performed with various variables to determine 365-day mortality. Age, NLR, PLR, lymphocyte count, platelet count and hemoglobin level were included into the established multivariate model that was found acceptable by Hosmer-Lemeshow test, it was deemed clinically inapplicable to determine 365-day mortality in consideration of these parameters. Similar to 30-day mortality, though the age variable was statistically feasible, it did not have any effect when the width of CI was considered independently from the significance on the table (p<0.001, OR=1.081 95% CI: 1.053-1.11) (Table 5).

Table 1. Demographic and clinical characteristics of patients

Gender, n (%)	
Female	381 (55.4)
Age, years (IQR 25-75%)	76 (70-82)
Comorbid Diseases, n (%)	
Diabetes Mellitus	198 (28.8)
Hypertension	168 (24.4)
Coronary Artery Disease	204 (29.7)
Congestive Heart Failure	81 (11.8)
Chronic Renal Failure	28 (4.1)
Malignancy	35 (5.1)
Surgically treated patients, n (%)	77 (12)
Type of Surgery, n (%)	
Midline Laparotomy	35 (45)
Appendectomy	13 (17.3)
Hernia Repair	6 (8)
Cholecystectomy	10 (12)
Perforation Repair	8 (11)
Colectomy	5 (6.7)
ASA Score	
ASA-2	53 (7.7)
ASA-3	609 (88.5)
ASA-4	26 (3.8)
ASA-5	0 (0)
Diagnosis n (%)	
Ileus	57 (8.3)
Acute cholecystitis	39 (5.7)
Acute appendicitis	19 (2.8)
Perforation	9 (1.3)
Hernia	4 (0.6)
Acute pancreatitis	45 (6.5)
Mesenteric ischemia	7 (1)
Other	508 (73.8)
Laboratory results (IQR%25-75)	
WBC (/µL)	11100 (8400-14875)
Hemoglobin (g/dL)	13.1 (11.8-14.3)
Platelet count (x10^3)	232 (188-295)
Neutrophil (/µL)	8450 (5800-12100)
Lymphocyte (/µL)	1400 (900-2100)
NLR	5.73 (3.22-11.0)
PLR	161.4 (104.95-255.41)
30-day mortality, n (%)	91 (13.7)
365-day mortalit, n (%)	189 (27.5)
Length of hospital stay (IQR 25-75%)	6 (4-10)

ASA: American Society of Anesthesiology, WBC: white blood cells, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio

Discussion

Regarding the values of routine complete blood count parameters (especially NLR and PLR values) in predicting 30-day and 365-day mortality in elderly patients admitted to emergency department with abdominal pain, we underline two significant results considering the results obtained by our study. First of all, in terms of NLR and PLR values standing as the primary research subjects in our study in accordance with 30-day and 365-day mortality estimates, the NLR and PLR values of non-survivors according to 30-day and 365-day mortality were statistically

Table 2. Clinical characteristics of patients according to 30-day mortality

	Non-survivor	Survivor	p
Gender, n (%)			
Female	51 (56)	330 (55.3)	0.8
Male	40 (44)	267 (44.7)	
Age, years (IQR 25-75%)	82 (76-85)	75 (69-81)	<0.001
Surgically treated patients, n (%)	13(14.3)	64 (10.7)	0.3
ASA Score			
ASA 2	1 (1.1)	52 (8.7)	0.03
ASA 3	86 (94.5)	523 (87.6)	
ASA 4	4 (4.4)	22	
*Laboratory (IQR%25-75)			
WBC (/µL)	11400 (8500-14300)	11100 (8500-14300)	0.3
Hemoglobin (g/dL)	13 (11.7-13.9)	13.2 (11.8-14.3)	0.1
Platelet count (x103)	242 (187-318)	231 (188-292)	0.5
Neutrophil (/µL)	9100 (5800-14200)	8400 (5800-11700)	0.1
Lymphocyte (/µL)	1000 (700-1700)	1500 (1000-2200)	<0.001
NLR	9.2 (4.4-16.1)	5.5 (3.1-10.1)	<0.001
PLR	234.2 (139-349.5)	154.1 (101.7-238)	<0.001

ASA: American Society of Anesthesiologists, WBC: white blood cells, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio *Mann-Whitney U test

Table 3. Clinical characteristics of patients according to 365-day mortality

	Non-survivor	Survivor	p
Gender, n (%)			
Female	97 (25.5)	284 (74.5)	0.1
Male	92 (30)	215 (70)	
Age, years (IQR 25-75%)	80 (74-85)	75 (69-81)	<0.001
Surgically treated patients, n (%)	26(33.8)	51 (66.2)	0.1
ASA Score			
ASA 2	6 (11.3)	47 (88.7)	0.01
ASA 3	178 (29.2)	431 (70.8)	
ASA 4	5 (19.2)	21 (80.8)	
*Laboratory (IQR%25-75)			
WBC (/µL)	11200 (8500-15000)	11000 (8400-14300)	0.3
Hemoglobin (g/dL)	12.5 (11.4-13.9)	13.3 (12-14.3)	<0.001
Platelet count (x103)	249 (188-338)	229 (188-282)	0.009
Neutrophil (/µL)	8900 (6200- 13250)	8300 (5600-11700)	0.081
Lymphocyte (/µL)	1100 (725-1675)	1500 (1100-2200)	<0.001
NLR	7.6 (3.7-13.8)	5.4 (3.0-10)	<0.001
PLR	230 (133-330)	148 (101-222)	<0.001

ASA: American Society of Anesthesiologists, WBC: white blood cells, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio *Mann-Whitney U test
RDW: Red Cell Distribution Width, MPV: Mean Platelet Volume

Table 4. Multivariate logistic regression analysis to predict 30-day mortality

	Wald	p	OR (95% CI)
Age	30.7	<0.001	1.1 (1.06-1.14)
NLR	7.6	0.006	1.004 (1.001-1.074)
PLR	1.1	0.2	1.001 (0.9-1.003)
Lymphocyte	1.9	0.1	1.0 (1.0-1.0)

OR: odds ratio, CI: confidence intervals, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio

Table 5. Multivariate logistic regression to predict 365-day mortality

	Wald	p	OR (95% CI)
Age	34.087	<0.001	1.081 (1.053-1.11)
NLR	1.562	0.2	1.018 (0.99-1.04)
PLR	2.506	0.1	1.002 (1.00-1.004)
Lymphocyte	0.88	0.3	1.0 (1.00-1.00)
Hemoglobin	3.457	0.06	0.92 (0.84-1.004)
Platelet count	1.427	0.2	1.00 (1.00-1.00)

OR: odds ratio, CI: confidence intervals, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio

significantly higher compared to survivors (p<0.001). Although the OR values for mortality estimation were statistically significant with multivariate logistic regression analysis, we believe that the use of OR in clinical practice is not feasible since the OR values are very close to 1. In addition, the secondary important outcome is that hemoglobin levels were lower in non-survivors according to 365-day mortality compared to survivors, however, platelet counts were higher. However, both statistically and clinically significant results were not achieved in multivariate logistic regression analyzes in terms of determining clinical utility in a similar way. In conclusion, we found that these parameters were not useful in predicting mortality in abdominal pain in the elderly patients.

Physiological changes occur in many systems in the elderly. In addition to these, additional age-related diseases, changes due to previous operations, multidrug use, weakening of the immune system lead to the detection of diseases at a more advanced stage, thus causing an increase in mortality rate (6, 7). Abdominal pain in the geriatric age group is one of the most complicated and time-consuming causes of emergency department admissions. Due to obscure findings of physical examinations and low sensitivity of laboratory results in geriatric patients, new indicators are still needed for the diagnosis of acute abdomen in elderly. In the literature, NLR and PLR values, which are regarded as the indicators of diagnosis and predictors of mortality, were higher in certain diseases in all age groups in comparison to the control group (8). Furthermore, this rate was found to be higher in geriatric patient groups (9). Yavuz et al. (10) suggested that preoperative NLR value is a significant data that is easily performed and used for the diagnosis of appendicitis. However, there are numerous studies expressing that these parameters are insufficient as mortality predictor. In the study of Emektar et al. (11) regarding the importance of NLR and PLR values to predict mortality in patients over 65 years of age with femoral fractures, they found that NLR and PLR values were higher in survivors compared to non-survivors. However, the authors noted that the relevant values were not reliable for clinical use when both sensitivity and specifity were considered. In the study conducted by Vaughan-Shaw et al. (12), the relationship between mortality rates and NLR values of patients who underwent abdominal surgery were

examined, and 30-day and 365-day mortality rates were calculated as 31% and 50%, respectively. In our study, 30-day and 365-day mortality rates were 13.7% and 27.5%, respectively. Contrary to Vaughan-Shaw et al. (12), our study population included both patients with and without surgery, therefore this could be one of the reasons of lower mortality rates in our study.

Although our results are not consistent with the current literature, NLR and PLR values were insufficient to predict mortality in patients over 65 years of age with abdominal pain. Therefore, the clinical use of NLR and PLR are poor indicators as a prognostic marker. However, we would encounter these ratios as subtitle in the scoring systems to be developed in accordance with future researches.

Study Limitations

The retrospective and single-centered structure of this study is the main limitation. The postoperative hematological parameters of the patients were not analyzed. The inflammatory process is a complex process, therefore, other inflammatory parameters were excluded from the scope of this study.

Conclusion

It is important to identify new risk factors in predicting mortality in geriatric patients with abdominal pain. NLR and PLR are cost-effective, universally accessible and routine parameters that can be easily and rapidly measured without additional cost. According to our study results, we believe that NLR and PLR values are not clinically applicable as a prognostic value in predicting 30-day and 365-day mortality rates in the elderly patients with abdominal pain.

Ethics Committee Approval: The study was conducted retrospectively between 01.08.2016 and 31.12.2016 following the approval from Ethics Committee of Ankara Keçiören Training and Research Hospital (dated 27.07.2016 and numbered 1193).

