Rheumatology International (2019) 39:1001–1006
https://doi.org/10.1007/s00296-019-04275-y

Rheumatology
INTERNATIONAL

IMAGING

Color Doppler imaging of ocular hemodynamic changes in patients with rheumatoid arthritis unrelated to disease activity

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Received: 22 January 2019 / Accepted: 6 March 2019 / Published online: 12 March 2019

Abstract

We aimed to investigate how orbital blood flow rates in patients with rheumatoid arthritis (RA) are affected by the active and remission phase of the disease. This prospective study included a total of 56 patients with RA (study group) and 24 control individuals (control group). All RA patients were divided into two groups, as active (Group 1) and remission (Group 2) according to the disease activity index (DAS 28) score. For each eye, retrobulbar vascular structures were evaluated [central retinal artery (CRA), posterior ciliary artery (PCA), and ophthalmic artery (OA)], respectively. The peak systolic velocity (PSV) and end-diastolic velocity (EDV) values were obtained for each artery and the vascular resistance index (RI) measurement was calculated. The median RI of the OA was 0.70 (0.57; 0.79) in the control group, 0.77 (0.55; 0.87) in group 1, and 0.73 (0.47; 0.87) in group 2. The median RI in the PCA was 0.70 (0.56; 0.82) in the control group, 0.76 (0.52; 0.88) in the group 1, and 0.74 (0.52; 0.86) in the group 2. The median RI of CRA was 0.73 (0.48; 0.81) in the control group, 0.71 (0.64; 0.81) in group 1, and 0.68 (0.61; 0.85) in group 2. The RI value was a significant difference between control and group 1 ($p < 0.05$). Active and remission RA patients had different effects on the flow rate of eye blood vessels.

Keywords Blood flow rate · Doppler ultrasonography · Rheumatoid arthritis · Vascular structures

Introduction

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease that can affect more than one joint at the same time. It is a systemic disease with a chronic course and the etiology is not fully known. In different populations, the prevalence varies between 0.5% and 1% [1]. Although RA may be seen at any age, it is most common in the 35–60 year range. The female-to-male ratio is 3:1 [2, 3].

RA causes inflammation in the joint synovium and leads to primary synovitis. Then inflammation may spread beyond the joint and can involve the cardiovascular, hematological, neurological, and respiratory systems, and other organs such as the liver, muscles, kidneys, and eyes [4, 5]. Of the extra-articular involvements, ocular involvement is one of the most well-defined extra-articular symptoms [6, 7]. All the layers of the eye may be involved [8], with keratoconjunctivitis sicca (KCS) the most common involvement at the rate of 10–35% [9]. Other ocular findings secondary to

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inflammation are uveitis, keratitis, episcleritis, scleritis, and anterior ischaemic optic neuropathy [6].

The normal arterial wall has an intima layer covered with a row of endothelial cells on the surface facing the lumen [10]. These endothelial cells regulate vascular permeability and vascular tone, and play an important role in vascular health while maintaining blood flow. If endothelial damage occurs, as in patients with RA and chronic systemic inflammation, the first stage of atherosclerotic plaque development (atherogenesis) begins [11]. As a result of this mechanism, the predisposition to atherosclerosis was reported to be a known risk factor in RA patients [12].

In addition, vasculitis seen in RA has been defined as an extra-articular finding of RA. Functional and structural changes occur in the arteries such as increased vascular resistance and the development of endothelial dysfunction secondary to inflammation in RA. This changes arterial compliance and arterial stiffness. The previous studies have shown that RA affects the choroid and retinal arteries, just as it affects the vascular structures in other organs [13].

