RESEARCH ARTICLE

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Geliş tarihi / *Received* : December 08, 2024
Kabul Tarihi / *Accepted* : July 27, 2025

Bu makalede yapılacak atıf
Cite this article as
Kaban N, Harman H, Balcı MA.
Can the Development and Recurrence of Uveitis in Behçet's Disease be Predicted? Which Predictors Are at the Forefront?
Akd Med J 2026;12: 1-9

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Can the Development and Recurrence of Uveitis in Behçet's Disease be Predicted? Which Predictors Are at the Forefront?

Behçet Hastalığında Üveit Gelişimi ve Rekürrensi Öngörülebilir mi? Ön Planda Hangi Öngörücüler Yer Almaktadır?

ABSTRACT

Objective

One of the main manifestations of Behçet's disease (BD) with the highest morbidity rate is uveitis. Uveitis recurrence (UR) rate is still high and can cause significant physical and mental distress in patients with BD, and prolonged treatment is also a major financial burden. We aimed to determine the factors predicting the development and recurrence of uveitis and to calculate the time to development and recurrence of uveitis.

Material and Methods

In a two-center retrospective study, a total of 78 BD patients who met the International Criteria for Behçet's Disease (ICBD), 41 patients with uveitis and 37 patients without uveitis, were included.

Results

The absence of genital ulcer (GU) alone was found to be an independent factor with 65.3% probability of the development of uveitis (DoU). The rate of predicting DoU was 72.2% when the prolonged time to diagnosis and the absence of GU were combined. In patients with a body mass index (BMI) of 25 kg/m2, the risk of UR was 70%.

Conclusion

Two main findings of this study were that uveitis and UR were more common in patients without GU and with high BMI, respectively.

Key Words

Behçet's disease, Body mass index, Genital ulcer, Uveitis

DOI: 10.53394/akd.1597825

ÖZ

Amaç

Üveit, Behçet hastalığının (BH) en yüksek morbidite oranına sahip olan ana manifestasyonlarından biridir. BH'da üveit rekürrens (UR) oranı hâlâ yüksektir ve bu hastalarda fazlaca fiziksel ve ruhsal strese neden olabilir, uzun süreli tedavi de aynı zamanda büyük bir mali yük getirmektedir. Bu çalışmada üveit gelişimi ve rekürrensini öngören faktörleri belirlemeyi ve üveit gelişimi ve rekürrensine kadar geçen süreyi hesaplamayı amaçladık.

Gereç ve Yöntemler

İki merkezli retrospektif çalışmada, Behçet hastalığı için uluslararası kriterleri (ICBD) karşılayan 41 üveiti olan ve 37 üveiti olmayan toplam 78 BH hastası çalışmaya dahil edildi.

Bulgular

Sadece genital ülser (GU) olmaması, üveit gelişimi (DoU) için %65,3 olasılıkla bağımsız bir faktör olarak bulundu. Tanıya kadar geçen uzun süre ve GU'nun yokluğu kombine edildiğinde DoU'yu öngörme oranı %72,2 idi. Vücut kitle indeksi (VKİ) 25 kg/m2 olan hastalarda UR riskinin %70 olduğu belirlendi.

Sonuç

Çalışmamızın iki ana bulgusu, GU olmayan ve yüksek VKİ'si olan hastalarda üveit ve UR'nin daha yaygın olmasıdır.

Anahtar Kelimeler

Behçet hastalığı, Vücut kitle indeksi, Genital ülser, Üveit

INTRODUCTION

Behçet's disease (BD), also known as Behçet's syndrome, is a rare systemic vasculitis. Defined in 2012 as 'variant vasculitis' in the Chapel Hill consensus conference vasculitis nomenclature, BD manifests with mucocutaneous disease typically characterized by recurrent oral and/or genital ulcers (GUs) in addition to involvement of the ocular, joint, GUstrointestinal tract, and/or central nervous system (CNS) (1, 2). In general, the frequency of ocular involvement in BD is around 50% (3). Uveitis can be the initial symptom of BD but is found in only 10–20% of cases, and is thus typically not the first manifestation. It generally develops within 2-3 years after the onset of extraocular symptoms (4). Non-granulomatous panuveitis (PaU) is the most common form of ocular involvement in BD, affecting the anterior, posterior, or both chambers of the eye. Bilateral involvement is usually seen in 75-95% of patients. Bilateral uveitis is more common and more severe in young men (5-7). The most common types of ocular diseases in BD are posterior uveitis (PoU) and PaU, which pose a serious risk to vision and have a high likelihood of long-term consequences (8). Isolated anterior uveitis (AU) affects less than 10% of patients (9). In addition to uveitis, other ophthalmologic disorders such as episcleritis, scleritis, conjunctival ulcers, keratitis, orbital inflammation, isolated optic neuritis and extraocular muscle paralysis have been described (10).

