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CLINICAL STUDY

Is choroidal thickness related with disease activity and joint damage in patient with rheumatoid arthritis

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ABSTRACT

OBJECTIVE: Aim of the study was to evaluate the choroidal thickness (CT) in patients with RA and detect the relation with disease activity and joint damage in patients with rheumatoid arthritis

BACKGROUND: Rheumatoid arthritis (RA) is a systemic inflammatory disease associated with various extra-articular organ manifestations including ocular manifestations

MATERIALS AND METHODS: We included 59 eyes of 59 patients with RA and 59 eyes of 59 controls without RA in the study. Subfoveal and perifoveal CT were measured using enhanced depth imaging optic coherence tomography. Disease activity score 28 (DAS 28) and Larsen score were calculated for each patient with RA and compared with measurements of CT.

RESULTS: CT was statistically thinner in patients with RA than controls, at subfoveal CT (p = 0.008), at 500 μm temporal to the fovea (p = 0.004), at 1000 μm temporal to the fovea (p = 0.010), at 1500 μm temporal to the fovea (p = 0.005), at 500 μm nasal to the fovea (p = 0.035). Additionally there was no correlation measurements of CT with disease activity and joint damage.

CONCLUSIONS: Subfoveal and perifoveal CT was significantly thinner in patients with RA than in healthy controls but there was no correlation detected between CT measurements and DAS 28 or Larsen scores *(Tab. 5, Ref. 33)*. Text in PDF *www.elis.sk.*

KEY WORDS: Choroidal thickness, rheumatoid arthritis, joint damage, disease activity, optical coherence tomography.

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease associated with various extra-articular organ manifestations and has a global incidence of 0.5–1.0 % in the adult population (1–2). Ocular manifestations are present in 25 % of RA patients and can include keratoconjunctivitis sicca, episcleritis, scleritis, corneal changes, anterior uveitis and retinal vasculitis (1–3, 4).

Rheumatoid vasculitis (RV) has a heterogeneous clinical presentation and can have various manifestations such as skin disorders, neuropathy, eye symptoms and systemic inflammation. Approximately 2–5 % of RA patients suffer from RV. Arteries are usually involved but the disorder can also affect the veins (5).

Previous studies have reported various pathologies involving the retinal and choroidal vascular network such as occlusive retinal arteritis, retinal venous occlusion, choroiditis, and retinal vasculitis in RA patients (5–9). These reports indicate that the choroid, a vascular structure, can be involved in these patients and that the developing ischemia can alter choroidal thickness (CT). Detailed visualisation of the choroid in vivo is now possible thanks to enhanced depth imaging (EDI) optical coherence tomography (OCT) (10). Various studies that have used OCT to evaluate CT in several systemic autoimmune and inflammatory disorders are available (11–14). The aim of our study was to evaluate the choroidal thickness (CT) in patients with rheumatoid arthritis (RA) and detectthe relation with disease activity and joint damage in patients with rheumatoid arthritis, additionally compare it with healty controls.

Material and method

59 eyes of 59 patients with RA and 59 eyes of 59 controls without RA were included in the study. Written consent was obtained from all subjects after they were informed about the study. The study was approved by the Local Ethics Committee and followed the Helsinki Declaration principles.

CT values were measured in RA patients, who were referred to the Physical Medicine and Rehabilitation Department of Ahi Evran University Training and Research Hospital. EDI-OCT was used at the foveal center and at 500 μm, 1000 μm, and 1500 μm from the foveal center temporally and nasally in each eye (T500, T1000, T1500, N500, N1000, N1500). CT was measured from horizontal sections obtained by OCT (Heidelberg Engineering, Heidelberg, Germany) under the center of the fovea by two ophthalmologists (AK-RK) and averaged for analysis. The measurements were taken in the morning hours to eliminate diurnal CT fluctuation (15). The RA diagnosis of the patients being followed up by the physical

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Tab. 1. Demographic features of RA patients and healthy subjects.

