






Orbital Doppler ultrasonography evaluation in patients with ankylosing spondylitis: A prospective study

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ABSTRACT

OBJECTIVE: Our aim in this study is to compare patients with ankylosing spondylitis (AS), a rheumatologic disease that can cause eye involvement and the normal population in terms of orbital Doppler findings, which is an inexpensive and easily applicable method that can be used in early diagnosis and follow-up.

METHODS: The study was planned prospectively. The data of patients with AS were compared to those of age- and gender-matched healthy volunteers. A total of 42 participants, 23 (54.8%) males and 19 (45.2%) females, with a mean age of 42.4±12.6 years were included in the study. In addition to demographic information, such as age and gender, the diameter, peak systolic velocity, end-diastolic velocity, mean velocity, resistive index, pulsatility index, and blood flow volumes of the central retinal artery of the left eye were measured using spectral Doppler ultrasonography.

RESULTS: According to the comparison of the patients with and without AS according to orbital Doppler ultrasonography findings, the mean velocity, resistive index, and volume measurements of the patients with AS were significantly higher than those without AS ($p=0.028$, $p=0.039$, and $p=0.038$, respectively). However, in the subgroup analysis of the AS group, the Doppler findings did not significantly differ between the patients with and without anterior uveitis.

CONCLUSION: In the patient group with AS, independent of anterior uveitis (AU), there was a difference in Doppler parameters and therefore in ophthalmic vasculature. In patients with AS, orbital vascularity changes can be detected with orbital Doppler US before clinical signs appear.

Keywords: Ankylosing spondylitis; anterior uveitis; orbital Doppler ultrasonography.

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Ankylosing spondylitis (AS) is a chronic systemic rheumatological disease, typically presenting with sacroiliac joint inflammation. Although the etiology of AS remains unknown, a genetic predisposition is observed [1, 2]. AS affects 0.1 to 1.4% of the global population. AS susceptibility is highly influenced by an individual's genotype, with approximately 95% of patients with AS showing positivity for the gene expression of

the MHC Class I molecule, HLA-B27. AS primarily affects the axial skeleton and is characterized by spinal inflammation, particularly sacroiliitis, bone formation, and joint damage [3]. The presence of AS is associated with certain ophthalmic diseases [4]. Acute anterior uveitis (AU) is the most common ophthalmologic manifestation of AS [5]. In a previous study, any history of uveitis was observed in 32% of the AS population [6]. In



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addition, although less common than iridocyclitis, chorioretinitis and panuveitis have also been observed in the presence of AS [7]. Other ophthalmic diseases associated with AS include papillitis, retinal vasculitis, vitritis, cystoid macular edema, pars plana exudates, and epiretinal membranes [8].

Orbital color Doppler ultrasonography is an inexpensive, easily applicable and non-invasive method that is frequently used in the evaluation of orbital vessels in various orbital and ocular diseases [9].

In this study, we aimed to evaluate orbital Doppler findings as a potential method for the early diagnosis and follow-up of patients with AS and compare the data to those of a healthy population.

MATERIALS AND METHODS

Study Population

The study was planned prospectively and included patients with AS and those with both AS and AU who were referred to our hospital from January 1, 2020, through December 31, 2021, as well as age- and gender-matched healthy volunteers as controls. The study has been approved by the Sakarya University Faculty of Medicine Clinical Studies Ethics Committee (date: 24.03.2021, no: 08) and conducted in accordance with the Declaration of Helsinki. A total of 42 patients aged over 18 years were included in the sample. None of the patients included in the study had any active ophthalmic findings. Individuals aged under 18 years, who did not have bilateral retinal artery measurements or who had additional pathologies such as malignancies that could affect these measurements were excluded from the study.