Recurrent attacks of eye disease result in structural changes leading to loss of vision if left untreated (5). Remission of ocular illness, which is defined as the lack of relapse or indications of active inflammation three months after discontinuing all anti-inflammatory medications, is the primary treatment outcome. Evidence suggests that with adequate therapy, a long-term, drug-free remission should be possible in two to three years (11). Though there have been significant advancements in the treatment of uveitis, the condition still has a high recurrence rate and uveitis recurrence (UR) can cause significant physical and psychological burden in patients with BD. Prolonged therapy can also be quite expensive (12). Moreover, there are only a few studies evaluating the factors predicting the risk of UR and the time to UR in BD.

In the light of this information, we aimed to determine the factors predicting the development and recurrence of uveitis, which is an important cause of comorbidity in BD, and to calculate the time to development and recurrence of uveitis.

MATERIAL and METHODS

The study comprised 145 patients over the age of 18 with a diagnosis of BD who were monitored from 2010 to 2022 at the rheumatology departments of two tertiary hospitals. All patients met the International Criteria for Behçet's Disease (ICBD) (13). The study excluded patients with findings inconsistent laboratory and clinical examinations, and those with an unclear onset of symptoms, patients below the age of 18, pregnant women, and patients with

other viral or inflammatory diseases that could cause uveitis. Following the application of the exclusion criteria, 41 patients with ocular involvement and 37 patients without ocular involvement (the control group) were included in the study.

All participants provided their written informed consent. This study was approved by the Institutional Review Board (approval date 23.01.2024 approval number 2024-01). Figure 1 shows the inclusion process.

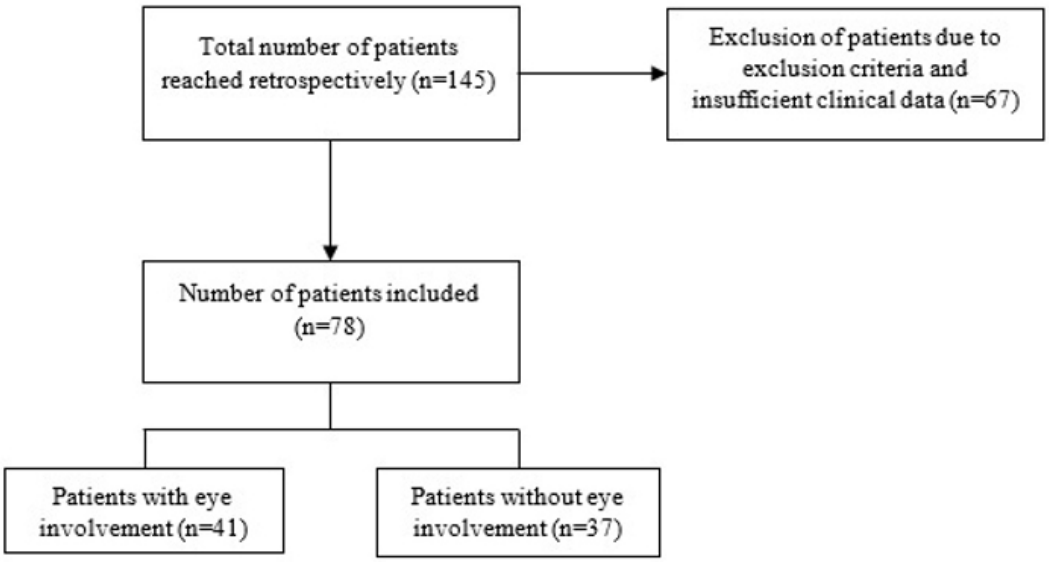

Figure 1. Inclusion process of patients.

