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Original Article

The Correlation with Enthesitis and the Severity of the Disease in Behçet's Syndrome

Behçet Sendromunda Entezit ile Hastalığın Şiddeti Arasındaki Korelasyon

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ABSTRACT

Objective: The aim of this study was to determine the frequency of enthesitis using the Maastricht Ankylosing Spondylitis Enthesitis Score and the intensity of enthesitis with Maastricht Ankylosing Spondylitis Enthesitis Score in patients with Behçet's syndrome, to examine the relationship with Behçet's syndrome severity, and to evaluate whether enthesitis and higher enthesitis scores are associated with more severe disease.

Methods: The study included 232 Behçet's syndrome patients and 139 healthy control subjects. The presence of enthesitis in Maastricht Ankylosing Spondylitis Enthesitis Score-defined areas was evaluated using the standard palpation method. In the group with enthesitis, the intensity was assessed with Maastricht Ankylosing Spondylitis Enthesitis Score. Krause's assessment of Behçet's syndrome activity was used to evaluate the severity of Behçet's syndrome. The Krause's scores were compared between the groups, and then correlations were investigated between the Krause score and Maastricht Ankylosing Spondylitis Enthesitis Score in the enthesitis group.

Results: Enthesitis was present in 23.2% of patients with Behçet's syndrome. Both enthesitis frequency and Maastricht Ankylosing Spondylitis Enthesitis Scores were higher in Behçet's syndrome patients compared to the healthy control group. Behçet's syndrome patients with enthesitis had higher Krause's scores (P < .001), vascular involvement (P = .001), arthritis (P = 01), papulopustular lesion (P = .01), and ocular involvement (P = .014). A correlation was determined between Krause's score and Maastricht Ankylosing Spondylitis Enthesitis Score in the Behçet's syndrome patients with enthesitis.

Conclusion: The results of this study showed that Behçet's syndrome patients with enthesitis could have a severe Behçet's syndrome clinical condition. When evaluating Behçet's syndrome

ÖZ

Amaç: Bu çalışmanın amacı, Behçet sendromu (BS) hastalarında Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) kullanılarak entezit sıklığını belirlemek, MASES skoru ile belirlenen entezit yoğunluğunun BS şiddeti ile ilişkisini incelemek, entezit varlığının ve daha yüksek entezit skorlarının daha şiddetli hastalıkla ilişkili olup olmadığını değerlendirmektir.

Yöntemler: Çalışmaya 232 BS hastası ve 139 sağlıklı kontrol deneği dahil edildi. MASES tanımlı bölgelerde entezit varlığı standart palpasyon yöntemi kullanılarak değerlendirildi. Entezitli grupta yoğunluk MASES ile değerlendirildi. Krause's BS aktivitesi değerlendirmesi, BS hastalığının şiddetini değerlendirmek için kullanıldı. Gruplar arasında Krause's skorları karşılaştırıldı, daha sonra entezit grubunda Krause's skoru ile MASES arasındaki korelasyonlar araştırıldı.

Bulgular: BS'li hastaların %23,2'sinde entezit mevcuttu. BS hastalarında entezit sıklığı ve MASES skorları sağlıklı kontrol grubuna göre daha yüksekti. Entezitli BS hastalarında Krause's skoru (P < ,001), vasküler tutulum (P = ,001), artrit (P = ,01), papülopüstüler lezyon (P = ,01) ve oküler tutulum (P = ,014) daha yüksekti. Entezitli BS hastalarında Krause's skoru ile MASES arasında korelasyon saptandı.

Sonuç: Bu çalışmanın sonuçları entezitli BS hastalarının ciddi BS klinik durumu olabileceğini göstermiştir. BS hastalarını değerlendirirken, enteziti olanlar daha şiddetli hastalık seyrine sahip olabileceğinden hastalar entezit açısından incelenmelidir.

Anahtar Kelimeler: Behçet sendromu, Entezit, Spondilartrit

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patients, patients should be examined in terms of enthesitis as those with enthesitis may have a more severe disease course.