Radiological Measurements

Patients who presented to our rheumatology clinic and were followed up in this clinic were called to the hospital outside working hours to sign consent forms after the procedure was explained. Volunteers were those who presented to our hospital for reasons not included in the exclusion criteria, and they were also informed about the procedure and provided written consent. The age and gender of the participants were recorded. The participants were informed in detail that during the procedure, there would be pressure on their eyelids with the use of the ultrasound probe, and if they felt uncomfortable, the procedure would be terminated. No problem occurred in relation to the technique used during the procedure, and

Highlight key points

- The presence of AS is associated with certain ophthalmic diseases.
- Orbital Doppler can be used for the diagnosis and follow-up of ocular pathologies.
- In patients with AS, orbital vascularity changes can be detected with orbital Doppler US before clinical signs appear.

there was not enough pressure to necessitate the termination of the procedure in any of the patients. For standardization of the study and easy evaluation of the results, all measurements were made from the left eye, similar to the other study in the literature [10]. Subsequently, the orbital anatomy of the left eye of the participants was evaluated using the B-mode examination with the 7.5-Mhz linear probe of the ultrasound device (Samsung, Korea). After measuring the diameter of the central retinal artery (Fig. 1) to confirm that there was no abnormality in the anatomy, the color Doppler ultrasonography examination was started. Subsequently, a spectral Doppler examination was undertaken by placing the angle correction cursor. After the participants were instructed to stay still and not move their eyes, necessary measurements were made using the angle cursor and device settings.

The peak systolic velocity, end-diastolic velocity, mean velocity, resistive index, pulsative index, and flow volumes of the central retinal artery for the left eye were calculated and recorded (Fig. 2).

Statistical Analysis

Jamovi (Version 2.2.5.0, Sydney, Australia) and JASP (Version 0.16.1, Amsterdam, The Netherlands) were used for statistical analysis. The descriptive statistics were given as median (minimum–maximum) and mean \pm standard deviation. Categorical variables were stated as frequencies and percentages. The normality of the distribution of numeric variables was tested using the Shapiro-Wilk and Kolmogorov-Smirnov tests.

The comparison of differences between the groups in terms of categorical variables based on 2x2 tables was undertaken using the Pearson chi-square test when the expected value of a cell was ≥ 5 , and Fisher's exact test when it was < 5 . For RxC tables with expected cells below 5, the Fisher-Freeman-Halton test was used. The independent samples t-test was used for the comparison of continuous variables with normal distribution and the Mann-Whitney U and Kruskal Wallis tests for the data



FIGURE 1. Central retinal artery diameter measurement on the B-mode ultrasonography image.

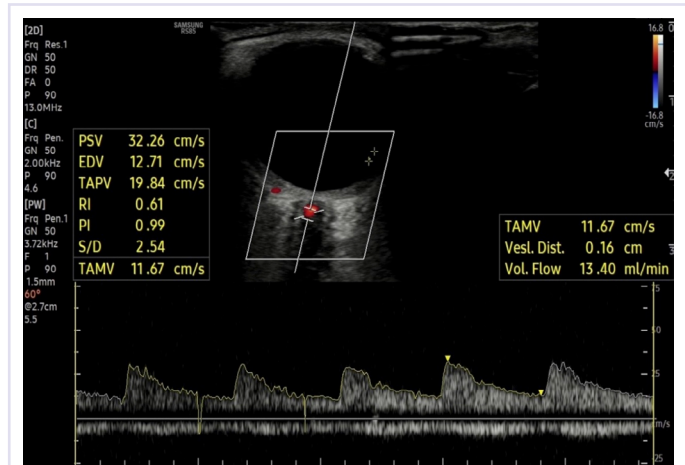


FIGURE 2. Measurements of the peak systolic velocity, end-diastolic velocity, mean velocity, resistive index, pulsative index, and flow volumes of the central retinal artery for left eye on spectral Doppler ultrasonography.

TABLE 1. Demographic and clinical characteristics of all the patients included in the sample

| | Overall (n=42) |
|----------------------|----------------|
| Age (years), Mean±SD | 42.4±12.6 |
| Gender, % | |
| Male | 54.8 |
| Female | 45.2 |
| AS, % | |
| Negative | 50.0 |
| Positive | 50.0 |
| Anterior uveitis, % | |
| Negative | 61.9 |
| Positive | 38.1 |
| Groups, % | |
| AS (+) AU (+) | 19.0 |
| AS (+) AU (-) | 31.0 |
| AS (-) AU (-) | 50.0 |

SD: Standard deviation; AS: Ankylosing spondylitis; AU: Anterior uveitis.