Medical records were retrospectively reviewed to collect clinical signs and symptoms that developed after the diagnosis of BD. A standardized data collection form was used to record information about the onset of disease manifestations during the follow-up period, the results of routine ocular examination, vascular and CNS imaging, and endoscopic evaluations.

OrGUn involvement was assessed based on medical history, orGUn-related symptoms, physical examination findings, imaging studies, laboratory tests, and endoscopic results. Patients with ocular involvement were diagnosed with BD uveitis by an experienced ophthalmologist. The type of uveitis (anterior, posterior, panuveitis), presence of retinal vasculitis (RV) and duration of BD uveitis were also recorded. In addition, UR (present/absent) which was defined as the reactivation of a previously controlled uveitis that has been inactive for at least 3 months without treatment modification in the context of SUN criteria, the occurrence of more than three relapses was investiGUted (11). The immunosuppressive treatments received for uveitis were also noted. Using a modified Delphi approach including endoscopic findings and criteria derived from colonoscopic features and clinical signs, intestinal BD was diagnosed (14, 15). Behçet's Disease Current Activity Form (BDCAF), the most commonly used index, was used to assess disease activity.

Demographic and clinical data collected included: This index records the presence of clinical symptoms including headache, oral and genital ulcers, skin manifestations, joint involvement, ocular involvement, major vascular and nervous system involvement, and GUstrointestinal symptoms observed during the four weeks preceding the assessment, with a maximum total score of 12 (16).

Statistical analysis

SPSS 26.0 was used to conduct the statistical analysis (IBM Corp., Armonk, NY, USA). With a power of 80% and a margin of error of 5%, the standard effect size was found to be 0.82. For the uveitis and non-uveitis groups, it was adequate to include n = 30 cases in each group. Descriptive findings were calculated using the median, minimum, and maximum values. We examined whether the kurtosis and skewness values of our data were distributed between -1.5 and +1.5 in order to evaluate the premise of normality (17). As our data were normally distributed, independent sample t test was used for the comparison of quantitative data that may affect the development of uveitis. To compare categorical variables, the chi-square test was used. For parameters with a significant level of $p < 0.1$, the existence of uveitis development was predicted using a multivariate logistic regression model. We assessed the time to development of uveitis using Kaplan-Meier analysis (with log-rank test). The impact of clinical quantitative data and demographic data (gender, smoking, and family history) on the expected time to uveitis development was evaluated using Kaplan-Meier Analysis. Statistical significance was defined as $p \leq 0.05$ for all analyses.

RESULTS

A total of 78 patients with BD who met the ICBD criteria, 41 patients with uveitis and 37 patients without uveitis, were included in this study. Positive pathergy test, GU and papulopustular lesions (PPL) were statistically more common in the non-uveitis group. Table I shows the demographic, clinical and laboratory characteristics of the patients.

Among the patients with uveitis, 90.2% (n=37) used azathiopurine, 24.3% (n=10) corticosteroids, 17% (n=7) adalimumab, 4.8% (n=2) infliximab, 2.4% (n=1) mycophenolate mofetil, 36.5% (n=15) colchicine.

The most significant independent factor for the development of uveitis, according to multivariate studies, was the lack of GU. The prolonged time to diagnosis, neGUtive pathergy test, and absence of PPL also continued to be significant factors affecting the development of uveitis (Table II).