	RA group (n=59)	Control (n=59)	p	RA subgroups		
				Remission (DAS-28<2.6) (n=18)	Active (DAS-28>2.6) (n=41)	p
Sex						
Female	16(27.1%)	15(25.4%)	0.834	8(44.4%)	17(41.46%)	0.635
Male	43(72.9%)	44(74.6%)		10(55.6%)	24(58.4%)	
Age (years)						
Mean±SD	55.46±10.45	55.05±10.30	0.831	54.94±11.96	55.68±9.86	0.961
Range	(28–76)	(27–76)		(28–72)	(35–76)	
DAS-28 score		–	–			
Mean±SD	3.32±1.28			1.93±0.57	3.93±0.99	<0.001
Range	(0.77–6.40)			(0.77–2.56)	(2.68–6.40)	
Larsen score		–	–			
Mean±SD	7.59±8.07			4.17±2.92	8.57±8.84	0.188
Range	(0–41)			(0–8)	(1–41)	
Disease Duration (years)		–	–			
Mean±SD	10.76±9.48			13.89±11.36	9.50±8.45	0.119
Range	(0–45)			(0.25–45)	(0–33)	

RA – rheumatoid arthritis

medicine and rehabilitation clinic had been made according to the American College of Rheumatology 2010 criteria (16).

Disease Activity Score 28 (DAS-28) was used to measure disease activity in patients . The score was calculated using the number of tender and swollen joints and the erythrocyte sedimentation rate. RA patients were divided into 2 subgroups as remission (DAS-28 ≤ 2.6) and active (DAS-28 > 2.6). The active group was further divided into the mild (2.6 < DAS-28 ≤ 3.2), moderate (3.2 < DAS-28 ≤ 5.1), and severe (DAS-28 > 5.1) subgroups (17). Larsen score was also used to show radiographic damages. X-rays of the hands and feet were obtained from each of the subjects and 20 joints (the wrists, 1st to 5th metacarpophalangeal joints, and 2nd to 5th metatarsophalangeal joints) were evaluated. Both erosions and joint space narrowing in each joint as a single score, on a scale of 0 to 5 according to reference radiographs, were assessed. The amount of damage was quantified by using the Larsen score, ranging from 0 to 100 for all 20 joints (18).

A full ophthalmological examination including best-corrected visual acuity (BCVA) with the Snellen chart, intraocular pressure (IOP) measurement with Goldmann applanation tonometry, biomicroscopy and dilated fundus examination was performed in every subject. We only included patients with a BCVA of at least 20/25 in the study.

Exclusion criteria were a spherical equivalent value greater than ± 1.5, IOP greater than 21 mmHg, a history of ocular surgery, ocular trauma, anterior or posterior segment disease, smoking and alcohol use, migraine, a history of systemic disease such as hypertension, diabetes mellitus, as these factors could affect the choroid and/or retina (10).

OCT Scan Protocol

The EDI-OCT method has been described previously (19). We used a Heidelberg spectral domain OCT (Heidelberg Engineering, Heidelberg, Germany) and software version 6.3.3.0. A superluminescent diode with a wavelength of 870 nm was used. The device could acquire 40.000 A-scans per second, with axial and transverse resolutions of 7 and 14 μm, respectively. We obtained two high-quality horizontal line scans through the fovea by using a 1x30-degree area. A total of 100 scans were averaged for each section. The automatic real-time averaging mode was used to maximize the signal-to-noise ratio so as to obtain high-quality images. The CT measurements were then evaluated using these images. The choroidal depth was measured manually between the outer reflective retinal pigment epithelium (RPE) layer and the inner sclera border. The sections were measured horizontally across the fovea at 500-μm intervals. The digital calipers provided

Tab. 2. CT values of RA patients and healthy subjects with p values.