Informed Consent: The study was a retrospective study and the consent was not obtained from the patients.

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Evaluation of Receptor Activator of Nuclear Factor Kappa-B Ligand and Osteoprotegerin Levels in Patients with Type 2 Diabetes Mellitus Treated with Oral Anti-diabetics (Sulfonylurea and Metformin) or Insulin: Bone Tissue Perspective

Oral Anti-diyabetik (Sülfonilüre, Metformin) ya da İnsülin ile Tedavi Edilen Tip 2 Diabetes Mellituslu Hastalarda Reseptör Aktivatör Nükleer Kappa-B Ligandı, Osteoprotegerin Düzeylerinin Kemik Dokusu Yönünden İncelenmesi

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ABSTRACT

Introduction: We aimed to investigate the levels of receptor activator of nuclear factor kappa-b ligand (RANKL) and osteoprotegerin (OPG) in order to evaluate the negative effects of type 2 diabetes mellitus on bone health and their relationship to the severity of disease based on the treatment. We also evaluated the relationship between hemoglobin A1c (HbA1c), parathyroid hormone (PTH) and bone specific alkaline phosphatase (BAP) levels and RANKL and OPG levels.

Methods: The study group consisted of 19 volunteers (15 females and 4 males) and 65 patients with type 2 diabetes mellitus (49 females and 16 males). In order to evaluate the relationship between the treatment and the disease severity, the patient group was divided into two subgroups: patients treated with oral anti-diabetics (OAD) (sulfonylurea and metformin) or insulin. The levels of glucose, calcium, phosphorus, HbA1c, BAP, PTH, RANKL and OPG were compared.

Results: The RANKL and OPG levels of patients treated with insulin were significantly higher than the control group (p=0.008, p=0.033, respectively). However, there was no significant difference in the OAD group for both parameters (p=0.1, p=0.46, respectively). There was no significant difference between the groups in terms of PTH and BAP levels (p=0.97, p=0.66, respectively).

Conclusion: We believe that RANKL and OPG levels are higher in patients with poor glycemic control and that they may be indicators of disease severity.

Keywords: Insulin, metformin, osteoprotegerin, receptor activator of nuclear factor kappa-B ligand, sulfonylurea, type 2 diabetes mellitus

ÖZ

Amaç: Tip 2 diabetes mellitusun kemik sağlığı üzerindeki olumsuz etkilerini, tedaviye bağlı olarak hastalığın ağırlığı ile olan ilişkisini değerlendirmek için reseptör aktivatör nükleer kappa-B ligandı (RANKL) ile birlikte osteoprotegerin (OPG) düzeylerini araştırdık. Ayrıca hemoglobin A1c (HbA1c), paratiroid hormon (PTH), kemik spesifik alkalen fosfataz (BAP) düzeylerinin hem RANKL hem de OPG düzeyleri ile ilişkisini değerlendirmektir.

Yöntemler: Çalışma grubunu 19 gönüllüden (15 kadın, 4 erkek), hasta grubunu ise 65 tip 2 diabetes mellituslu (49 kadın, 16 erkek) hasta oluşturdu. Uygulanan tedavi ile hastalık ağırlığı arasındaki ilişkiyi değerlendirebilmek için hasta grubu oral anti diyabetik alan (sülfonilüre, metformin) ya da insülin kullanalar olmak üzere iki alt gruba ayrılarak glikoz, kalsiyum, fosfor, HbA1c, BAP, PTH, RANKL, OPG düzeyleri karşılaştırıldı.

Bulgular: Kan glikozun insülinle düzenlenen tip 2 diabetes mellituslu hastaların hem RANKL hem de OPG düzeyleri kontrol grubuna göre anlamlı derecede yüksekti (sırasıyla; p=0,008, p=0,033). Ancak OAD grubu her iki parametre için de farklı değildi (sırasıyla; p=0,1, p=0,46,). Gruplar arasında PTH ve BAP değerleri açısından anlamlı fark yoktu (sırasıyla; p=0,97, p=0,66).

Sonuç: RANKL ile OPG düzeylerinin, glisemik kontrol bozukluğu olan hastalarda daha yüksek olduğunu, hastalık şiddetinin birer göstergesi olabileceğini düşünüyoruz.

Anahtar Kelimeler: İnsülin, metformin, osteorrotegerin, reseptör kapa-B faktörü receptör etkinleştirici bağlayıcı, sülfonilüre, tip 2 diabetes mellitus

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Introduction

The World Health Organization reported that the number of patients with diabetes mellitus (DM) reached 422 million in 2014 (1). The prevalence of DM is reported to be between 4.75% and 11.3% in Turkey (2). The vast majority of DM patients (90-95%) suffer from type 2 DM (DM2) (3). DM2 is a disease characterized by hyperinsulinemia and hyperglycemia due to insulin resistance. Hyperglycemia has an important role in the pathogenesis of diabetic complications, because it increases protein glycation and allows gradual accumulation of advanced glycation end products (AGEs) in body tissues. Recent studies suggest that the interaction of AGEs with receptor for AGEs alter intracellular signaling, gene expression, and release pro-inflammatory molecules and free radicals that contribute to the pathology of DM complications (4). These factors lead to a condition characterized by low-level chronic inflammation. By observing immune responses, changes can be observed in many parameters that affect the skeletal system, such as osteocalcin, vitamin-D, adiponectin, leptin, receptor activator of nuclear factor kappa-B ligand (RANKL) and osteoprotegerin (OPG) (5). More commonly recognized DM complications, such as macro vascular disease, retinopathy, nephropathy and neuropathy, DM-related bone disease, have gained growing attention (6). DM2-related bone disease is a latent, progressive pathological process and is difficult to diagnose using routine clinical, radiological and biochemical methods. Although DM2 patients have normal or increased bone density, their bone turnover is reduced and bone quality is altered. Consequently, DM2 patients experience increased bone fragility and fracture risk (7,8). The relationship between DM and bone disease has been known for more than 50 years, and both diseases share similar socio-economic characteristics (9). To clarify this relationship, many different parameters have been evaluated. RANKL and OPG are parameters that are currently being studied to reveal the mechanisms of this relationship.

Bone tissue is constantly renewed due to mechanical stress and hormonal changes. This regeneration depends on the balance between osteoclastic bone resorption and osteoblastic bone formation. RANKL is expressed by osteoblasts and other bone marrow stromal cells, whereas RANK is expressed by other members of pre-osteoclast and osteoclast cells (10). RANKL-RANK interactions activate transcription factors that regulate osteoclastogenesis, resulting in osteoclast assembly and differentiation. OPG, synthesized by osteoblasts, inhibits this interaction by acting as a trap receptor for RANKL and prevents proliferation, differentiation and bone resorption activity of osteoclasts (11,12). OPG is a glycoprotein synthesized by the TNFRSF11B gene located on chromosome 8 and is a cytokine receptor from the tumor necrosis factor receptor superfamily (13). Recent studies suggest that RANKL and OPG have a central role in DM-related bone pathologies (14-17).

Parathyroid hormone (PTH) is a calciotropic hormone that promotes bone resorption and inhibits calcium extraction to maintain adequate levels of plasma calcium. PTH exerts its effects on bone density thorough osteoclasts. Interestingly, PTH receptors are located on osteoblasts. Communication between osteoblasts and osteoclasts is thought to be mediated by RANKL (18). Therefore, if the relationships between RANKL, RANK, OPG and DM-related bone diseases are to be examined, then PTH is an important parameter to be considered. Bone specific alkaline phosphatase (BAP) (EC 3.1.3.1) is considered to be a highly specific marker of bone-forming activity of osteoblasts (19). Previous studies have suggested that serum BAP is useful in predicting bone mineral density (20, 21). Therefore, PTH and BAP are useful tools to evaluate the bone turnover process.

Several factors such as hemoglobin A1c (HbA1c), duration of disease, presence of certain complications and treatment method used, have been used to determine the severity of DM. Some of these variables can be used together to calculate the disease severity index (22). We determined the severity of the disease based on whether patients use insulin treatment because it is a simpler and easier method to determine poor glycemic control. We divided the patient group into two subgroups, as patients receiving oral anti-diabetic (OAD) treatment and patients receiving insulin treatment. If glycemic control could not be achieved with OAD treatments, it was replaced with insulin treatments. Therefore, insulin therapy is an indicator of poor glycemic control and can be used as a marker for assessing the severity of the disease.

In this study, we aimed to investigate the levels of RANKL and OPG in patients and healthy subjects to evaluate the negative effects of DM on bone health, as well as their relationship with the severity of disease, which is determined by the treatment method. In addition, we assessed the relationship between HbA1c, PTH, and BAP levels and RANKL and OPG levels.

Methods

Patient Characteristics

This study was conducted at the Medical Biochemistry Laboratory and Internal Medicine Clinic of İstanbul Haseki Training and Research Hospital in İstanbul. Sixty-five (49 female, 16 male) DM2 patients volunteered for this study and the control group (15 female, 4 male) was selected from healthy volunteers. Consent was obtained from all participants. All the patients were surveyed regarding age, gender, time of diagnosis, smoking history and the presence of other systemic diseases. Patients who suffered from cardiac problems, advanced nephropathy, neurologic symptoms, smoking history and other osteoporotic problems, were excluded from the study. The patients were grouped based on the clinical evaluations by internal medicine specialists. The patient group was divided into two subgroups: patients receiving OAD treatment (OAD group) (n=25) and patients receiving insulin treatment (insulin group) (n=40).