Keywords: Behcet's syndrome, enthesitis, spondylarthritis

INTRODUCTION

Behcet's syndrome (BS) is an inflammatory vasculitis characterized by ocular and central nervous system involvement, mucocutaneous and joint symptoms, and recurrent thrombophlebitis/thrombosis.[1] The pathogenesis of BS is believed to be closely correlated with genetic, internal, and external factors, despite the fact that the etiology of BS is still unknown.[2] Between 80 and 420 people per 100 000 in Türkiye have BS.[3] Musculoskeletal involvement in BS is frequent; however, the likelihood of joint involvement varies significantly by location.[4] Some authors thought BS could be categorized as a type of spondylarthritis (SpA) complex due to some shared characteristics, especially in a subset of BS patients with acne-associated arthritis.[5,6]

Enthesitis is recognized as a unique pathological and clinical hallmark of the SpA group disorders and is described as inflammation of the tendon, ligament, and joint capsule attachments to the bone. Our understanding of treating enthesitis has improved as a result of recent developments in the anatomy, physiology, and pathophysiology of this illness.[7] Enthesitis can occur in polymyalgia rheumatica, crystal arthropathies, and diffuse idiopathic skeletal hyperostosis.[8]

The diagnosis of enthesitis in clinical practice is made based on a clinical examination, which includes an interview (pain at the location of an enthesis that goes away after physical activity) and the observation of pain in an enthesis upon compression.[9] To measure the extent of enthesitis in patients, several clinical enthesitis indices have been created. There is no agreement on an ideal index, making comparisons challenging because they were created using various patient groups and location options. The most frequently used enthesitis indices in clinical studies are Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), Spondylarthritis Research Consortium of Canada (SPARCC) Index, and the Leeds Enthesitis Index (LEI). It has been shown that the MASES scoring index has some advantages over other scoring indices.[10]

MAIN POINTS

- Enthesitis is accepted as a distinctive pathological and clinical feature of the spondylarthritis group diseases.
- Ultrasound-based studies have revealed subclinical enthesitis and patients with Behçet's syndrome (BS).
- The frequency of enthesitis through Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) and the intensity of enthesitis with MASES scoring were studied in patients with Behçet's syndrome.
- More frequent enthesitis was found in Behçet's syndrome patients than in healthy controls and enthesitis was determining finding for more severe disease.

Recent ultrasound-based studies conducted in patients with BS and SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome have examined the enthesis of patients and found the increased prevalence of asymptomatic enthesitis compared to control groups.[11,12] However, the increased power Doppler ultrasound signal, which is typical for SpA enthesitis, has been rarely seen, and the true significance of the phenomenon identified through ultrasound has not been determined clearly.

Only clinical criteria are used to diagnose BS, and other diagnosis must be ruled out. Behcet's syndrome does not have pathognomonic laboratory findings.[2] In some circumstances, an active disease may be accompanied by normal erythrocyte sedimentation rate and c-reactive protein readings.[13] Several ultrasound-based studies examined the relationship between subclinical enthesitis and BS; however, a study evaluating subclinical entheseal involvement with MASES has not been carried out. Our research's purpose is to ascertain the frequency of enthesitis with MASES and the intensity of enthesitis with MASES scoring in patients with BS and to evaluate their relationship with BS severity.

METHODS

The study consisted of 232 BS patients (102 females and 130 males) who met the criteria of the International Behcet's Disease Study Group[14] and 139 healthy gender- and age-matched controls (60 females and 79 males). Patients and the healthy control group, out of the 18-65 age range, breastfeeding and pregnant, who had inflammatory bowel disease, fibromyalgia, orthopedic, neuromuscular, or peripheral vascular illness, as well as other rheumatological diseases, a history of recent severe trauma, and corticosteroid injection to the structures under examination were disqualified.

We evaluated the enthesitis with the standard palpation method. Enthesitis was defined as tenderness at the entheseal area by applying a pressure of ~4 kg/cm^2 with the standard palpation method (sufficient to whiten the tip of the nail of the examiner).[15] We noted the patients'