	RA group (n=59)	Control (n=59)	p
SFC			
Mean±SD	264.36±66.82	294.95±45.61	0.008*
Range	(135–392)	(163–392)	
T500			
Mean±SD	252.24±62.56	283.98±43.57	0.004*
Range	(127–383)	(163–394)	
T1000			
Mean±SD	248.59±62.40	276.07±41.98	0.010*
Range	(127–377)	(173–368)	
T1500			
Mean±SD	235.79±63.89	264.98±42.44	0.005*
Range	(94–366)	(158–374)	
N500			
Mean±SD	252.33±70.72	276.29±44.77	0.035*
Range	(123–382)	(163–379)	
N1000			
Mean±SD	239.31±69.46	261.80±43.95	0.053
Range	(95–369)	(154–361)	
N1500			
Mean±SD	222.09±66.99	240.29±49.03	0.057
Range	(78–360)	(132–369)	

RA – rheumatoid arthritis, CT – choroidal thickness, SFC – subfoveal choroidal thickness, T500 – choroidal thickness at 500 μm temporal to the fovea, T1000 – choroidal thickness at 1000 μm temporal to the fovea, T1500 – choroidal thickness at 1500 μm temporal to the fovea, N500 – choroidal thickness at 500 μm nasal to the fovea, N1000 – choroidal thickness at 1000 μm nasal to the fovea, N1500 – choroidal thickness at 1500 μm nasal to the fovea, n – number of eyes

Tab. 3. CT values according to DAS-28 classification and compared with controls.

	Remission (DAS-28<2.6) (n=18)	Active (DAS-8>2.6) (n=41)	Control (n=59)	p		
				Control vs remission	Control vs active	Remission vs active
SFC						
Mean±SD	286.56±63.44	254.38±66.64	294.95±45.61	0.437	0.003*	0.086
Range	(155–392)	(135–371)	(163–392)			
T500						
Mean±SD	167.11±59.33	245.55±63.54	283.98±43.57	0.076	0.006*	0.313
Range	(163–383)	(127–350)	(163–394)			
T1000						
Mean±SD	262.33±58.47	242.40±63.83	276.07±41.98	0.185	0.010*	0.368
Range	(129–377)	(127–368)	(173–368)			
T1500						
Mean±SD	247.94±59.56	230.33±65.73	264.98±42.44	0.100	0.006*	0.373
Range	(116–366)	(94–336)	(158–374)			
N500						
Mean±SD	273.56±65.62	242.78±71.63	276.29±44.74	0.866	0.008*	0.110
Range	(144–382)	(123–377)	(163–379)			
N1000						
Mean±SD	259.00±67.45	230.45±69.35	261.80±43.95	0.952	0.012*	0.155
Range	(157–369)	(95–356)	(154–361)			
N1500						
Mean±SD	247.50±59.87	210.65±67.56	241.29±49.03	0.861	0.010*	0.044
Range	(150–360)	(78–334)	(132–369)			

p < 0.017 is significant, CT – choroidal thickness, SFC – subfoveal choroidal thickness, T500 – choroidal thickness at 500 μm temporal to the fovea, T1000 – choroidal thickness at 1000 μm temporal to the fovea, T1500 – choroidal thickness at 1500 μm temporal to the fovea, N500 – choroidal thickness at 500 μm nasal to the fovea, N1000 – choroidal thickness at 1000 μm nasal to the fovea, N1500 – choroidal thickness at 1500 μm nasal to the fovea, n – number of eyes

Tab. 4. Comparison of CT according to DAS-28 classification.

	Mild (n=10)	Moderate (n=24)	Severe (n=7)	p		
				Mild vs moderate	Mild vs severe	Moderate vs severe
SFC						
Mean±SD	268.20±65.60	257.87±68.07	217.33±59.13	0.669	0.147	0.210
Range	(169–371)	(135–370)	(149–298)			
T500						
Mean±SD	263.30±59.02	246.70±64.59	211.33±63.16	0.491	0.118	0.251
Range	(175–327)	(137–350)	(127–290)			
T1000						
Mean±SD	266.60±51.51	245.13±62.79	191.17±67.17	0.360	0.056	0.116
Range	(185–325)	(149–368)	(127–286)			
T1500						
Mean±SD	250.10±53.36	232.75±66.12	187.67±73.99	0.564	0.181	0.230
Range	(181–333)	(96–336)	(94–274)			
N500						
Mean±SD	252.60±73.69	246.63±74.12	211.00±59.18	0.809	0.313	0.273
Range	(123–353)	(124–377)	(136–184)			
N1000						
Mean±SD	244.10±70.75	232.33±69.86	200.17±67.54	0.552	0.368	0.374
Range	(138–345)	(95–356)	(120–182)			
N1500						
Mean±SD	229.50±75.55	208.58±66.26	187.50±61.26	0.467	0.368	0.561
Range	(115–334)	(78–325)	(114–243)			