Patients in the OAD group were treated with metformin (biguanide group OAD) or gliclazide (sulfonylurea group OAD) or a combination of two drugs. The insulin group used only insulin preparations and did not receive any additional OAD as part of the treatment protocol. The treatment protocols were unchanged for the participants in the patient groups in the last six months. After the patients fasted for 12-16 hours, venous blood samples were collected in gel-separated tubes without anticoagulants to determine levels of RANKL, OPG and other routine parameters. Serum samples were stored at -20 °C for approximately 10-90 days after incubating for 30 minutes, and centrifugation at 1500 × g for 10 minutes. Additionally, whole blood samples were collected in EDTA tubes for HbA1c analysis.

Analytical Methods

A solid-phase sandwich immunoassay ELISA kit with a reported linearity range of 31-4000 pg/mL, within-run CV of 2.7% and within-day CV of 4.5% (Assaybiotech Omnikine S-RANKL ok-0161, Assaybiotech, California, USA) was used to analyze RANKL levels. Also, another solid-phase sandwich immunoassay ELISA kit with a reported linearity range of 93.7-6000 pg/mL, within-run CV of 2.2% and within-day CV of 4.3% (Immunoleader Boster Technology OPG ek0480, Boster, California, USA) was used to analyze OPG levels.

RANKL and OPG units: RANKL and OPG are not routinely measured, and therefore, there is currently no consensus on units of measurement. Currently, studies report their levels in ng/mL for convenience. Therefore, we reported our results using ng/mL.

HbA1c levels were measured using an HPLC technique via Arkray Adams A1c analyzer (Arkray, Kyoto, Japan). Glucose, calcium, and phosphorus levels were measured via AU2700 (Beckman Coulter, California, USA) biochemistry auto-analyzer. PTH and BAP levels were measured via DXI-800 auto-analyzer (Beckman Coulter, California, USA).

Statistical Analysis

The results were analyzed using the SPSS version 17 (Statistical Package for Social Sciences) software package (IBM, New York, USA). Mean, standard deviation (SD), minimum and maximum values were calculated. Quantitative data were conformed to normal distribution characteristics and groups were treated independently. ANOVA was applied to determine the differences in the measured parameters between the groups with 95% confidence interval. The probability value (p) was set at < 0.05. The post-hoc Tukey HSD test was applied for pairwise group comparisons. The power was calculated using the PASS 12 package program (NCSS, Utah, USA).

Ethical Approval

The authors declare that all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Ethics Committee of İstanbul HasekiTraining and Research Hospital (decision number: 24.09.2014/181).

Results

Descriptive Analysis

Age, gender, duration of disease and duration of insulin use for each group are shown in Table 1. In all groups, gender and age had no significant effect on the parameters measured (p=0.256, p=0.313, respectively). The duration of diabetes was significantly different between OAD and insulin groups ($p<0.05$).

The power of this study was calculated as 0.9017 using the ANOVA test procedure for all pairs with the current design containing three groups (one control group and two patient groups). The type I error (α value or p-value) was set to 0.05. The power of present study was calculated from the results after the study was completed.

Descriptive statistics of the measured parameters are shown in Table 2.

The bar graphs illustrate the distribution of RANKL and OPG levels between the groups (Figures 1, 2).

The power of this study with the current design, which contains three groups (one control group and two patient groups) was calculated to be 0.88 using ANOVA for all pairs. The type I error (α value or p value) was set at 0.05. The power of the present study was computed from the results after the study was completed.

Group Comparisons

The three groups (control, OAD and insulin) were compared using ANOVA and differences in RANKL and OPG levels were observed between the groups (p=0.004, p=0.031, respectively). In order to understand the causes of these differences, we performed a post-hoc Tukey test and observed significant differences between the control group and the insulin group both in RANKL and OPG levels (p=0.008, p=0.033, respectively). However, OAD group did not differ significantly for both parameters (p=0.1, and p=0.46, respectively). As expected, HbA1c levels were significantly different between all groups ($p<0.001$). There was no significant difference between the groups in terms of PTH and BAP levels (p=0.97, p=0.66, respectively).

Correlation of the Evaluated Parameters

A weak but significantly positive correlation was detected between RANKL and OPG levels by Pearson correlation analysis ($r=0.264$, $p<0.05$). Moreover, OPG levels had weak but significantly positive relationships

Table 1. The mean age, duration of diabetes mellitus and insulin use for each group

	Control group (n=19)		OAD group (n=25)		Insulin group (n=40)		p
Age, years	52±6.75		54.6±6.38		54.7±5.81		0.256
Duration of diabetes mellitus, years	-		7.4±5.08		11.2±5.7		-
Duration of insulin use, years	-				5.1±3.9		-
Gender	n	%	n	%	n	%	0.313
Female	15	78	19	76	30	75	-
Male	4	22	6	24	10	25	-

OAD: oral anti-diabetics

with HbA1c levels and DM2 duration (r=0.230, p<0.05 and r=0.242, p<0.05).

Discussion

DM2 is a multi-systemic disease that affects bone tissue by impairing the quality of bone structure and thus increasing bone fragility. The bone is traditionally considered a rigid organ that protects visceral organs and supports the body. However, we now know that bone is a complex and highly active, metabolic and endocrine organ. Energy hemostasis affects bone metabolism and osteocalcin has been reported to mediate this interaction (23). Insulin induces the production of under-carboxylated osteocalcin through post-translational modification in osteoblasts. Increased under-carboxylated osteocalcin stimulates pancreatic insulin synthesis and secretion, while increasing adiponectin production in fat tissues, thereby altering energy expenditure by increasing tissue sensitivity to insulin production (24). Adiponectin is a major cytokine secreted from adipocytes during glucose metabolism (25). Adiponectin, which is known to increase insulin sensitivity, has been reported to decrease in patients with DM. Previous studies have shown that adiponectin negatively affects bone formation (26). Increased RANKL and OPG levels have been reported in DM2 (14-17,27). Adiponectin is reported to be the main regulator of OPG levels. There is a negative correlation between adiponectin and OPG levels. In previous studies on OPG and RANKL, experiments have been frequently performed in patients with advanced-stage DM with microvascular pathology or in patients with cardiovascular system problems (28,29).

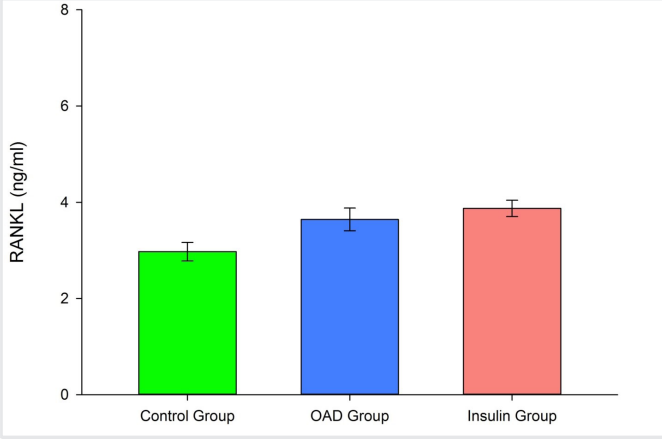

Figure 1. The average Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL) concentration in each group. The error bars represent the standard errors of the respective groups (Control Group: 0.19, OAG Group: 0.23, Insulin Group: 0.16).

OAD: oral anti-diabetics, RANKL: receptor activator of nuclear factor kappa-b ligand

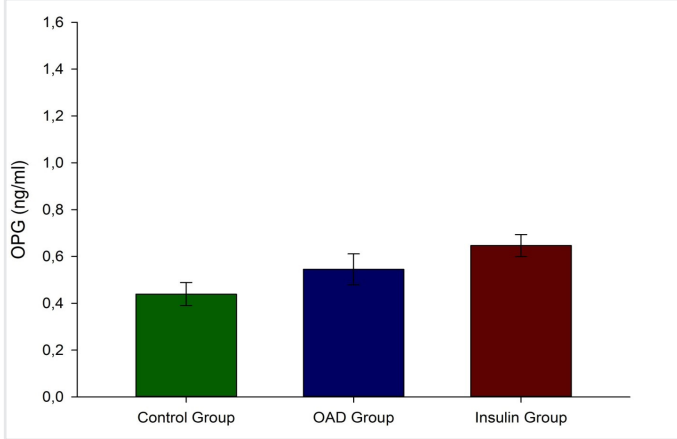

Figure 2. The average Osteoprotegerin (OPG) concentration in each group. The error bars represent the standard errors of the respective groups (Control Group: 0.049, OAD Group: 0.065, Insulin Group: 0.040).

OAD: oral anti-diabetics, OPG: osteoprotegerin

Table 2. The mean, standard deviation, minimum and maximum levels of glucose, hemoglobin A1c, calcium, phosphorus, parathyroid hormone, bone specific alkaline phosphatase, receptor activator of nuclear factor kappa-B ligand and osteoprotegerin and the number of subjects (n) in each group. P values obtained from group comparison statistics for each parameter are given in the table

		Glucose (mg/dL)	HbA1c (%)	Ca (mg/dL)	P (mg/dL)	PTH (pg/mL)	BAP (µg/L)	RANKL (ng/mL)	OPG (ng/mL)
Control group (n=19)	Mean	95	5.3	10	3.9	31.1	12.5	2.97	0.43
	Min	76	4.7	9	2.5	6.3	6.3	1.67	0.09
	Max	125	5.7	11.4	5.1	59.2	30.6	5	0.79
	SD	11.4	0.26	0.54	0.63	13.1	5.9	0.83	0.21
OAD group (n=25)	Mean	135	7.2	10.1	4.4	29.7	13.5	3.64	0.54
	Min	82	5.9	9.4	3.5	15	5.6	2.06	0.01
	Max	251	10.2	11.3	5.7	53	30.6	6.78	1.31
	SD	43.5	1.05	0.46	0.54	11.1	5.17	1.18	0.32
Insulin group (n=40)	Mean	181	8.9	10.2	4.1	31.8	12.7	3.87	0.64
	Min	95	6.5	9.5	3.2	10.6	6	2.06	0.18
	Max	360	13	11.4	5	80.7	27.8	7.42	1.4
	SD	67.5	1.64	0.46	0.43	15.6	4.44	1.06	0.29
p		<0.001	<0.001	0.091	0.07	0.975	0.66	0.031	0.004

Min: minimum, Max: maximum, SD: standard deviation, HbA1c: hemoglobin A1c, OAD: oral anti-diabetics, Ca: calcium, P: phosphorus, PTH: parathyroid hormone, BAP: bone specific alkaline phosphatase, RANKL: receptor activator of nuclear factor kappa-b ligand, OPG: osteoprotegerin

The unique aspect of our study was the investigation of RANKL and OPG levels in patients with DM2 using either OAD or insulin and in healthy volunteers (control group). In addition, we aimed to investigate the effects of disease severity on these parameters.