As CDI is a painless, non-invasive, and repeatable method, it is the most common imaging method used in the evaluation of blood flow velocity. Evaluation of the retrobulbar vascular structures (central retinal artery, posterior ciliary artery, and ophthalmic artery) and measurement of blood flow velocity have been made with CDI in several studies [13–15]. Although the Color Doppler Imaging (CDI) method has become important in the investigation of the effect on the blood flow velocity of the changes occurring in vascular structures secondary to inflammation in RA, there has been no previous study that has evaluated orbital blood flow velocity of RA patients in the active and remission phases. Therefore, the aim of this study was to compare the blood flow velocity of retrobulbar vascular structures measured with CDI in RA patients in the active and remission phases.

Materials and methods

This prospective study was conducted between June 2016 and December 2016. A total of 56 RA patients (25 active, 31 in remission) and 24 healthy control subjects were included. Approval for the study was granted by Clinical Research Ethics Committee of Ankara Keçiören Research and Training Hospital, and all procedures were applied in compliance with the principles of the Helsinki Declaration. Informed consent was obtained from all the study participants.

Disease activity was evaluated by a rheumatology specialist using the Disease Activity Score 28 (DAS-28) [16]. In addition, general health was evaluated on a Visual Analog Scale (VAS), C-reactive protein (CRP) was examined, and the number of 28 swollen and tender joints was used for DAS-28 [16]. The RA patients were separated into two groups according to the DAS-28 points of >2.6 (Group 1: active) and <2.6 (Group 2: remission). The active group was further divided into three subgroups as follows: mild ($2.6 < \text{DAS-28} \leq 3.2$) ($n=1$), moderate ($3.2 < \text{DAS-28} \leq 5.1$) ($n=22$), and severe ($\text{DAS-28} > 5.1$) ($n=2$) (Table 1).

A single, experienced physician applied full ophthalmological examinations to all the patients, including best corrected visual acuity (BCVA) on a Snellen chart, anterior segment, and dilated fundus examination with slit-lamp and intraocular pressure (IOP) measured with Goldmann applanation tonometry.

Patients were excluded from the study if they had a history of corneal or intraocular surgery, patients with hyperlipidemia, eye trauma, corneal scar, active corneal lesion, the use of topical medication, use of contact lenses, glaucoma, retina disease, pregnancy, uncontrolled diabetes, use of systemic corticosteroids, hypertension, carotid artery pathology determined on CDI, connective tissue disease, or any systemic disease that could affect the eyes.

The retrobulbar circulation values of both eyes were evaluated in all cases by the same experienced radiologist blinded to the groups and using an Aplio 500 device (Toshiba Medical Systems, Co, Ltd, Otawara, Japan). A high-resolution 12–17 MHz linear probe was used in the measurements. Real-time gray-scale and color Doppler images were obtained with the patient supine and eyes closed, and other than the application of sterile gel to the eyelids, no pressure was applied to the eyes [17].

The retrobulbar vascular structures (CRA, PCA, and OA) were evaluated in both eyes. All the measurements were taken at an angle ($<60°$) in the same direction as the blood flow. The OA measurement was taken approximately 20 mm posteromedial of the globe, the PCA was measured from the lateral of the optic nerve in the posterior of the globe, and the CRA was measured in the optic nerve approximately 3–4 mm posterior of the globe. From these measurements, the end-diastolic velocity (EDV) and the peak systolic velocity (PSV) values were obtained for each artery. Then, the vascular resistance index (RI) was calculated using the formula of RI = (PSV-EDV)/PSV [18].

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS vn 20.0 software (SPSS Inc., Chicago, IL, USA). All continuous variables were tested with respect to conformity to normality of distribution. The categorical variables between the groups were analyzed using the Chi-square test. An independent *t* test was used to compare variables. The Mann–Whitney *U* test was applied for the comparison between the groups of median values. Correlations between two variables were determined with Pearson correlation