Table I. Demographic, clinical, and laboratory characteristics of study patients

	Uveitis (n=41)	Nonuveitis (n=37)	p
Age (years), median (range)	39 (18-67)	34 (22-60)	0.132
Sex (M/F)	26/15	23/14)	0.356
BMI (kg/m^2), median (range)	27.1 (18.6-35.3)	26.6 (16.6-32.1)	0.954
Presence of family history (%) (n)	7.5 (3)	10.8 (4)	0.441
HLA-B51 positivity (%) (n)	48.7 (20)	43.2 (16)	0,132
Presence of smoking (%) (n)	29.2(12)	29.7 (11)	0.575
Pathergy test positivity (%) (n)	46.3 (19)	59.4 (22)	**0.050**
Age at diagnosis of BD (years), median (range)	28 (1-50)	28.5 (20-50)	0,852
Age at first uveitis of BD (years), median (range)	30 (18-51)	NA	NA
Symptom duration (years), median (range)	15 (2-44)	11 (1.5-36)	0.489
Diagnosis duration (years), median (range)	8 (1-40)	5 (1-30)	0.057
Delay in diagnosis (years), median (range)	3 (1-31)	5 (0-36)	0.111
Follow-up duration (years), median (range)	11 (4-20)	10 (2-18)	0,745
ESR levels (mm/hour), median (range)	18.5 (1-108)	17 (1-17)	0.421
CRP levels (mg/L), median (range)	7.55 (0-28)	7 (0-25)	0.632
Oral ulceration, (%) (n)	100 (41)	100 (37)	0.999
Genital ulcer, (%) (n)	48.8 (20)	75.7 (28)	**0.013**
Erythema nodosum, (%) (n)	17.1 (7)	21.6 (8)	0.412
Papullopustuler lesions, (%) (n)	48.8 (20)	78.4 (29)	**0.006**
Deep vein trombosis, (%), (n)	12.2 (5)	10.8 (4)	0.478
Superficial thrombophlebitis, (%), (n)	4.9 (2)	2,7 (1)	0.273
Arthritis, (%) (n)	26.8 (11)	37.8 (14)	0.213
Gastrointestinal system involvement, (%) (n)	2.4 (1)	0(0)	0.526
Nervous system involvement, (%) (n)	2.4 (1)	2.7 (1)	0.727
BDCAF scores, median (range)	1 (0-10)	3 (0-10)	0.061

*BMI: Body mass index, HLA: Human Leukocyte Antigen, BD: Behçet's Disease, BDCAF: Behçet's Disease Current Activity Form, C reactive protein, ESR: Erythrocyte sedimentation rate, F: Female, M: Male, NA: Not applicable

The absence of GU was found to be an independent factor, predicting the development of uveitis with a 65.3% probability. The rate of predicting the development of uveitis was found to be 72.2% when the prolonged time to diagnosis and the absence of GU were combined.

Uveitis was classified as AU in 46.3% (n=19), PoU in 34.1% (n=14), PaU in 19.5% (n=8) and RV in 7.3%. Uveitis recurred in 53.7% of patients (n=22). On the other hand, 34.1% of the patients (n=14) had more than 3 uveitis attacks. The median time to the occurrence of the second uveitis attack was 6 months (range: 1–180 months). Age, gender, family history, time to diagnosis, delay in diagnosis, ESR, CRP, BDCAF scores, GU, PPL, arthritis, erythema nodosum, involvement of the CNS, and intestinal involvement did not statistically correlate with UR. BMI was statistically significantly higher in patients with UR.

Table II. Multivariate analysis of the factors associated with uveitis in patients with Behçet syndrome

Dependent variable	Independent variables	p value	Beta	Wald	OR	95%CI
Presence of uveitis						
	Genital ulcer	**0.022**	-1.343	5.233	0.261	0.086-0.897
	Diagnosis duration	**0.011**	-1.278	6.628	1.101	1.023-1.185
	Pathergy test	**0.032**	-1.278	4.586	0.279	0.083-0.825
	Papullopustuler lesions	**0.037**	-1.272	4.333	0.281	0.085-0.928
	Constant	0.023	1.526	5.151	4.602	

BMI was statistically significantly higher in patients with UR. In patients with a BMI of 25 kg/m2, UR risk was found to be 70% (Figure 2).

The median time to development of uveitis was 2 years after diagnosis (range: 1–25 years). It was determined that the estimated time for the development of uveitis was 4.34 years after diagnosis. Uveitis was the initial manifestation of the disease in 21.9% of patients (n=9) (Figure 3).