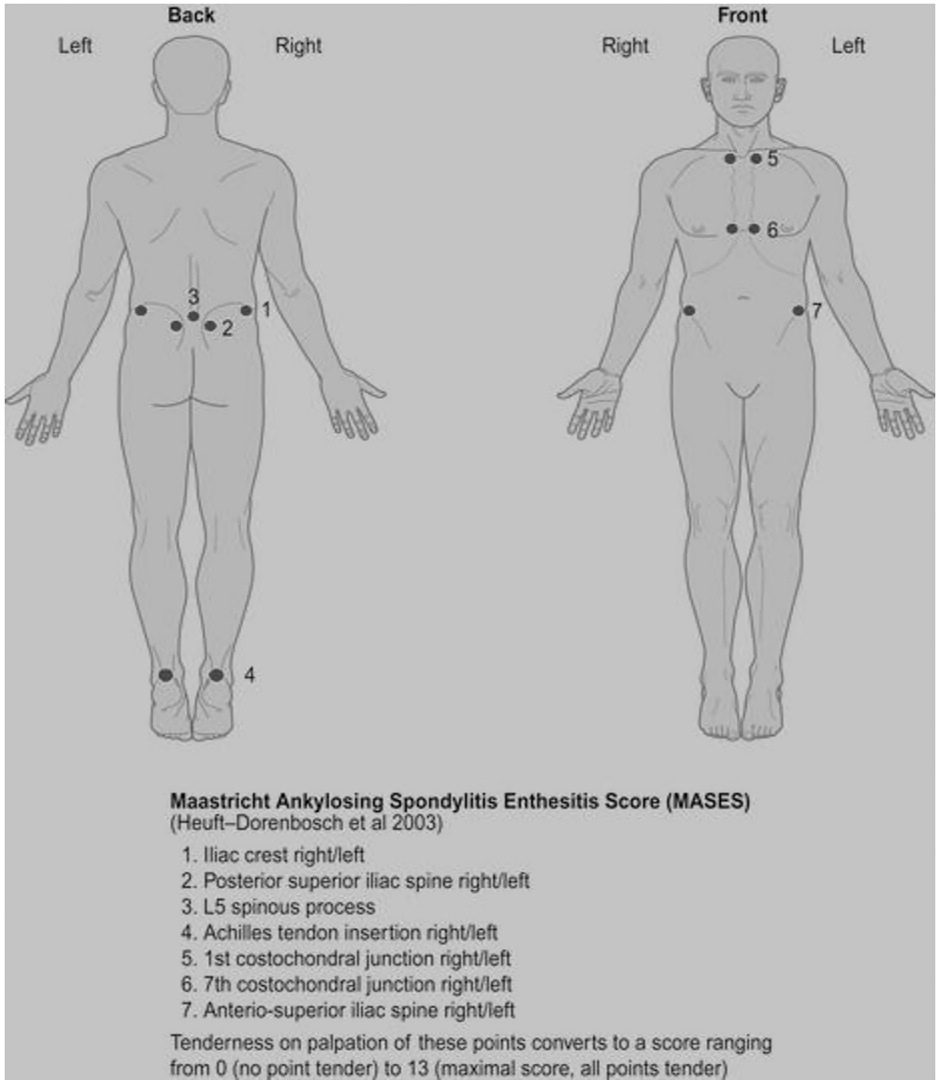


Figure 1. Maastricht Ankylosing Spondylitis Enthesitis Score.

responses to this standard palpation. The examined entheseal areas were selected according to MASES. It includes 13 different entheseal areas (Figure 1).[16] We also used the MASES score to determine the extensity of enthesitis. Maastricht Ankylosing Spondylitis Enthesitis Scores are between 0 and 13. Patients with enthesitis in any of the 13 entheseal areas in MASES were accepted as the BS enthesitis group, while patients without enthesitis were accepted as the BS without enthesitis group.

Krause's assessment of BS activity (Table 1) was used to evaluate the disease severity of patients with BS. Patients were categorized according to their disease severity score: severe group, ≥ 7 points; moderate group, points between 4 and 6; mild group, < 4 points.[17]

The MASES scores, enthesitis frequency, and demographic traits between BS patients and healthy controls were compared. Patients with BS enthesitis and those without it were compared in terms of all research variables. Additionally, Krause's evaluation of BS activity scores was connected with MASES scores to analyze the association between the severity of the disease and the level of enthesitis in BS patients.

Approval for the study was granted by the Clinical Research Ethics Committee of Erzurum Region Training and Research Hospital (decision no:2021/02-27, dated: 18.01.2021). Written and informed consent was obtained from the patients and the control group, and the work was performed after the Declaration of Helsinki.