The RANKL and OPG levels in patients with DM2 using insulin were significantly higher than the control group. Previous studies have reported a higher risk of fracture in DM2 patients treated with insulin (30,31). Yaturu et al. (32) reported increased OPG levels in DM2 patients. The same study indicated a significant relationship between OPG levels and insulin resistance indicators, such as fasting glucose. In our study, the RANKL and OPG levels of patients with DM2 who regulated blood glucose with insulin were significantly higher than the control group and the relationship between OPG levels and HbA1c levels as well as DM2 duration was another finding suggesting that OPG levels were affected by disease severity. Gaudio et al. (33) reported that plasma OPG levels in DM2 patients were significantly higher in the patient groups than in the control group, but the RANKL levels were significantly lower. Additionally, we found that both OPG and RANKL levels were significantly higher in DM2 patients in our study. However, Gaudio et al. (33) performed their study in postmenopausal women and did not conduct treatment-related evaluation of the data between the groups. In support of this information, Jung et al. (34) reported that RANKL levels may be related to the gender of patients.

One of the limitations of our study was the dominance of female gender in all three groups. In such a case, the effect of menopause must be taken into consideration. However, the groups did not differ in terms of age.

Insulin is a metabolic hormone with strong effects on glucose and lipid metabolism. Insulin for DM2 treatment, in addition to its glycemic effects, also acts as an anabolic agent in bone and induces anti-inflammatory effects (35). It has been reported that C-reactive protein levels are lowered in DM2 patients who are being treated with insulin, although the glucose levels remain unchanged (36). On the other hand, previous observations indicate that fracture risk is higher in DM2 patients treated with insulin (31,37). The anti-inflammatory properties of insulin are insufficient to limit the chronic, low-grade inflammation, which is the underlying pathology of DM2. However, insulin treatments are derived from synthetic preparations, and although they treat hyperglycemia, they may not adequately prevent the negative effects due to low levels of chronic inflammation caused by DM2. On the other hand, the adverse effects of DM2 on bone health may cumulatively increase over time. The duration of DM2 was longer in insulin group than in OAD group. Therefore, the adverse effects that are not observed in the early stages may become more pronounced in the advanced stages. Significant differences between the control group and the insulin group may be indicative of this phenomenon.

There were no significant differences between the control group and the OAD group in terms of OPG and RANKL levels. OADs are agents that induce endogenous insulin production. Sulfonylureas are the most common prescribed drug for DM2 treatment. There are studies reporting that sulfonylureas reduce fracture risk in DM2 patients (37,38). Except for enhancing pancreatic insulin secretion, sulfonylureas have no known, direct effect on bone tissue. However, the effects of metformin are not limited to insulin release alone. Metformin improves glucose metabolism via activation of adenosine monophosphate (AMP)-activated protein kinases (AMPK), which is also expressed in bone tissue (39). AMPK is a potential stimulator of bone marrow progenitor cells. Stimulation of AMPK results in the activation of osteoblasts in cell culture experiments (40). Shao et al. (41) reported that high serum glucose levels could suppress osteoblast proliferation, but the use of metformin ameliorated this suppression. In addition, metformin is also effective in correcting the pathology underlying diabetes. Zhen et al. (42) reported that treatment with metformin significantly decreases reactive oxygen species production. Experimental studies have implicated that metformin limits osteoclast activity through RANKL (43). Zinman et al. (44) concluded that a combination of metformin and sulfonylurea reduces levels of carboxy-terminal collagen crosslinks that serve as a marker for bone resorption in DM2 patients. Therefore, the OADs evaluated in our study may act as bone preservatives (45). It has been reported that the risk of osteoporotic bone fracture is higher in patients with DM2 who received insulin monotherapy than those receiving combined therapy (46). In our study, the absence of significant differences in RANKL and OPG levels between the OAD group and the control group may be related to the protective effects of OADs.

Conclusion

We did not observe significant differences between the groups in terms of Ca, P, PTH and BAP levels. In their meta-analysis, Linde et al. (47) reported that PTH and BAP levels did not significantly differ between diabetic and control groups. Our findings were consistent with their data. We have demonstrated that there are no differences between OAD and insulin groups.

Although impairment of bone quality could not be conclusively demonstrated with routine assay parameters in terms of Ca, P, PTH and BAP levels, and was not related to disease severity in this study, OPG presented correlation with HbA1c and DM duration. So, OPG may confer benefits in determining and monitoring the DM2-dependent bone quality deterioration, and risk stratification of fractures in diabetics. Additional larger (blood pressure and anthropometric measurements, questioning life-style conditions, other routine laboratory parameters) and long-term (monitoring the individuals) studies are needed to accumulate sufficient data on this subject.

Ethics Committee Approval: This study was approved by the Ethics Committee of İstanbul Haseki Training and Research Hospital (decision number: 24.09.2014/181).

Informed Consent: Consent was obtained from all participants.

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Obesity Status of University Employees and Associated Factors: Turkey-2015

Bir Üniversite Çalışanlarının Obezite Durumu ve İlişkili Etmenler: Türkiye-2015

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ABSTRACT

Introduction: Obesity is a growing public health concern with increasing prevalence in the world. It is aimed to investigate the relationship between socio-demographic features, dietary habits, physical activity level and body mass index (BMI) of the officers and contracted staff between the ages of 18-64 working in administrative units of a university and some factors affecting these relationships.

Methods: The population of this cross-sectional study consists of officers and contracted staff working at a university campus. The data were evaluated by using SPSS 20.0 program. Descriptive statistics, chi-square test and three different binary logistic regressions were conducted in the study.

Results: The mean age of the employees was 36.4±8.23 years and 67.4% of the participants were male. Half of the participants had bad dietary habits, 15.8% of the participants were physically "active" and 68.2% were overweight and obese. Being male and the importance given to health (good and above) were found to be protective factors against the bad dietary habits. Low educational level (1.88) and being married (2.32) were the risk factors for bad dietary habits. Males (2.78), married participants (1.94), participants with good and above importance given to health (1.62) and participants working as a contracted staff (2.68) were found to be physically more active. Being male (2.16), having children (2.32) and being physically active (1.78) were found to be risk factors for overweight and obesity.

Conclusion: It was found that there were differences in nutrition, physical activity and obesity among university staff with different social structures. Awareness of BMI values, healthy nutrition and physical activity levels should be increased in the intervention programs aimed at changing the lifestyle of individuals working in different statuses in the society.

Keywords: Adult, body mass index, dietary habits, obesity, physical activity

ÖZ

Amaç: Dünyada giderek artış gösteren obezite büyüyen bir halk sağlığı endişesidir. Bir üniversitede, 18-64 yaş arasında idari teşkilatta görev yapan memurların ve sözleşmeli olarak çalışan personelin sosyo-demografik özellikleri, beslenme alışkanlıkları, fiziksel aktivite düzeyi ve vücut kitle indeksi (VKİ) ile aralarındaki ilişkiyi etkileyen bazı faktörlerin incelenmesi amaçlanmıştır.

Yöntemler: Kesitsel araştırmanın evrenini, bir üniversiteye bağlı yerleşkelerde memur ve sözleşmeli personel olarak çalışan katılımcılar oluşturmaktadır. Verilerin değerlendirilmesi SPSS 20.0 programı kullanılarak yapılmıştır. Çalışmada tanımlayıcı istatistikler, ki-kare testi ve üç farklı ikili lojistik yapılmıştır.

Bulgular: Çalışanların yaş ortalaması 36,4±8,23 yıl olup %67,4'ü erkektir. Katılımcıların yarısı kötü beslenme alışkanlıklarına sahiptir ve katılımcıların %15,8'i fiziksel olarak "aktif" ve %68,2'si kilolu ve şişman olarak bulunmuştur. Erkek olmak ve sağlığa verilen önem (iyi ve üzeri) kötü beslenme alışkanlıklarına karşı koruyucu faktör olarak bulunmuştur. Düşük eğitim düzeyi (1,88) ve evli olma (2,32) durumu kötü beslenme alışkanlıkları için risk faktörleridir. Erkekler (2,78), evliler (1,94), sağlığa verilen önem (iyi ve üzeri-1,62) ve sözleşmeli işçi (2,68) olarak çalışanlar fiziksel olarak daha aktif olduğu bulunmuştur. Erkek cinsiyet (2,16), çocuk sahibi olma (2,32) ve fiziksel aktif olma (1,78) durumu aşırı kiloluluk ve obezite için risk faktörleri olarak bulunmuştur.

Sonuç: Aynı üniversitede çalışan farklı sosyal yapıya sahip olan kesimler arasında beslenme, fiziksel aktivite ve şişmanlık düzeylerinin farklılıkları olduğu bulunmuştur. Toplum içindeki farklı statülerde çalışan bireylerin yaşam tarzının değiştirilmesine yönelik müdahale programlarında, VKİ değerleri konusunda bilinçlendirilmesi, sağlıklı beslenme ve fiziksel aktivite düzeylerinin artırılması gerekmektedir.