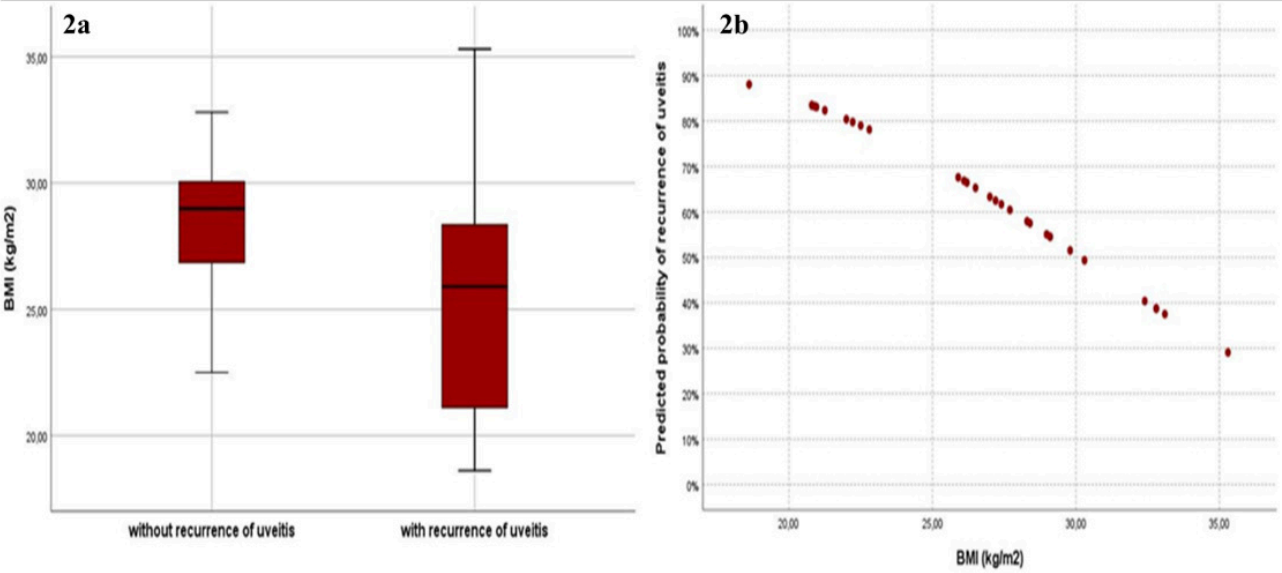

Figure 2. a) Comparison of BMI between with and without recurrence of uveitis b) Predicted probability of occurence of recurrence of uveitis according to BMI in patients with Behçet's Disease, BMI: Body mass index

The estimated time to development of uveitis was 2.90 years after diagnosis in males and 6.86 years in females.

The log-rank test revealed that this difference was statistically significant (p=0.021) (Figure 4).

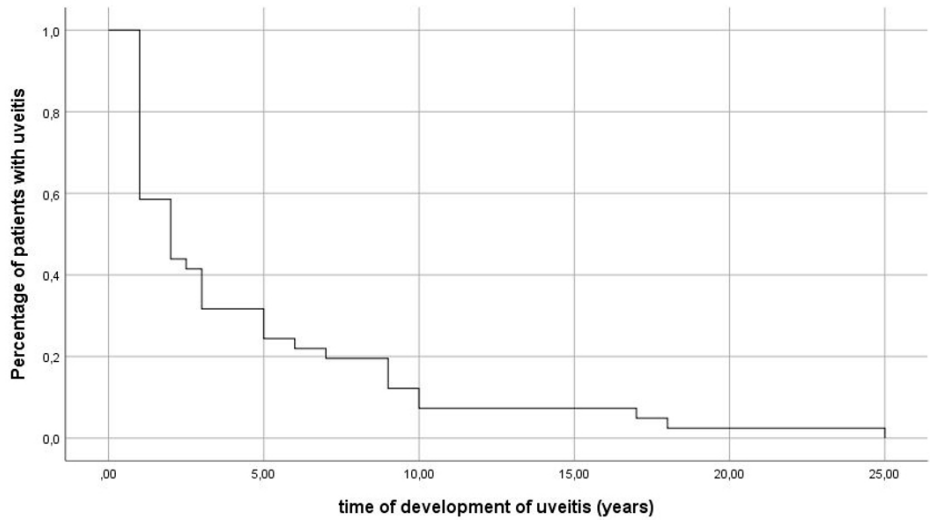

Figure 3. Kaplan–Meier curves of percentage of patients who develops uveitis in patients with Behçet's