Statistics

Statistical Package for the Social Sciences software 17.0 (IBM Inc, Chicago, IL, USA) was used for the analysis. To check whether the data were normally distributed, the Shapiro–Wilk test was carried out. The majority of the

Table 1. Krause's Assessment of Behcet's Syndrome Activity (Krause et al[17]).

Mild (each one 1 point)	Oral aphthosis
	Genital ulcer
	Typical skin lesions (erythema nodosum, papulopustular, folliculitis, leukocytoclastic vasculitis)
	Arthralgia
	Recurrent headaches
	Epididymitis
	Mild gastrointestinal symptoms (chronic diarrhea, chronic recurrent abdominal pain, colic)
	Pleuritic pain
	Superficial vein thrombosis
Moderate (each one 2 points)	Arthritis
	Deep vein thrombosis of the legs
	Anterior uveitis
	Gastrointestinal bleeding
Severe (each one 3 points)	Posterior/panuveitis
	Retinal vasculitis
	Arterial thrombosis or aneurysm
	Large vein (vena cava, hepatic) thrombosis
	Neuro-Behçet disease
	Bowel perforation

parameters did not have a normal distribution. In order to compare continuous and categorical variables between the study and control groups, the Mann–Whitney *U* test and the Chi-square test were used. In addition, the Kruskal–Wallis test was used to compare enthesitis areas between healthy controls and BS patients. Due to the small number of subjects with enthesitis in the healthy control group, we did not compare the enthesitis regions between those of BS patients and healthy controls. Spearman's correlation was used to investigate the relationship between the MASES and Krause's measurement of the activity score for BS. We used the intraclass correlation coefficient test to look at intra-observer variability. Additionally, using kappa and Cronbach's alpha methodologies, we assessed interobserver variability for the diagnosis of enthesitis and interobserver variability for the MASES score. The outcomes were presented as mean standard deviation. A *P* value of .05 or less was regarded as statistically significant.

RESULTS

In our study, 54 (23.2%) of 232 patients with BS had enthesitis. However, only 4 of 139 patients (2.8%) in the healthy control group had enthesitis. Maastricht Ankylosing Spondylitis Enthesitis Scores were greater in BS patients compared to healthy controls (Table 2). Age, gender, comorbidity, and smoking frequencies of BS patients with and without enthesitis were similar. The onset age of BS symptoms was higher, the age of diagnosis was lower, and the acute phases were higher in the comparison of BS patients with enthesitis and BS patients without enthesitis. No statistically significant difference was found in treatments used by BS patients with enthesitis compared to BS patients without enthesitis (Table 3).

Table 2. Comparison of Demographic and Enthesitis Characteristics of Patients with Behçet's Syndrome and Healthy Controls

	Patients with BS (n = 232)	Healthy Controls (n =139)	*P*
Age (years)	38.7 ± 11.2	39.2 ± 9.8	.46
Gender (F/M), n (%)	102/130	60/79	.16
Smoking, n (%)	53 (22.3%)	39 (28,1)	.74
Co-morbidities, n (%)[1]	47 (20.2%)	11 (7.9)	<.001
Enthesitis, n (%)	54 (23.2%)	4 (2.8)	<.001
Enthesis points, n (%)[2]			
First costochondral joint	11 (4.7)	2 (1,4)	
Seventh costochondral joint	9 (3.8)	0 (0)	
Posterior superior iliac spine	19 (8.1)	1 (0.7)	
Anterior superior iliac spine	16 (6.7)	1 (0.72)	
Iliac crest	21 (8.8)	1 (0.72)	
Fifth lumbar spinous process	14 (5.8)	1 (0.72)	
Proximal insertion of Achilles tendon	34 (14.2	2 (1.5)	
MASES score (0-13)[3]	4.2 ± 3.2	2.1 ± 1.5	

BS, Behçet's syndrome; F, female; M, male; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score.
Values a represented as mean ± standard deviation or number (%).
[1]Hypertension, hypothyroidism, hyperthyroidism, cardiovascular diseases, coronary artery diseases, cerebrovascular diseases, chronic renal disease, chronic obstructive pulmonary disease, and diabetes mellitus.
[2]Enthesitis in at least one side of the individual enthesis points.
[3]MASES scores of the individuals with enthesitis.