TABLE 2. Comparison of the AS subgroups in terms of demographic characteristics

| | AS (+) AU (+) (n=8) | AS (+) AU (-) (n=13) | p |
|----------------------------------|------------------------|-------------------------|---------|
| Age (years), Median (min–max) | 38.5 (24.0–61.0) | 45.0 (27.0–64.0) | 0.562* |
| Gender, % | | | 0.847** |
| Male | 50.0 | 61.5 | |
| Female | 50.0 | 38.5 | |

AS: Ankylosing spondylitis; AU: Anterior uveitis; *: Kruskal Wallis-H test; **: Pearson chi-square or Fisher-Freeman-Halton test.

that did not conform to normal distribution. The comparison of more than two independent groups was performed using the Kruskal-Wallis H test in cases where numerical variables did not show a normal distribution. The differences between the groups were evaluated using the Dwass-Steel-Critchlow-Fligner test as a non-parametric method. A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

A total of 42 patients with a mean age of 42.4 ± 12.6 years were included in the study. Of the patients, 23 (54.8%) were male, and 19 (45.2%) were female. AS was detected in 21 (50%) of the patients, of whom eight (38.1%) also had AU. Accordingly, the AS group consisted of eight (19.0%) AS (+) AU (+) patients and 13 (31.0%) AS (+) AU (-) patients, and the control group comprised 21 (50.0%) AS (-) AU (-) patients (Table 1). The median age of the AS (+) AU (+) subgroup was lower than those of the AS (+) AU (-) subgroup and the control group, but there was no significant difference ($p = 0.562$). The gender distribution was similar between the groups ($p = 0.847$) (Table 2).

TABLE 3. Comparison of the patient groups with and without ankylosing spondylitis according to orbital Doppler US findings

| | Ankylosing spondylitis | | p |
|---|------------------------|-----------------|----------------|
| | Negative (n=21) | Positive (n=21) | |
| Doppler US variables | | | |
| Retinal artery diameter (mm), Median (min–max) | 1.5 (1.0–1.7) | 1.5 (0.8–1.9) | 0.459* |
| Peak systolic velocity (cm/s), Median (min–max) | 12.2 (8.0–17.4) | 13.9 (9.8–21.0) | 0.554* |
| End-diastolic velocity (cm/s), Mean±SD | 3.6±1.0 | 3.2±1.0 | 0.178** |
| Mean velocity (cm/s), Mean±SD | 5.4±1.5 | 6.4±1.4 | 0.028** |
| Resistive index, Median (min–max) | 0.7 (0.6–0.8) | 0.8 (0.6–0.9) | 0.039* |
| Pulsatility index, Median (min–max) | 1.7 (1.2–2.6) | 1.8 (0.8–2.5) | 0.880* |
| Volume (mm ³), Mean±SD | 8.7±3.2 | 11.4±4.7 | 0.038** |

SD: Standard deviation; US: Ultrasonography; *: Mann-Whitney U test; **: Independent-samples t-test.

TABLE 4. Comparison of the patients with and without AU in the AS group according to orbital Doppler US findings

| | AU (+) (n=8) Median (min–max) | AU (-) (n=13) Median (min–max) | p* |
|-------------------------------|----------------------------------|-----------------------------------|-------|
| Doppler US variables | | | |
| Retinal artery diameter (mm) | 1.6 (0.8–1.7) | 1.4 (1.2–1.9) | 0.735 |
| Peak systolic velocity (cm/s) | 13.6 (9.8–16.2) | 13.9 (11.0–21.0) | 0.525 |
| End-diastolic velocity (cm/s) | 2.4 (1.3–4.7) | 3.6 (2.1–5.0) | 0.176 |
| Mean velocity (cm/s) | 6.2 (4.3–8.2) | 6.8 (4.5–8.8) | 0.135 |
| Resistive index | 0.8 (0.6–0.9) | 0.8 (0.6–0.9) | 0.055 |
| Pulsatility index | 1.8 (1.0–2.0) | 1.8 (0.8–2.5) | 0.908 |
| Volume (mm ³) | 12.2 (2.2–16.4) | 9.9 (5.9–21.7) | 0.138 |

US: Ultrasonography; AU: Anterior uveitis; AS: Ankylosing spondylitis; *: Kruskal Wallis-H test.