Anahtar Kelimeler: Yetişkin, beden kitle indeksi, beslenme alışkanlıkları, şişmanlık, fiziksel aktivite

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Introduction

In recent years, being overweight and obesity have been emphasized as global public health problems with dramatic increase, Unhealthy nutrition and physical inactivity are among the leading causes of obesity. One of the main causes of obesity is the energy imbalance between calorie intake from foods and calories consumed. Globally, the food choice of people is becoming more unhealthy and there is an increase in physical inactivity due to increased consumption of high-fat foods, widespread consumption of fast-food products, rapid urbanization, changes in transport and working styles depending on the developments in technological areas, increase in the sedentary lifestyle arisen from the increase in the level of welfare, and lack of supportive environments. These changes provide a basis for various health problems, especially obesity (1).

According to the World Health Organization (WHO), obesity is a health problem defined as "abnormal or excessive fat accumulation that may impair health" (1). Overweight and obesity are among the important risk factors for most of the Non-Communicable Diseases (NCD) such as diabetes, cardiovascular diseases and cancer (2). According to the report of Turkey Nutrition and Health Survey (TNHS) in 2010, it was stated that prevalence of mild obesity among adults in Turkey was 34.6% and prevalence rate of obesity was 30.3% (3).

WHO states that physical inactivity is the fourth most important cause for mortality at the global level and that it has caused the death of approximately 3.2 million people worldwide. According to WHO, one out of every four adults are not active enough and this situation is similar in Turkey (4). In the TNHS report, it was stated that the percentage of people who did not exercise was 71.9%. There are approximately seven out of every ten men and eight out of every ten women who do not exercise throughout the country (3). Several studies have found a positive correlation between regular physical activity and prevention, treatment and management of NCD. In addition, the role of regular physical activity in improving health and preventing diseases has been inclusively described (5,6). Regular physical activity facilitates body weight management by providing energy expenditure (2). It is possible to reduce the incidence of NCD by modifying and managing behavioral risk factors that cause obesity and physical inactivity (7,8). In physically active adults, the risk of premature death can be reduced by 20-30%, and the risk of NCD development can be reduced by up to 50% (9,10).

In Turkey, as in the world, an unhealthy diet and physical inactivity are among the preventable, serious risk factors for obesity and associated NCDs (1). Based on the fact that working style is an important factor in the development of obesity, it is necessary to determine the dietary habits, physical activity levels and body mass index (BMI) values of the employees working at desk jobs and contracted staff, and to provide evidences based on the situation determination researches for these interventions. Conducting studies on obesity status of people from different segments of society and examining these studies especially in terms of the relationship between dietary habits and physical activity level are important for the evaluation of the obesity prevention and control program.

Methods

The necessary institutional permission was obtained from the Ahi Evran University Ethics Committee rectorate and ethical approval (number:78968926-051/1076-5326) was received from the university ethics committee within the scope of ethical conduct in human research number 20696. Employees have been informed about the content and purpose of the research and it was stated that participation in the survey was based on voluntariness, and verbal consent of the employees were taken.

This cross-sectional study was conducted with a total of 554 employees working at the administrative units of a university as officer and contracted staff. The working statuses used in the study were defined as "officer is a person who performs fundamental and continuous public services by the state" and contracted staff was defined as "a person working in temporary jobs in the required areas in case of a vacant position" (11).

The data of the study were collected by visiting 9 different campuses in November-December 2015. The sample was not selected. The university employee or contracted personnel between 18-64 years of age who were at least primary school graduates were tried to be reached and the rate of participation was 85.9%. Some of the employees did not participate in the study due to reasons such as being on leave, attending meetings, being on maternity leave and working hard due to supervision. The data obtained from the participants were collected by observation-based survey technique.

The dependent variables of the study were the dietary habits questionnaire scoring form, the International Physical Activity Questionnaire-Short Form (IPAQ-Short Form) and WHO adult BMI classification. The independent variables of the study were age, gender, educational status, employment type, marital status, parental status, family type, dietitian application status and level of importance given to health. Physical activity level and dietary habits were also evaluated as independent variables.

Dietary Habits Questionnaire: A questionnaire on dietary habits scoring developed by Arslan et al. (12) was used in the evaluation of dietary habits. When the person gets a healthy, adequate and balanced nutrition, she/he gets full score from the questionnaire. The total number of questions in the questionnaire is nine and the maximum score is 62. Dietary habits were evaluated as poor (<35 points), moderate (35-48 points) and good (> 48 points) in accordance with the scores obtained from the questionnaire (12).

IPAQ-Short Form: The validity and reliability of the IPAQ Short Form has been validated in Turkish. The questionnaire used in this study includes questions about the types (walking, moderate-intensity and vigorous-intensity physical activities and sitting duration), duration and frequency of physical activity performed at least 10 minutes in the "last seven days". In order to determine the level of physical activity, the total score is calculated by converting the data of walking, moderate-intensity and vigorous-intensity physical activities into metabolic equivalent of task (MET) values. According to the total score obtained, the physical activity levels of the participants were determined and classified as MET-

min/ week. Physical activity levels were evaluated in three categories: inactive (<600 MET-min / week), minimally active (600-3000 MET-min / week) and active (> 3000 MET-min / week (13).

Anthropometric Measurements: Body weights and statuses of the employees participated in the study were measured by visiting the relevant department in the first hours of morning shift. The anthropometric measurements were made in the Frankfort plane through the SECA 813 electronic scale (Seca, Hamburg, Germany) and the SECA 213 stadiometer (Seca, Hamburg, Germany), with their underwear, by taking off their clothes and shoes. All measurements were made by the same researcher in an appropriate room, preferably with an empty stomach. The BMIs of the employees were calculated from the equation [body weight/stature (m^2)] (14). BMI results were evaluated according to the WHO classification of adult BMI. Participants were classified as underweight (<18.5), normal (18.5-24.9), overweight (25.0-29.9) and obese (≥30.0) according to the values obtained from the BMI equation (15).

Statistical Analysis

Statistical analyzes were assessed by using the SPSS 20 (SPSS 20.0 for Windows, Chicago, III. USA) package program. Descriptive statistics (percent distribution, mean and standard deviation, median, distribution interval) were used in the summary of the data and chi-square test was used for comparing the groups. For multivariate analysis, the possible factors identified with univariate analyses were further entered into the logistic regression (Forward Stepwise-Likelihood Ratio) analysis to determine independent predictors of dependent variables. Hosmer-Lemeshow goodness of fit statistics were used to assess model fit. Odds ratio (Odds Ratio) and 95% confidence interval (CI) were calculated. A 5% type-I error level was used to infer statistical significance.

In the further analysis, dependent variables were categorized and analyzed as [poor (reference), moderate and good] for dietary habits, [inactive (reference), minimal active and active] for physical activity level and BMI [normal and below (reference), overweight and above] for BMI values.

Table 1. Distribution of sociodemographic characteristics of employees

	Total	
	Number	Percentage
Gender (n=476)		
Male	321	67.4
Female	155	32.6
Education Status (n=476)		
Primary school and below	67	14.1
High school	127	26.7
Associate degree and above	282	59.2
Type of employment (n=476)		
Officer	301	63.2
Contracted staff	175	36.8
Marital status (n=476)		
Married	370	77.7
Single	106	22.3
Parental statıs * (n=475)		
Yes	337	70.8
No	139	29.2
Level of importance given to health* (n=468)		
Very poor	11	2.3
Poor	25	5.3
Average	172	36.8
Good	216	46.2
Excellent	44	9.4

*Eight people did not specify the level of importance given to health

Results

The mean age of the 471 university employees participated in the study was 36.4 ± 8.23 years, median age was 35, and the youngest and oldest participants were 20 and 62 years old (not given in the Table).

Sixty-seven point four percent of the employees were male, 59.2% were graduated from “associate degree and above” and 63.2% were employed as officers. Seventy-seven point seven percent of the employees stated that they were married, 70.8% stated that they had children and 55.6% stated that they gave importance to their health at the level of “good and above” (Table 1).

Forty-eight point five percent of the employees had moderate and good dietary habits. Males had better dietary habits than females (p=0.017) (Table 2).

The physical activity level of 58.9% of the employees was found to be “minimally active and above”. Physical activity level of males (65.1%) was higher than the females (45.8%) (p<0.001). The percentage of physical activity of employees graduated from “high school and below” was higher than the employees graduated from “associate degree and above” (p=0.017). The physical activity level of 55.9% of married employees and 68.9% of single employees was “minimally active and above” (p = 0.017). Seventy-two percent of contracted staff and 51.2% of officers were physically “active” (p <0.001). Sixty-three point eight percent of the employees who declared the level of importance given to health as “good and above” and 52.9% of the employees who declared the level as “poor and below” were found to be physically active (p=0.017) (Table 2).

Sixty-eight point two percent of the employees were overweight and obese, and males (74.2%) were more overweight and obese than the females (55.8%) (p<0.001). The ratio of “overweight and obese” was higher in the age group “40 years and older” than other age groups (p<0.001). Seventy-three point five percent of married individuals and 49.0% of single individuals were “overweight and obese” (p<0.001). The percentage of being “overweight” and “obese” was higher in the employees who had children (p<0.001) (Table 2).

Odds Ratio and 95% CI were calculated through logistic regression analysis by correcting the factors such as gender, marital status and level of importance given to health through dietary habits. The constant coefficient of the model for the dietary habits was found to be -0.523. Males have 1.68 (1.13-2.50) times better dietary habits than females (p=0.010). Single individuals have 1.61 (1.03-2.51) times better dietary habits than the married individuals (p=0.033) (Table 3).