p < 0.017 is significant, CT – choroidal thickness, SFC – subfoveal choroidal thickness, T500 – choroidal thickness at 500 μm temporal to the fovea, T1000 – choroidal thickness at 1000 μm temporal to the fovea, T1500 – choroidal thickness at 1500 μm temporal to the fovea, N500 – choroidal thickness at 500 μm nasal to the fovea, N1000 – choroidal thickness at 1000 μm nasal to the fovea, N1500 – choroidal thickness at 1500 μm nasal to the fovea, n – number of eyes

by the Heidelberg Spectralis software were used to measure CT horizontally at the subfoveal region. We made the measurements at 1500 μm temporal and 1500 μm nasal to the fovea.

Statistical analysis

IBM SPSS version 20.0 (IBM Corporation, Armonk, NY, USA) software was used for statistical analyses. Measured data were described as the arithmetic mean ± standard deviation, whereas cat-

Tab. 5. Correlation analyses between CT and clinicals parameters in study group.

	Larsen Score		Disease duration years	
	r	p	r	p
SFC	–0.045	0.822	0.121	0.377
T500	–0.023	0.909	0.079	0.567
T1000	0.001	0.915	0.012	0.929
T1500	–0.031	0.879	–0.016	0.910
N500	0.052	0.798	0.816	0.535
N1000	0.099	0.623	0.066	0.632
N1500	0.056	0.781	0.138	0.316

$p < 0.05$ is significant, CT – choroidal thickness, SFC – subfoveal choroidal thickness, T500 – choroidal thickness at 500 μm temporal to the fovea, T1000 – choroidal thickness at 1000 μm temporal to the fovea, T1500 – choroidal thickness at 1500 μm temporal to the fovea, N500 – choroidal thickness at 500 μm nasal to the fovea, N1000 – choroidal thickness at 1000 μm nasal to the fovea, N1500 – choroidal thickness at 1500 μm nasal to the fovea

egorical data were described as percentages (%). Normal distribution of the values before statistical analysis was verified with the Kolmogorov–Smirnov test. Parametric statistical analysis was performed with the independent t-test. The non-parametric tests used were the Mann–Whitney U test and Kruskal–Wallis variance analysis. A p value of < 0.017 was considered statistically significant for the post hoc analysis. The chi-square test was used for group comparisons, indicated p value < 0.05 was considered statistically significant.

Results

The ages and genders of the cases and controls were similar ($p > 0.05$) (Tab. 1). The CT was statistically significantly thinner in the RA patients than the controls at SFC ($p = 0.008$), T500 ($p = 0.004$), T1000 ($p = 0.010$), T1500 ($p = 0.005$), and N500 ($p = 0.035$) (Tab. 2). Dividing the patients into two groups as remission and active according to DAS-28 revealed that the CT was statistically significantly thinner in the active RA patients than the controls at SFC ($p = 0.003$), T500 ($p = 0.006$), T1000 ($p = 0.010$), T1500 ($p = 0.006$), N500 ($p = 0.008$), N1000 ($p = 0.012$), and N1500 ($p = 0.010$) (Tab. 3). RA patients were also classified into three groups as mild, moderate and severe according to DAS-28. There was no difference between these groups regarding CT values (Tab. 4). Significant correlation was not detected between the Larsen score or disease duration and the CT measurements of RA patients (Tab. 5).