Table 1 Patient demographics and characteristics of each group

	Rheumatoid arthritis group ($n=56$)	Control group ($n=24$)	p^a	Rheumatoid arthritis subgroups		
				Remission (DAS-28 ≤ 2.60) ($n=31$)	Active (DAS-28 > 2.60) ($n=25$) Mild 2.6 < DAS-28 ≤ 3.2 ($n=1$) Moderate 3.2 < DAS-28 ≤ 5.1 ($n=22$) Severe DAS-28 > 5.1 ($n=2$)	p^a
Age (years)						
Mean ± SD	49.78 ± 9.91	47.25 ± 5.16	0.222	49.87 ± 9.61	49.67 ± 10.15	0.210
Sex						
Female	45 (80.3%)	22 (91.6%)	0.746[b]	25 (80.6%)	22 (88%)	0.462[b]
Male	11 (19.7%)	2 (8.3%)		6 (19.4%)	3 (12%)	
Disease duration (years)						
Mean ± SD	7.59 ± 7.80	NA	–	8.82 ± 8.77	6.04 ± 6.09	0.062
DAS-28 score						
Mean ± SD	3.05 ± 1.13	NA	–	2.12 ± 0.37	4.17 ± 0.63	< 0.001

DAS-28 disease activity score-28, *NA* not applicable, *SD* standard deviation

[a]Independent samples *t* test

[b]Chi-square test

analysis. All results were stated as median (Min; Max) values. A value of $p < 0.05$ was accepted as statistically significant.

Results

Demographic characteristics

No statistically significant difference was determined between the groups with respect to the male:female ratio; control group 2:22 and RA patient group 11:45 ($p = 0.746$). The mean age of the patients was 47.25 years (37; 55) in the control group and 49.78 years (37; 55) in the RA patient group, with no statistically significant difference determined ($p = 0.222$). The demographic characteristics of the study subgroups and the control group are shown in Table 1.

Results of the blood flow velocity parameters

The blood flow velocity parameters in both groups (study and control) are presented in Table 2. The median RI values of OA, PCA, and CRA were statistically significant different between study and control groups.

The median RI value of the OA was 0.70 (0.57; 0.79) in the control group, 0.77 (0.55; 0.87) in active (Group 1), and 0.73 (0.47; 0.87) in remission (Group 2). The median RI value of the PCA was 0.70 (0.56; 0.82) in the control group, 0.76 (0.52; 0.88) in Group 1, and 0.74 (0.52; 0.86) in Group 2. The median RI value of the CRA was 0.73 (0.48; 0.81) in the control group, 0.71 (0.64; 0.81) in Group 1, and 0.68 (0.61; 0.85) in Group 2. The median RI values of OA, PCA, and CRA were statistically significant different between control and group 1 ($p < 0.05$).

The blood flow velocity measurements of study subgroups and control group are summarized in Table 3.

A significant positive correlation was determined between the RI of OA and DAS-28 ($p = 0.02$, $r = 0.199$). No statistically significant correlation was determined between the other blood flow velocity parameters and DAS-28.

Discussion

In our study, we compared the blood flow rates of retrobulbar vascular structures of active and remission RA patients with CDI. Because vascular involvement, which is an integral part of RA pathogenesis [11], is very important and is characterized histologically by mononuclear cell intensity of the postcapillary venules associated with inflammation in the synovium [19]. However, it has been shown in blind biopsies and in autopsy studies that vascular inflammation is

Table 2 Comparison of retrobulbar hemodynamics measurements between study and control groups

Characteristics	Control[b]	Rheumatoid arthritis	p[a]
Ophthalmic artery			
RI	0.70 (0.57; 0.79)	0.75 (0.47; 0.87)	0.025
PSV (cm/s)	30.70 (13.60; 58.90)	29.00 (18.50; 44.40)	0.453
EDV (cm/s)	6.85 (3.20; 14.60)	7.10 (3.20; 16.40)	0.606
Posterior ciliary arteries			
RI	0.70 (0.56; 0.82)	0.75 (0.52; 0.88)	0.003
PSV (cm/s)	17.95 (13.60; 26.30)	16.50 (9.30; 24.80)	0.025
EDV (cm/s)	5.65 (2.90; 9.90)	4.10 (2.00; 7.20)	< 0.001
Central retinal artery			
RI	0.73 (0.48; 0.81)	0.69 (0.61; 0.85)	0.008
PSV (cm/s)	11.30 (7.10; 15.80)	11.80 (7.40; 16.70)	0.345
EDV (cm/s)	3.35 (2.20; 5.70)	3.20 (1.70; 5.50)	0.026