Table 2. Distribution of body mass index values, physical activity levels and dietary habits according to sociodemographic characteristics of employees

	Dietary Habits						Physical Activity Levels						Body Mass Index Values					
	Poor		Moderate and Good		Total	p	Inactive		Minimally active and active		Total	p	Underweight and normal		Overweight and Obese		Total	p
	n	%	n	%	n		n	%	n	%	n		n	%	n	%	n	
Gender																		
Male	153	47.7	168	52.3	321	0.017	112	34.9	209	65.1	321	<0.001	78	25.8	224	74.2	302	<0.001
Female	92	59.4	63	40.6	155		84	54.2	71	45.8	155		65	44.2	82	55.8	147	
Age Groups†																		
20-29 years	49	48.0	53	52.0	102	0.649	46	45.1	56	54.9	102	0.643	45	48.9	47	51.1	92	<0.001
30-39 years	120	52.2	110	47.8	230		94	40.9	136	59.1	230		74	34.3	142	65.7	216	
40-49 years	50	54.3	42	45.7	92		37	40.2	55	59.8	92		18	19.8	73	80.2	91	
≥50 years	21	44.7	26	55.3	47		16	34.0	31	66.0	47		4	8.9	41	91.1	45	
Education Status																		
Primary school and below	30	44.8	37	55.2	67	0.417	21	31.3	46	68.7	67	0.017	13	19.7	53	80.3	66	0.064
High school	64	50.4	63	49.6	127		44	34.6	83	65.4	127		39	32.2	82	67.8	121	
Associate degree and above	151	53.5	131	46.5	282		131	46.5	151	53.5	282		91	34.7	171	65.3	262	
Marital Status																		
Married	199	53.8	171	46.2	370	0.059	163	44.1	207	55.9	370	0.017	93	26.5	258	73.5	351	<0.001
Single	46	43.4	60	56.6	106		33	31.1	73	68.9	106		50	51.0	48	49.0	98	
Parental status																		
Yes	174	51.6	163	48.4	337	0.913	146	43.3	191	56.7	337	0.138	80	24.9	241	75.1	321	<0.001
No	71	51.1	68	48.9	139		50	36.0	89	64.0	139		63	49.2	65	50.8	128	
Family Types																		
Core family	200	51.7	187	48.3	387	0.972	165	42.6	222	57.4	387	0.141	113	31.2	249	68.8	362	0.176
Extended family	29	50.0	29	50.0	58		17	29.3	41	70.7	58		16	28.1	41	71.9	57	
I live alone.	16	51.6	15	48.4	31		14	45.2	17	54.8	31		14	46.7	16	53.3	30	
Type of employment																		
Officer	154	51.2	147	48.8	301	0.860	147	48.8	154	51.2	301	<0.001	92	32.5	191	67.5	283	0.695
Contracted staff	91	52.0	84	48.0	175		49	28.0	126	72.0	175		51	30.7	115	69.3	166	
Importance given to health †																		
Poor and below	117	56.2	91	43.8	208	0.066	98	47.1	110	52.9	208	0.017	64	32.5	133	67.5	197	0.838
Good and above	124	47.7	136	52.3	260		94	36.2	166	63.8	260		78	31.6	169	68.4	247	
Total	245	51.5	231	48.5	476		196	41.1	280	58.9	476		143	31.8	306	68.2‡	449	

† Five people did not specify the age and eight people did not respond to the question of giving importance to their health,

‡ Figures in table may not add up to totals due to rounding

Table 3. Relationship between variables with dietary habits, physical activity level and body mass index values

OR (%95 CI) p		Dietary Habits1		Physical Activity2		Body Mass Index3	
		OR (%95 CI)	p	OR (%95 CI)	p		
Age						1.636(1.214-2.205)	0.001
Gender	Female	Reference	0.010	Reference	<0.001	Reference	0.002
	Male	1.688 (1.136-2.508)		2.728(1.779-4.184)		2.045(1.307-3.202)	
Marital Status	Married	Reference	0.033	Reference	0.005		
	Single	1.618 (1.039-2.519)		2.021(1.231-3.318)			
Parental status	Yes	-	-	-	-	2.048(1.235-3.398)	0.006
	No	-		-		Reference	
Importance given to health	Poor and below	-	-	Reference	0.020	-	-
	Good and above	-		1.596 (1.077-2.364)		-	-
Type of employment	Officer	-	-	Reference	<0.001	-	-
	Contracted staff	-		2.984(1.937-4.599)		-	-
Level of physical activity	Inactive	-	-	-	-	Reference	0.015
	Minimally active and active	-	-	-	-	1.724(1.113-2.670)	

1Model 1: Correct classification rate (CCR)=54.7% / Hosmer-Lemeshow p=0.908, 2Model 2: CCR=64.3% / Hosmer-Lemeshow p=0.940, 3Model 3: CCR=71.8% / Hosmer-Lemeshow p=0.66

Odds Ratio and 95% CI were calculated through logistic regression analysis by correcting the factors such as gender, education status, marital status, parental status and family types through physical activity levels. The constant coefficient of the model for the level of physical activity was found to be -1.081. Males were 2.72 (1.77-4.18) times, single individuals were 2.02 (1.23-3.31) times, those who gave importance to their health at the level "good and above" were 1.59 (1.07-2.36) times and contracted staff was 2.98 (1.93-4.59) times more physically active than the others (p<0.001, p=0.005, p=0.020, p<0.001) (Table 3).

Odds Ratio and 95% CI were calculated through logistic regression analysis by correcting the factors such as age, gender, education status, family types, marital status, parental status and level of physical activity through BMI. The constant coefficient of the model for BMI was found to be -1.536. The advancing age increased the risk of being overweight and obese by 1.63 (1.21-2.20) times (p=0.001). When the effect of gender on body mass index was examined, significant results were obtained. The risk of being "overweight and obese" was 2.04 (1.30-3.20) times higher in males and 2.04 (1.23-3.39) times higher in those who had children (p=0.002, p=0.006). Individuals with "minimally active and active" physical activity level were 1.72 (1.11-2.67) times more likely to be "overweight and obese" than those who are inactive (p=0.015) (Table 3).

Discussion

Unhealthy dietary habits and inadequate physical activity cause obesity problems. In this study, it was aimed to determine dietary habits, physical activity levels and obesity status of employees working in a university and some sociodemographic characteristics affecting them. Nutrition is one of the major determinants of health and many important NCDs can be prevented or delayed. Almost half of the employees (48.5%) had better dietary habits, which means about 5 out of 10 people ate healthy. This shows that approximately half of the surveyed group was fed healthy.

In this study, it was found that men's dietary habits were 1.68 times better. Unlike these findings, different studies have shown that women's dietary habits are better than men (16,17). The reason why our results are different is that male participants are outnumbered in administrative staff and that the working status has revealed more regular nutritional behaviors.

Single individuals have 1.61 times better dietary habits. In this study, it can be said that men have regular nutritional habits because they mostly work in office services and professional occupational groups. In this study, employees working at different campuses of the university were contacted. Healthy nutrition environment may not be provided in every campus. The characteristics of the nutritional environment are likely to affect the sociodemographic characteristics of the people (18). For this reason, it is also an important and controversial issue that it is necessary to investigate the obstacles for adequate and balanced nutrition of people, as well as their knowledge, and to provide solutions for these, and to establish nutrition friendly circles.

In the TNHS-2010 report, the percentage of individuals aged 12 years and over who exercise 1-2 times a week in the last 7 days is reported to be 9.7% in total (3). In this study, physical activity level of 9.3% of the employees working at desk jobs was found to be "active". In studies conducted with people working at desk jobs in Turkey, the percentage of physically "active" participants is 5.8%-25.9% (19-21). In this study, it was seen that the officers working at desk jobs were living more sedentarily than the other groups.

In the study, men were physically 2.72 times more active than women. A systematic review of the different studies conducted in our country

(14,22,24) and in other countries (23) suggests that men have higher level of physical activity than women. When we compared our study with the other studies in which the level of physical activity of men was higher than that of women, the study was consistent with the literature.

Single employees were 2.02 times more physically active. Trost et al. (23) have stated in the systematic study that there are studies that show a positive relationship between marital status and physical activity and that there are also conflicting studies (23). Similar results have been found in the study of the Deniz and Bulut (22,25). In our study, the reason why physical activity levels of single individuals were higher was that married individuals spend their free time with their families and they are older.

Individuals who give importance to their health at the level of "good" and "above" were 1.59 times more physically active than those with "poor and below" level. Trost et al. (23) reported that there was a positive correlation between perceived health status and physical activity, and that it was repeated in all study findings . Likewise, in the study of Yetim (24), it was stated that the average IPAQ scores was highest among those evaluating general health status as very good. Unlike the findings of this study, Bulut (22) stated that there was no significant difference in the physical activity levels of those who assessed their health status through their statements as "very good / good" "not bad" or "bad / very bad" (22). In order to obtain a better health level, individuals need to have a healthy life style. It is expected that those who give importance to their health should avoid the risky behaviors and apply healthy living principles that will protect and improve their health. It is essential to quit using tobacco and tobacco products, to avoid excessive alcohol consumption, to get healthy nutrition and to do regular physical activities for living a healthy life.

Contracted staff was 2.98 times more physically active than officers. Similarly, in the study of Bulut (22), it was stated that the level of physical activity of private company personnel was higher than the administrative personnel and it was found to be statistically significant (22). Contracted personnel, who has high levels of activity, are working in jobs that require to exert more power and energy and that sometimes require working overtime (security, cafeterias, cleaning etc.).

In parallel with the increase in BMI values in the world, it is observed that the percentage of obesity is also increasing. In TNHS-2010 report, it was stated that the prevalence of mild obesity was 34.6% and the prevalence of obesity was 30.3% in Turkey (3). In TURDEP-II study, the prevalence overweight and obesity in Turkey was reported to be 37.0% and 36.0%, respectively (26). In this study, the percentage of overweight was 47.4% and percentage of obesity was 20.7%. Various studies conducted in Turkey have shown different results in terms of the prevalence of overweight (25.0%-47.4%) and obesity (19.4%-32.0%) (27-29). The results of this study have similar values. The results suggest that obesity is a primary health problem in this group.