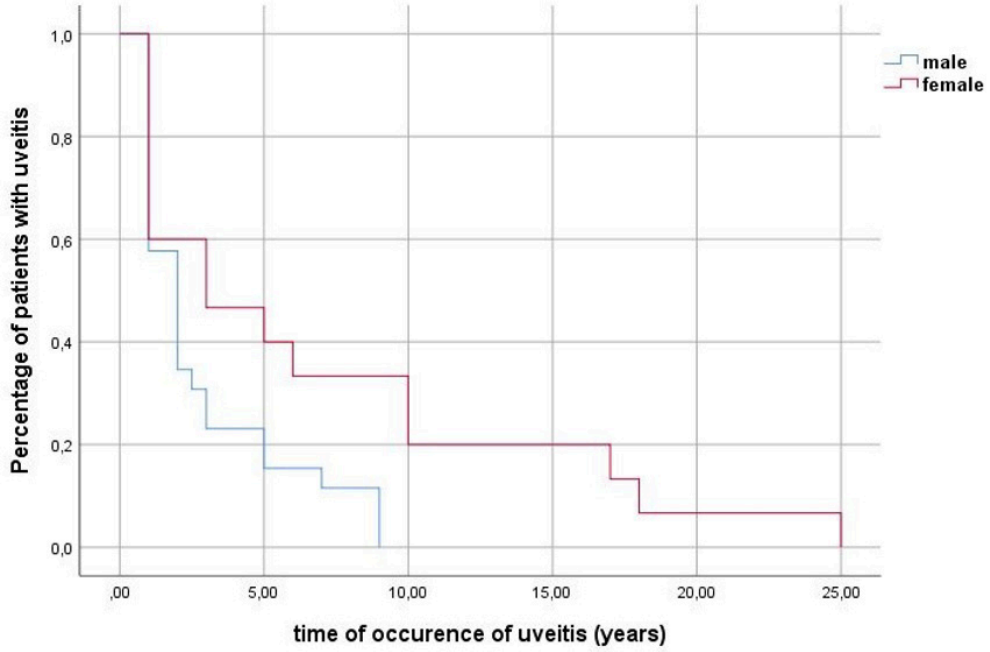

Figure 4. Kaplan–Meier curves of percentage of patients who develops uveitis according to gender in patients with Behçet's Disease

DISCUSSION

Uveitis is one of the major manifestations of BD with the highest morbidity rate (18). In general, the frequency of ocular involvement in BD is around 50%. However, this rate may be as high as 70% in males and young individuals, it may be as low as 30% in the elderly and women (3, 19). The rate of uveitis in the patients included in this study was 52.5%, and it was higher in males, reaching a rate of 63.4%, similar to the findings of the abovementioned study. The frequency of ocular involvement was found to be substantially correlated with a history of smoking in a retrospective investiGUtion of 2118 Turkish patients with BD (20). Nevertheless, in this study, no correlation was found between smoking and BD uveitis. In addition, in our study, the absence of GU was the strongest independent risk factor for uveitis development, with the prolonged time to diagnosis, absence of PPL, and neGUtive pathergy test. Although this finding needs support from further studies, we may suggest that more attention should be paid to the development of uveitis in patients without GU.

BD–related uveitis is usually not the initial manifestation and occurs only in 10-20% of cases as the first manifestation within 2-3 years following additional ocular symptoms (4). Uveitis appeared as an initial symptom in 21.5% of patients and developed during follow-up in 43% of patients, according to a retrospective review of 396 Italian patients with BD (21). Similarly, in this study, uveitis was the initial manifestation in 21.9% of patients. An important finding of this study relates to the timing of uveitis development. The median time to uveitis onset was 2.90 years after diagnosis in males compared with 6.86 years in females. We can conclude that the risk of uveitis development is higher and occurs earlier in males, which is in line with previous studies.

There is no conclusive evidence that shows an association between a specific Human Leukocyte Antigen (HLA) allele and uveitis in BD. Nonetheless, prior research has shown that individuals with eye conditions have higher positivity rates for specific HLAs. Some studies have shown that it is not associated with HLA-B51 (22). In this study, no association was found between the frequency of uveitis and HLA-B51. This suggests that there may be different genetic variants associated with uveitis and accordingly, there is a need for further large-scale genetic studies to address this issue.