Discussion

The vascular network of the choroid supplies the outer retinal layers and can be imaged in vivo in detail with EDI-OCT. This technique has enabled the birth of a new scientific field where the CT is measured to evaluate normal and pathological processes (10). Systemic disorders that affect the vascular structure such as diabetes mellitus and hypertension have been found to also affect the choroid (20, 21). The research has also made it possible to more clearly understand the pathology in some ocular disorders such as central serous chorioretinopathy, degenerative myopia and age-related macular degeneration (10).

Rheumatoid arthritis has an incidence of 1–2 % in the general global population and continues to be the most common inflammatory joint disorder. A lymphocytic infiltrate in the synovial membrane is a constant characteristic (22). Similarly, vascular involvement is one of the main factors in RA pathogenesis (23). Such involvement is characterized by mononuclear cell infiltration within postcapillary venules of the inflamed synovium (24). However, this vascular inflammation is not limited to the synovium (25).

Rheumatoid vasculitis is a disorder of small to medium-sized blood vessels (25). Common histopathological findings include fibrinoid necrosis and intima proliferation. Leukocytoclasis and a transmural inflammatory infiltrate accompany the vessel wall necrosis. The endothelial damage can also trigger thrombus formation. The potential end result is ischemia in the area supplied by the occluded vessels (26, 27). Biopsies from RA patients have revealed widespread inflammation in blood vessels, even in clinically normal tissues (28, 29). Many organs can be involved in RV, including the skin, central and peripheral nervous system, eye, heart, lung, kidney, and gastrointestinal tract (30).

Rheumatoid arthritis primarily affects the joints but other tissues are also involved and such manifestations can be seen in about 40 % of these patients at some stage (22). The eyes can even be the cause of the first signs of the disease (3, 22). Keratoconjunctivitis sicca, the most common manifestation, can be found in 10 % of the patients (22). Other ocular problems, all associated with vasculitis, include episcleritis, scleritis, peripheral ulcerative keratitis, and retinal vasculitis (30). Approximately 16 % of rheumatoid vasculitis patients suffer these ophthalmic manifestations (3, 22–31). Retinal vasculitis, choroidal vessel involvement and retinal artery occlusion have also been reported (6, 8, 9). Another reported case involved a 37-year-old male RA patient who developed geographic choroiditis and retinal vasculitis. The patient had two recurrences in the following year. Indocyanine green angiography (ICG) demonstrated choroidal artery obstruction and also complete choriocapillaris obstruction in a fresh lesion (8).

We are aware of only two reports on the RA and CT relationship. Tetikoglu et al (32) reported higher CT values in RA patients while Duru et al (13) reported lower values. There is no consensus yet in this issue. Tetikoglu et al (32) have stated that the increased CT could be due to inflammation. Duru et al (13) also reported that the RA immunological mechanisms that cause vascular inflammation could also be a precursor to vascular damage in the choroid. They also found that the CT values of RA patients in remission according to DAS-28 were statistically significantly lower than in the healthy control group. They explain this by lack of an improvement in choroidal thinning even if the disease enters remission as the vessel wall degenerative changes and fibrinoid necrosis are permanent.

Subfoveal and perifoveal CT was statistically thinner in our RA patients than the healthy control group. CT was also statistically significantly thinner at all measurement points in active RA patients according to DAS-28 than control subjects. There was no statistically significant difference between the RA severity groups according to the DAS-28 score but we found that the mean CT value decreased with increasing disease severity. We believe that the occlusive and

degenerative condition triggered by the chronic choroidal vessel wall inflammation could lead to decreased CT as a result of ischemia and atrophy. Additionally there was no study before, which evaluated the relation between Larsen score and CT values. The Larsen score is used for the radiographic evaluation of joint damage (18).

We did not find a statistically significant correlation between the Larsen score and disease duration of the RA patients and the CT measurements. Although Makol et al reported that radiographic erosion can be a risk factor for rheumatoid vasculitis (33). The lack of a statistically significant relationship between the Larsen score and CT in RA could be explained by the fact that there were not very high average scores of the patients Larsen score in this study, this may be the limitation of our study. Another limitation of this study is that FFA and ICG measurements were not included. But an invasive procedure application in patients without symptoms is not ethical.

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