EDV end-diastolic velocity, *PSV* peak systolic velocity, *RI* resistance index

[a]Mann–Whitney *U* test

[b]Values are expressed as the median (max; min)

Table 3 Mean values of resistance index, peak systolic blood flow velocity, and end-diastolic blood flow velocity of the ophthalmic artery, central retinal artery, and posterior ciliary arteries in rheumatoid arthritis and controls

Characteristics	Control[b]	Rheumatoid arthritis subgroups		p[a]		
		Remission RA[b]	Active RA[b]	Control vs. remission	Control vs. active	Remission vs. active
Ophthalmic artery						
RI	0.70 (0.57; 0.79)	0.73 (0.47; 0.87)	0.77 (0.55; 0.87)	0.116	0.008	0.178
PSV (cm/s)	30.70 (13.60; 58.90)	27.80 (18.50; 40.60)	29.70 (19.80; 44.40)	0.252	0.893	0.145
EDV (cm/s)	6.85 (3.20; 14.60)	7.35 (3.60; 15.70)	6.80 (3.20; 16.40)	0.494	0.828	0.444
Posterior ciliary arteries						
RI	0.70 (0.56; 0.82)	0.74 (0.52; 0.86)	0.76 (0.52; 0.88)	0.023	0.001	0.113
PSV (cm/s)	17.95 (13.60; 26.30)	15.70 (9.30; 24.80)	16.60 (10.20; 24.80)	0.015	0.110	0.178
EDV (cm/s)	5.65 (2.90; 9.90)	4.10 (2.00; 7.20)	4.00 (2.10; 7.20)	0.001	0.001	0.693
Central retinal artery						
RI	0.73 (0.48; 0.81)	0.68 (0.61; 0.85)	0.71 (0.64; 0.81)	0.045	0.003	0.132
PSV (cm/s)	11.30 (7.10; 15.80)	11.65 (8.50; 16.70)	12.10 (7.40; 16.20)	0.419	0.347	0.746
EDV (cm/s)	3.35 (2.20; 5.70)	3.20 (1.70; 5.50)	3.00 (1.8; 5.30)	0.140	0.006	0.036

EDV end-diastolic velocity, *PSV* peak systolic velocity, *RA* rheumatoid arthritis, *RI* resistance index

[a]Mann–Whitney *U* test

[b]Values are expressed as the median (max; min)

not limited to the synovium, but widespread involvement is also seen in the blood vessels [20, 21]. All the layers of the vessel wall are infiltrated, primarily by lymphocytes [22].

There are also studies showing a relationship between atherosclerosis and inflammatory process. Some adhesion molecules [intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM), and endothelial leukocyte adhesion molecule-1 (ECAM-1)] found in blood circulation can cause endothelial dysfunction [23–27]. Increases in the blood levels of these molecules have been shown to predict atherosclerosis and cardiovascular events [25, 26].

Dessein et al. [28] compared 74 RA patients and a control group of 80 healthy subjects with respect to the level of adhesion molecules (VCAM-1, ICAM-1, and ELAM-1). The levels of adhesion molecules in blood circulation were determined to be higher in the RA patients. In addition, common carotid artery atherosclerosis was determined to be correlated with VCAM-1 in RA patients. In a study by Wallberg-Jonsson et al. [29], it was shown that the ICAM-1

level was higher in RA patients with atheromatous plaque in the femoral arteries. When these studies are taken into consideration, it can be concluded that there is an increased predisposition to atherosclerosis in the vascular structures of RA patients. In accordance with these results, the aim of the current study was to investigate to what extent this predisposition affected the retrobulbar vascular structures in RA patients in the active and remission phases. The results of the study showed that there was a significant difference between the active and remission phases with respect to the level of effect of RA disease on retrobulbar vascular structures.