Vascular involvement, arthritis, papulopustular lesion, and ocular involvement were more prevalent in enthesitis-related BS patients, although other symptoms of BS were similar in both groups. The BS group with enthesitis had

Table 3. Demographic and Disease-Related Characteristics of Patients with Behçet's Syndrome

	BS With Enthesis (n = 54)	BS Without Enthesis (n = 178)	*P*
Age (years)	37.0 ± 10.3	37.3 ± 11.4	.25
Gender (F/M), n	16/38	70/108	.19
Age at BS diagnosis (years)	30.8 ± 8.55	24.22 ± 9.17	.048
Smoking, n (%)	18 (33.3%)	49 (27.5)	.28
Co-morbidities, n (%)[1]	13 (24%)	35 (19.6)	.24
Ocular involvement, n (%)	23 (42.5)	51 (28.6)	.014
Arthritis, n (%)	19 (35.1)	38 (21.1)	.01
Erythema nodosum, n (%)	14 (26.0)	56 (31.4)	.27
Papulopustular lesions, n (%)	35 (64.8)	80 (44.9)	.01
Vascular involvement, n (%)	24 (44.4)	27 (15.1)	.001
Neuro-Behçet's disease, n (%)	5 (9.2)	11(6.6)	.411
Family history of BS, n (%)	36 (66.6)	78 (43.8)	.001
Oral ulcer, n (%)	54 (100)	178 (100)	N.S.
Genital ulcer, n (%)	44 (81.4)	154 (86.5)	.214
Headache, n (%)	19 (35.1)	106 (59.5)	.001
Pathergy test positivity*, n (%)	23 (51.1)	64 (42.6)	.316
HLA-B51 positivity**, n (%)	12 (40.0)	43 (44.7)	.103
Current medication, n (%)			
Colchicine	31 (57.4)	106 (59.5)	.872
Conventional immunosuppressants[a]	33 (61.1)	98 (55.0)	.611
Biological immunosuppressants[b]	12 (22.2)	35 (19.6)	.743
Elevated acute phase reactants, n (%)[2]	24 (44.4)	38 (21.3)	<.001
Krause's assessment of BS activity (0-35)	7.2 ± 2.4	4.3 ±1.6	<.001
Severe disease (≥ 7), n (%)	23 (42.5)	46 (25.9)	<.001
Intermediate disease (4-6), n (%)	17 (31.5)	42 (23.6)	
Mild disease (4 <), n (%)	14 (26.0)	90 (50.5)	

Abbreviations: M, male; F, female; BS, Behçet's syndrome; N.S., not significant at α ≥ 0.05.
Values are represented as mean ± standard deviation or number (%).
[1]Hypertension, hypothyroidism, hyperthyroidism, cardiovascular diseases, coronary artery diseases, cerebrovascular diseases, chronic renal disease, chronic obstructive pulmonary disease, diabetes mellitus.
[2]Erythrocyte sedimentation rate and/or c-reactive protein.
*Pathergy testing was conducted on 195 patients.
**HLA-B51 tissue type could only be studied in 126 patients.
[a]Conventional immunosuppressants include azathioprine, cyclosporin A, corticosteroids, and interferon α.
[b]Biological immunosuppressants include infliximab and adalimumab.

more patients with a history of BS in their families, but there was no statistically significant difference between the groups in terms of HLA-B51 or the frequency of pathergy test positivity. Headache was more common in the BS group without enthesitis than in BS patients with enthesitis (Table 3).

According to Krause's scoring system, 14 (26%) patients were in the mild group, 17 (31.5%) patients were in the moderate group, and 23 (42.5%) patients were in the severe group among the BS patients with enthesitis, while 90 (50.5%) patients were in the mild group, 42 (23.6%) patients were in the moderate group, and 46 (25.9%) patients were in the severe group among the BS patients without enthesitis. Krause's scoring was higher in the BS group with enthesitis than in the BS group without enthesitis (Table 3). We found a correlation between the prevalence and severity of enthesitis and BS illness. We discovered a statistically significant association between the 2 variables ($r = 0.31$, $P = .02$).