The increase in age also increases the risk of being overweight and obese by 1.63 times. According to the Turkey Nutrition and Health Survey (TNHS) 2010 report, which supports the finding of this study, it is stated that BMI increases with age and the percentage of being overweight and obese in the 51-64 age group is higher than other age groups (3).

In TNHS-2010 report, the prevalence of obesity (BMI ≥30 kg/m2) in male individuals was 20.5%, while it was 41.0% in female individuals and prevalence of overweight was higher in male individuals (M: 39.1%, F: 29.7%) (3). According to the findings of TURDEP II study, BMI values were higher in women compared to the mean of both genders (26). When the effect of gender on BMI was examined, significant results were obtained, and it was found that the risk of being overweight and obese for men was 2.04 times higher than women. According to our research, the prevalence of obesity in women was clearly lower than that of men, which might be because the age groups of the employees participating in the study are lower than the compared studies.

The risk of being "overweight and obese" in individuals with children was 2.04 higher than the others. According to the BMI evaluation in the study by Çayır et al. (30), the percentage of obesity also increases as the number of children increases. In the study of Erem et al. (28), it was stated that there was a linear relationship between the number of parity and the prevalence of obesity and BMI in women and that the prevalence of obesity and BMI level increases as the number of parity increases. The results are consistent with the results obtained in this study. In other words, the main demographic factors remain at the forefront in obesity. As the number of children increases with age, the age factor should not be ignored in these differentiations.

Population-based cross-sectional studies conducted to determine the relationship between physical activity and weight gain show an inverse relationship between physical activity level and weight gain, body fat increase, overweight or obesity prevalence (31). In our study, it was determined that the risk of being overweight and obese increased in individuals who are minimally active and active (1.72 times). In some studies, an inverse relationship between physical activity and BMI was reported (28). With these findings, which are inconsistent with the literature, it can be considered that individuals are trying to be physically active because of obesity.

Since participants are a group of people working as administrative and contracted staff at a university, they represent only a specific sub-group of the society, not the entire society. It should also be assessed in the interpretation of the findings that the dietary habits and physical activity level of the participants were determined by their own statements. The most important limitation of this study was that environmental conditions were not evaluated in terms of healthy nutrition and physical activity.

Conclusion

All these results suggest that interventions are needed to increase physical activity to prevent obesity. Interventions are needed to enable people to perform physical activities appropriate to their working and living conditions.

In conclusion, prominence of gender, which is a sociodemographic characteristic, in the formation of nutritional habits, physical activity and obesity is noteworthy. Marital status, the level of giving importance to health and employment type are important in eating habits and physical activity behaviors. The increase in age, having a child and the level of physical activity are important variables in obesity. All these

results suggest that interventions are needed to increase physical activity to prevent obesity. Interventions are needed to enable people to perform physical activities appropriate to their working and living conditions. In this respect, age and gender-specific nutrition, obesity and physical activity policies that address all employees and programs on promoting and improving health are required to be developed. It is also thought that it is necessary to learn the social and cultural lifestyle as well as the environmental conditions that may affect healthy nutrition and physical activity.

Ethics Committee Approval: The necessary institutional permission was obtained from the Ahi Evran University rectorate and ethical approval (number:78968926-051/1076-5326).

Informed Consent: Verbal consent of the employees were taken.

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Evaluation of Non-donor Brain-Dead Patients

Donör Olmayan Beyin Ölümü Olgularının Değerlendirilmesi

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ABSTRACT

Introduction: Patients with chronic organ failure receive organs from living donors or brain-dead donors. In our country, brain death and organ transplantation procedures are carried out with Turkish Laws #2238 on the Harvesting, Storage, Grafting, and Transplantation of Organs and Tissues (June 3, 1979). Improvements in legislation have been made on the criteria of diagnosis of brain death and how diagnosis will be made. The recommendation for termination of life support of non-donor brain-dead patients was removed. Due to this uncertainty, hesitancy arises in terms of the discontinuation of life support among healthcare workers. In our study, we aimed to draw attention to the issue about the fate of non-donor brain-dead patients.

Methods: In our study, we retrospectively evaluated data of brain-dead patients between January 1, 2011 and June 1, 2017 in our hospital.

Results: Of the 122 patients with brain death, 102 were not donors. The mean lifetime of non-donor patients was 29±56 hours. It was observed that cardiac death occurred in the longest surviving patient after 116 hours following declaration. Thirty-five patients were given new vasopressor or inotropic drugs after brain death.

Conclusion: The brain-dead person is considered medically and legally dead despite heartbeats. It is not reasonable to maintain the life support of the individual who is considered dead. Considering the insufficient number of intensive care units and the high cost of medical support, it is of great importance to establish legal arrangements that will allow the discontinuation of medical support that is useless in non-donor brain-dead patients and enable the use of life-supporting devices for the patients in the waiting list.

Keywords: Brain death, organ donation, discontinuation of life support

ÖZ

Amaç: Kronik organ yetmezlikli hastalar için organlar canlı vericilerden ya da beyin ölümü gerçekleşmiş kişilerden alınmaktadır. Ülkemizde beyin ölümü ve organ nakli işlemleri 1979 yılında çıkartılan 2238 sayılı "Organ ve Doku Alınması, Saklanması ve Nakli Hakkında Kanun" ile yürütülmektedir. Mevzuatta yapılan değişiklikler ile beyin ölümü tanısının kriteleri ve tanının nasıl konulacağı konusunda iyileştirmeler yapılmıştır. Beyin ölümü tanısı almış, ancak donör olmayan olguların yaşam desteğinin sonlandırılması önerisi kaldırılmıştır. Bu belirsizlik nedeni ile sağlık çalışanları içinde yaşam desteğinin kesilmesi konusunda tereddüt oluşmaktadır. Çalışmamızda organ nakli yapılamayan donörlerin akıbeti ile ilgili açıkta kalan konuya dikkat çekmeyi amaçladık.

Yöntemler: Çalışmamızda hastanemizde 1 Ocak 2011 ile 1 Haziran 2017 tarihleri arasında görülen beyin ölümü olguları retrospektif olarak incelendi.

Bulgular: Beyin ölümü tanısı konulmuş 122 hastanın 102'sinin donör olmadığı görüldü. Donör olmayan hastaların ortalama yaşam süresi 29±56 saattir. En uzun yaşayan hastamızın deklarasyon sonrasında 116 saat kardiyak ölümün gerçekleşmediği görülmüştür. Otuz beş hastaya beyin ölümü bildirimi sonrasında yeni vazopressör veya inotrop ilaç başlanmıştır.

Sonuç: Beyin ölümü gerçekleşmişse kalp atışı sürüyor olsa dahi kişi tıbben ve hukuken ölü kabul edilir. Ölü kabul edilen bireyin yaşam desteklerinin devam ettirilmesi makul değildir. Yoğun bakım yatak sayısının yetersizliği ve tıbbi destek maliyetinin yüksek olması dikkate alındığında, donör olmayan beyin ölümlü olgularda faydasız olan tıbbi desteğin kesilmesi ve yaşamı destekleyen cihazların öncelikle bekleyen hastaların kullanımına olanak sağlayacak yasal düzenlemelerin oluşturulması büyük önem taşımaktadır.

Anahtar Kelimeler: Beyin ölümü, organ nakli, yaşam desteğinin kesilmesi.

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Introduction

Organ transplantation is a surgical operation in which an irreversibly damaged organ is removed and replaced with a functioning organ harvested from a donor. Organs are received from living donors or brain-dead donors. Brain death was first described in 1959 by Mollaret and Goulon as "coma dépassé". The milestone for the definition of brain death was the publication of the Harvard criteria. Following this definition, brain death and organ transplantation issues have united and progressed on common ground (1). In our country, brain death and organ transplantation procedures are carried out with Turkish Laws #2238 on the Harvesting, Storage, Grafting, and Transplantation of Organs and Tissues (June 3, 1979). Improvements in legislation have been made over time on the criteria of diagnosis of brain death and how diagnosis will be made, however, there is no clarity about non-donor cases. Although brain-dead patients are considered legally dead (2), health workers may hesitate to terminate life support due to uncertainty in legislation.

In this study, a retrospective analysis of brain-dead patients in a training and research hospital between 2011 and 2017 was conducted, and it was aimed to draw attention to unclear points in the management of non-donor cases in the light of the data obtained.

Methods

Brain-dead patients between January 1, 2011 and June 1, 2017 were reviewed retrospectively after receiving approval from the İstanbul Training and Research Hospital Ethics Committee of our hospital (no: 23/06/2017-1018). According to the decision taken by the organ transplantation commission of our hospital, single-photon emission computed tomography is performed as a supportive test for the patients who are thought to be clinically brain-dead after the apnea test and then declaration is done.Demographic data, reasons for admission, "acute physiology and chronic health evaluation (APACHE 2)" scores, time to diagnosis, additional test rates, transplantation rates, time to transplantation, time to cardiac death of non-donor patients, and procedures performed during this period were recorded.

Statistical analysis was performed using Minitab 17 (Minitab Statistical Software, Pennsylvania, USA). Descriptive statistics were expressed as mean, minimum-maximum, standard deviation, numbers and percentage.

Statistical Analysis

Data with non-normal distribution were compared using Mann-Whitney U test and chi-square test was used to compare categorical variables.