BD uveitis is an isolated cluster that is unlikely to be linked to other systemic involvement, such as intestinal, cardiovascular, or CNS involvement, as several investiGUtions have consistently shown (23, 24). These data reflect the intrinsic relationship between the heterogeneity of BD and the affected orGUns. Although many clinical phenotypes and groups of frequently occurring symptoms have been found through cluster analysis and association studies, uveitis stands out as an isolated phenotype (25-27). Similarly, in this study, the finding of uveitis was not clustered with other symptoms and findings, and neGUtively differentiated from the finding of GU. This finding has not been observed in other studies.

According to the 2021 BD uveitis classification criteria, a uveitis syndrome consistent with BD is defined as the presence of AU, AU and intermediate uveitis, or PoU or PaU

with RV and/or focal retinal infiltrates (28). Non-granulomatous uveitis is the predominant ocular manifestation of BD. The anterior, posterior, or both chambers of the eye may be affected by panuveitis. 75-95 % of patients have bilateral involvement, typically following unilateral anterior uveitis that advances to affect both eyes (5-7, 30). In the present study, AU, PoU, PaU, and RV were detected in 41 uveitis patients, in descending order of frequency. The anatomically different frequency of uveitis in this study compared to the literature may be explained by the low frequency of bilateral uveitis, close follow-up and early aggressive treatment of our patients with uveitis, and the small number of patients.

There are limited data reGUrding the factors associated with the risk of UR in BD. 164 BD patients with a history of uveitis participated in a study by Cai et al. that sought to identify the variables influencing BD patients' risk of developing UR. Patients with UR were older and had higher serum amyloid A, total cholesterol, low-density lipoprotein, and triglyceride levels compared with those without UR. In addition, they exhibited a higher frequency and number of uveitis episodes, as well as an increased rate of oral ulcer occurrence within three months (31). In this study, lipid profile was not assessed and UR was significantly higher in patients with higher BMI and no gender difference was observed, which was a main finding. When a detailed review of the literature was performed based on this finding, it was determined that it was reported in the literature that adipose tissue is an endocrine orGUn that secretes bioactive mediators known as adipokines, which aid in controlling inflammation and immune responses, and leptin plays an important role in the pathogenesis of autoimmune and inflammatory diseases, including BD (30). Serum leptin concentration is related to adipose tissue mass, decreasing with weight loss and increasing with weight GUin, and it has also been shown that leptin levels are higher in normal-weight and over-weight women compared to men (31-33). The correlation between eye involvement in BD and serum leptin levels is contradictory in the literature; however, it was found in a study that serum leptin levels were higher only in female patients with uveitis compared to the healthy group, and unlike this study, no distinction was found between the groups reGUrding BMI (34-36). Taken together, these findings suggest that closer monitoring for UR may be warranted, particularly in female patients with BD and higher BMI. Nevertheless, longitudinal studies with longer follow-up periods are needed to confirm these observations. The study design the relatively small sample size and lack of FFA findings correlated with the frequency of uveitis attacks.

CONCLUSION

Two main findings of our study were that uveitis was more common in patients without GU and UR was more common in patients with high BMI. We believe that these two findings should be supported by further studies with a larger number of patients and more homogeneous patient groups in order to establish a common algorithm for other clinicians and to close the GUp in this subject.

Ethics Committee Approval

This research complies with all the relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration, and has been approved by the University of Health Sciences, İstanbul Physical Medicine and Rehabilitation Education and Research Hospital Ethical Committee (approval number: 23.01.2024/2024-01).

Informed Consent

All the participants' rights were protected and written informed consent was obtained before the procedures according to the Helsinki Declaration.

Author Contributions

Concept – N.K., H.H., M.A.B..; Design – N.K., H.H..; Supervision – N.K., H.H., M.A.B.; Resources – N.K., H.H., M.A.B..; Materials – N.K., M.A.B.; Data Collection and/or Processing – N.K., H.H., M.A.B.; Analysis and/ or Interpretation – N.K., H.H.; Literature Search – N.K., H.H., M.A.B.; Writing Manuscript – N.K., H.H., M.A.B.; Critical Review - N.K., H.H., M.A.B.

Conflict of Interest

The authors have no conflict of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

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