Ocular involvement is one the most commonly identified extra-articular symptoms of RA [6, 7]. In some RA patients, ophthalmological findings may be the first symptom of the disorder. Thus, ocular findings can be helpful in diagnosis as the first clue in rheumatological diseases which progress with indeterminate findings and symptoms [30]. In these cases, ocular findings will be of guidance for the clinician in diagnosis.

The measurement of blood flow velocity of the vascular structures with CDI has a very important role in the evaluation of capillary blood flow of the optic nerve head and the retina. In addition, changes in the blood flow velocity with disease activity in RA patients change the perfusion in the retinal vessels and primarily in the optic nerve. A change in the perfusion of these tissues, which are sensitive to ischaemia, has an impact on the development of ocular complications of RA patients in the remission phase, seen mainly as anterior ischaemic optic neuropathy [31] and retinal artery occlusion [32].

Inflammation in RA can cause to the destruction of various tissues including blood vessels. Blood vessels of all sizes may be affected, particularly small vessels. Vasculitis can also occur without displaying characteristic clinical symptoms, a condition known as subclinical vasculitis. In some studies, very minor inflammatory changes around the blood vessels have been reported [33]. In our study, we found significant different velocity parameters in small vessels. This result supports that vessels might be effected without any symptoms in different phases.

According to the literature information, Erdoğmuş et al. evaluated how ocular blood flow velocity was affected using CDI in RA patients. In the comparison of the RA patients with a control group, statistically significant differences were found in the EDV, PSV, and RI of the PCA and OA and in the RI values of the CRA. A significant relationship was also determined between the duration of disease and blood flow in the patient group [34]. However, in that study by Erdoğmuş et al., the patients were only defined as RA patients and they were not separated according to active and remission phases. It was stated in the study that "the ocular blood vessel flow velocity of every RA patient is affected". However, the other studies have reported that active RA showing a high degree of inflammation can rapidly lead to atherosclerosis. These results showed that there was a difference between the active and remission periods in the rate of development of atherosclerosis in the vascular structures. In addition, the previous studies have shown that subclinical vascular lesions develop before atherosclerosis becomes clinically evident, and it has been reported that this forms more rapidly in RA than in the general population [35]. Unlike the study by Erdoğmuş et al., the RA patients in the current study were evaluated with respect to blood flow velocity in the active and remission phases. The results of this study showed a significant difference between the control, active and remission groups in respect of the RI values of the OA, PCA, and CRA. A significant positive correlation was determined between the RI values of OA and DAS-28, but there was no statistically significant correlation between DAS-28 and any of the other blood flow velocity parameters.

In conclusion, this study of RA patients in active and remission periods evaluated with CDI, demonstrated that the blood flow velocity in retrobulbar vascular structures was better in the remission phase. From these results, it can be said that endothelial damage in the vessels feeding the eye and the development of atherosclerosis could occur later in the remission phase of RA, whereas, in the active phase, because of rapid endothelial damage and atherosclerosis development, the feeding of tissues will be impaired with a reduced flow and consequently more ocular complications will be seen. Nevertheless, there is a need for further studies to evaluate the importance of early determination of ocular vascular damage in RA with CDI.

Acknowledgements There are no any editing agencies or agent(s) involved.

Author contributions OU, EC, and AO drafted the manuscript, NC and EC performed statistical analysis, and OU, EO, and SE contributed to data collection and interpretation of data.

Funding No funding was received for this study.

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval The study was structured according to the Helsinki Declaration rules and approved by the Clinical Research Ethics Committee of Ankara Keçiören Research and Training Hospital.

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