According to the comparison of the groups with and without AS according to orbital Doppler ultrasonography findings, the mean velocity, resistive index, and volume measurements of the patients with AS were significantly higher than those without AS ($p=0.028$, $p=0.039$, and $p=0.038$, respectively). The remaining Doppler ultrasonography findings were similar between the groups ($p>0.05$) (Table 3).

According to the subgroup analysis of the AS group, there was no significant difference between the patients with and without AU in terms of Doppler ultrasonography findings (Table 4).

DISCUSSION

The most important result of our study is that the mean velocity, resistive index, and volume measurements of the patients with AS were significantly higher than those of the controls. In a similar study by Ozsahin et al. [10], no significant difference was found between the two groups in terms of Doppler parameters. However, the authors did not include patients with AU in their sample. Two important differences of our study from this study are the differences in the Doppler findings of patients with AS and the normal population, and the inclusion of patients with AU in our study. In a study by Akkurt et al. [11], in which

a patient group with psoriatic arthritis and a healthy population were compared, a significant difference was found between the two groups in terms of orbital Doppler parameters. In a recent study using optical coherence tomography, Koca et al. [12] found a significant difference between patients with axial spondyloarthritis and healthy controls in terms of the capillary plexus density which is also similar to our study. In another study, Kal et al. [13] compared patients with rheumatoid arthritis and controls in terms of orbital Doppler findings and reported a significant difference between the two groups. Therefore, the results of these last three studies are similar to those we obtained from the current study.

The pathogenesis of eye involvement in AS is not yet fully understood, and none of the hypotheses available in current studies are sufficient to elucidate it [14]. The most common ophthalmic finding is acute AU, which occurs in 40% of patients with AS and is more common in men than in women. It typically occurs in young adults aged 20–40 years [15]. It is estimated that one-third of patients with acute AU have AS, and 50% of these patients are positive for HLA-B27 [16]. Uveitis is anatomically classified as anterior, middle, pan, and posterior uveitis, with the most common subtype being AU. It may have a sudden or insidious onset, be limited in duration or persistent, and have an acute, recurrent, or chronic course. Most patients with this condition are 20–50 years of age, and this condition can cause blindness and have significant socioeconomic consequences [17]. Verhagen et al. [18] reported that after an average of 9.7 years, 20/212 (9%) of the patients developed permanent visual impairment or blindness in at least one eye due to uveitis. Therefore, the early diagnosis and treatment of eye involvement is crucial.

Doppler ultrasonography is a non-invasive, inexpensive, and easily applicable method for imaging normal and pathological vessels. Orbital Doppler can be used for the diagnosis and follow-up of ocular pathologies [19]. Studies have been conducted using orbital Doppler to evaluate eye involvement in Behçet's disease, which is the most common rheumatological disease. In this context, Doppler ultrasonography has been shown to be beneficial in determining both the activity of the disease and eye involvement [20, 21]. However, in a study by Isik et al. [22] evaluating Behçet's cases, there was no significant difference in orbital Doppler findings between the patients with and without uveitis, which is similar to our study. The lack of difference between the groups with and without anterior uveitis suggests that this may be due to other mechanisms rather than uveitis.

The most important feature that makes our study unique is that it is the first study in which positive findings were published in patients with AS. Negative results were reported in the only study on this subject in the literature [10].

Our study has certain limitations. First, only a small number of patients were included in the study. Second, Doppler ultrasonography was performed by a single operator, and therefore the difference between observers could not be evaluated. Lastly, since the optical coherence tomography data of the patients could not be simultaneously obtained, we were not able to perform an evaluation and comparison in this regard.

Conclusion

In the patient group with AS, independent of AU, there was a difference in Doppler parameters and therefore in ophthalmic vasculature. Thus, in patients with AS, orbital vascularity changes can be detected with orbital Doppler US before clinical signs appear.

Ethics Committee Approval: The Sakarya University Clinical Research Ethics Committee granted approval for this study (date: 24.03.2021, number: 08).

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