DISCUSSION

In comparison to healthy controls, BS patients experienced enthesitis more frequently, according to the study. The degree/prevalence of enthesitis was directly correlated with the severity of BS disease, and BS patients with enthesitis had more severe disease than those without enthesitis. Moreover, vascular involvement, papulopustular lesion, ocular involvement, and arthritis were clinically more common in BS patients with enthesitis. Furthermore, the onset age of symptoms and the acute phases were higher for BS patients with enthesitis than BS patients without enthesitis, but the age of diagnosis was lower.

In some patient groups, the clinical examination of enthesitis can fail to distinguish between inflammatory, metabolic, mechanical, and degenerative processes.[7,18] The main limitations in diagnosing enthesitis in daily practice are the absence of apparent findings, including an increase in acute phase reactants and objective swelling. Enthesitis is often evaluated by clinical examination and rarely by imaging methods in inconclusive examination. The MASES index had a superior or similar diagnostic rate to other methods to measure disease activity, including SPARCC, LEI, and sonography in SpA.[10] Therefore, the MASES index was used in the present study.

Research findings on the prevalence of enthesitis in BS are inconsistent. A higher prevalence of enthesitis (38%) was found in some clinical studies,[19,20] lower rates (3.4%) were nonetheless reported.[21] The many enthesitis scales that were employed and the variations in the chosen research groups were responsible for this substantial range. In our study, the frequency of subclinical enthesitis in BS patients was 23.2%.

Spondylarthritis group diseases have similar features. The most common clinical features in the SpA complex are enthesitis, HLA-B27 antigen, and ocular involvement.[6,21] Regarding the prevalence of HLA-B27 in BS patients, there are conflicting findings. Behcet's syndrome is associated with HLA-B51 rather than HLA-B27.[21,22] The higher prevalence of enthesitis in BS patients with acne and arthritis than in BS patients without arthritis lends credence to the idea that BS patients with acne and arthritis form a distinct cluster of BS patients.[6] According to certain reports, acne-related arthritis may fall within the SpA disease complex in a subset of patients with BS.[5] We found more frequent enthesitis in BS patients with vascular, ocular involvement, arthritis, and papulopustular lesions than in patients without these involvements. We did not find a difference between patients with and without enthesitis in the HLA-B51 positive frequency.

Ozkan et al[12] compared BS patients without clinical evidence of arthritis or enthesitis and healthy controls with Madrid sonographic enthesitis index (MASEI), and they found high scores in all entheseal areas in BS patients. They suggested that the MASEI scoring system should be included in the clinical protocol for detecting subclinical enthesitis in BS patients. In our study, a higher rate of enthesitis in BS patients without enthesitis and arthritis than in healthy people and more severe disease in patients with enthesitis were revealed through the MASES method. Enthesitis may give clues to the clinician for early detection of involvement of BS, which can sometimes be fatal (vascular involvement) and often lead to complications and sequela (ocular involvement). Therefore, enthesitis may be a risk factor for severe disease in BS, independent of its severity. Maastricht Ankylosing Spondylitis Enthesitis Score index could be a practicable, cost-effective method in the clinic as a part of the patient's physical examination.

Our research has some drawbacks. First, we did not assess enthesitis using imaging techniques. However, we evaluated enthesitis with a physical examination using a standardized and authorized procedure. Secondly, the study was conducted with a relatively small number of patients. Finally, our study was arranged retrospectively.

In conclusion, we determined that BS patients with enthesitis could have a severe BS clinic. It should be kept in mind to examine the patients regarding enthesitis. Maastricht Ankylosing Spondylitis Enthesitis Score index could be a practicable, cost-effective method to reveal enthesitis in a patient's physical examination in BS.

Ethics Committee Approval: Approval for the study was granted by the Clinical Research Ethics Committee of Erzurum Region Training and Research Hospital (Date: January 18, 2021, Decision No: 2021/02-27).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.G., N.A.; Design – H.G., N.G.; Supervision – H.G., N.A.; Resources – H.G., N.A.; Materials – H.G., N.G.; Data Collection and/or Processing – H.G., N.A.; Analysis and/or Interpretation – H.G., N.A.; Literature Search – H.G., N.A.; Writing Manuscript – H.G., N.A.; Critical Review – H.G., N.A.; Other – H.G., N.A.

Declaration of Interests: The authors have no conflicts of interest to declare.

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Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastalardan ve kontrol grubundan alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

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