Results

In our study, 122 patients were examined. The mean time from the intensive care unit admission to the suspicion of brain death was found to be 3.79±3.1 days. The distribution of the patients diagnosed with brain death according to years and diagnosis are shown in Figure 1 and Figure 2, respectively. It has been observed that the hemorrhagic cerebrovascular events take the first place among the causes of brain death. This is followed by ischemic cerebrovascular events, trauma, malignancy, successful resuscitation after cardiac arrest, infections and intoxications. Although four out of 122 patients were diagnosed with brain death after apnea test, declaration could not be made because no supportive test could be performed. Brain death declaration was made in 118 patients and 20 of these 118 patients became donors. Apnea test could not be performed due to hypoxia or hemodynamic instability in three donors and five non-donors. Demographic data of donors and non-donors are shown in Table 1. There was no significant difference between two groups in terms of age, APACHE 2 scores and time to declaration ($p>0.05$). Two of 15 patients who were non-citizens of the Republic of Turkey became donors. The mean organ harvesting duration was 18.15±15 hours. The mean cardiac death of the non-donor patients was 29±56 hours, and the longest period between brain death and cardiac death was 116 hours (Table 2). Thirty-five non-donor patients were given new vasopressor or inotropic drugs after brain death notification. Twelve of these patients had cardiopulmonary resuscitation (CPR) after cardiac arrest.

Discussion

Organ transplantation has been used as a salvage treatment in patients with end-stage organ failure. The organs required for these patients are harvested from living or brain-dead donors.

While death is a medical condition, it has psychological, economic, legal, ethical, religious and social consequences. Somatic death, which means cessation of heartbeats and breathing, is accepted and understood as death (3). Brain death is now accepted as the irreversible loss of brain and brain stem reflexes. For this reason, brain death is not sufficiently recognized and causes anxiety among relatives of patients and health workers. Furthermore, coma, persistent vegetative status and brain death cannot be clearly differentiated by society. Therefore, the improvements seen after these clinical conditions, although very rarely, are misunderstood by the society and cause them to move away from the idea of organ transplantation and discontinuation of life support after brain death (4,5).

Table 1. Demographic data of cases

	Donors (n=20)	Non-donors (n=102)
Age (years)	44.05±14.06	51.49±17.38
Gender, male/female	13/7	63/39
Nationality (RoT)	18 (90%)	89 (87.2%)
APACHE 2	26.85±7.9	26.34±6.23

RoT: republic of Turkey, APACHE 2: acute physiology and chronic health evaluation score
Data were expressed as n, n (%) and mean ± SD

Table 2. Declaration data

	Donors (n=20)	Non-donors (n=102)
Apnea test	17 (85%)	87 (85.2%)
Supportive test	20 (100%)	98 (96%)
Declaration (day)	3.8±2.46 (1-9)	3.79±3.1 (1-20)
Cardiac death (hours)	18.15±7.79 (12-36)	29.56±22.52 (1-116)

Declaration: The time until the diagnosis of brain death (day); Cardiac death: Time to cardiac death and/or organ donation (hours), Data were given as n (%), mean ± SD and minimum-maximum value

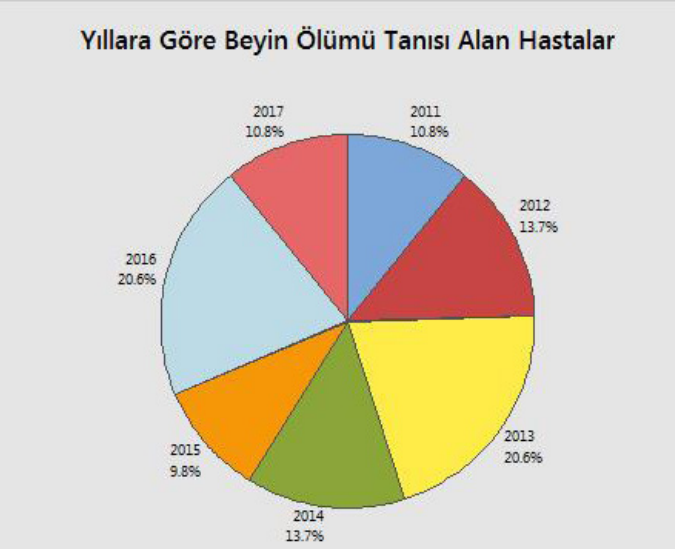

Figure 1. Patients diagnosed with brain death by years

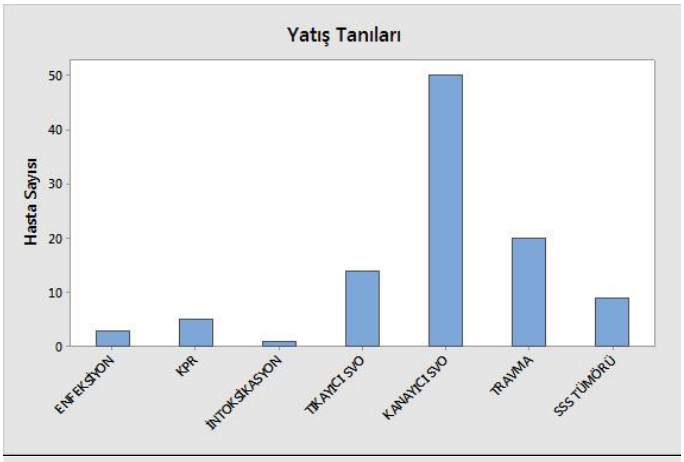

Figure 2. Diagnosis of patients with brain death

Another reason for rejecting discontinuation of life support is religious concerns. According to İslam, life is sacred and protected. However, according to the results of fiqh studies, it is accepted that brain death is also true death. In the published fatwa, it is stated that brain-dead people should be accepted as dead (6).

With the entry into force of the Law No. 2238 on 29 May 1979, it is decided that the organs can be taken from brain-dead people. Although there is no definition of brain death in the law, this situation did not create problems in practice. On 16 August 1990, the brain death criteria approved by the General Directorate of Therapy Services of the Ministry of Health have been notified. Brain death criteria were published in the Official Gazette on August 20, 1993, and the concept of brain death was given a legal dimension. Although there was a statement indicating that "If the organ donation permit cannot be obtained after the brain death is declared to the relative of the patient, the medical support applied to the patient will be discontinued" in the 1993 criteria, this approach was amended in the Regulation on Organ and Tissue Transplantation dated June 1, 2000, and was rephrased as "the medical support can be discontinued if the relatives of the patient permit". In the Regulation on Organ and Tissue Transplantation, dated February 1, 2012, the rules for the diagnosis of brain death have been re-published, but there was no statement on the decision to discontinue medical support in non-donor cases made by relatives of the patient and/or by the health team (1). This has led to hesitations in discontinuing medical support by making the issue of authority questionable. For Turkish law, as in Universal Medicine Law, death also occurs when a person's brain and brainstem functions are lost to an irreversible degree. The brain-dead person is considered medically and legally dead despite heartbeats. It is not reasonable to maintain the life support of a dead individual. Although this condition is not included in the new regulation, it should be noted that there is no need to wait for approval or request of the relatives of the patient for discontinuation of life support if there is no consent for organ transplantation in a person whose brain death has been realized and duly certified. In addition, in the presence of another patient in need of a life support device such as a mechanical ventilator, resources should be allocated to patients in need due to the fair use principle; otherwise, continuation of medical support with such a device could lead to the responsibility of the physician (7).

In our retrospective evaluation, it was seen that four patients were expected to undergo an additional test after apnea test; however, cardiac death was observed in these patients. Due to this delay, declaration could not be made to the family and potential organ donors were lost. In our evaluation, organ transplantation was not accepted by the relatives of 98 cases. In non-donors, the period between brain death and cardiac death was determined to be at least 1 hour, maximum 116 hours and mean 29.56 hours. Although the financial burden of 98 brain-dead patients with a mean of 29.56 hours of care could not be calculated, it can be regarded as futile. Karasu et al. (8) reported that 43 non-donor patients had lived for a mean of 2.5 days and continued life support in case their relatives change their minds. In addition, they stated that they had continued life support since relatives of patients did not allow life support to be discontinued before 2012. In our study, we identified 11 cases before 2012 and we found that five of them were started vasopressors.

In our study, we determined that 35 non-donor patients were started vasopressor agent after the family interview. Although the reason for the failure to discontinue life support could not be reached from our records, we have seen that one patient in 2011 and 11 patients in 2012 underwent CPR. A study showed that physicians and nurses who believe that life support should be maintained in these cases is 13.4% and 20.1%, respectively. In the same study, it was revealed that 11.2% of physicians did not believe that the brain-dead cases had died legally (9). The main reason for the continuation of life support by health care workers may be that medical law is not included in medical education and health workers cannot get enough support from the institutions. When this is the case, it will be reasonable to apply to the organ transplant management of the hospital. Health workers should be encouraged to participate in the trainings provided by the Ministry of Health and the lack of information should be avoided. It should also be kept in mind that healthcare professionals are individuals and may have concerns about discontinuing life support due to their religious, conscientious, and social presence

as well as their professional personality. Therefore, all health care workers responsible for patient care should also be supported in this direction.

Relatives of patients who cannot comprehend the definition of brain death hope that their patients can return to life and therefore they are reluctant to decide to discontinue medical support. Intimate early communication with the relatives of the patients can overcome this, however, relatives of patients who are difficult to communicate and who are in a state of denial in addition to the unwillingness of health workers to discontinue life support lead to occupation of beds by non-donor cases. This situation prevents the intensive care conditions from being used by intensive care patients. The lack of confidence in the existing legislation and the decision to interrupt the medical support in non-donor cases and the decision on who to make this decision is not being explicitly stated increases the doubts about this issue (10).

Conclusion

Considering the necessity of rational use of intensive care beds in our country and the high cost of medical support, we think that the legal arrangements that will allow us to discontinue medical support that is useless in non-donor cases and to direct the life supporting devices to the waiting patients should be implemented rapidly.

Ethics Committee Approval: The study was approved by the Ethics Committee of İstanbul Training and Research Hospital with the decision number 23/06/2017-1018.

Informed Consent: Externally peer-reviewed.

Peer-review:

Author Contributions: Concept - İ.C.; Design - İ.C., S.S.; Supervision - V.E.; Data Collection and/or Processing - S.S., S.B.; Analysis and/or Interpretation - İ.C.; Literature Search A.T.; Writing Manuscript - İ.C., S.S.; Critical Review - V.E.

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

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