Original Article

Choroidal thickness in patients with fibromyalgia and correlation with disease severity

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Purpose: To evaluate and compare choroidal thickness in patients with fibromyalgia (FM) and healthy controls. **Methods:** In this prospective, cross-sectional study, forty eyes of 40 patients with FM and 40 eyes of 40 age- and sex-matched healthy subjects were enrolled. FM was diagnosed according to the American College of Rheumatology criteria. The choroidal thickness measurements of the subjects were obtained using spectral-domain optical coherence tomography (RTVue-100, Optovue). Widespread pain index (WPI), symptom severity scale (SSS), and fibromyalgia impact questionnaire (FIQ) scores were recorded. The choroidal thickness measurements of the groups were compared, and correlations among the WPI, SSS, and FIQ scores and these measurements were calculated. **Results:** Choroidal thicknesses at 1500 µm nasally were 198.5 ± 46.7 µm and 306.3 ± 85.4 µm; at 1000 µm nasally were 211.7 ± 50.2 µm and 310.05 ± 87.26 µm; at 500 µm nasally were 216 ± 55.05 µm and 311.5 ± 83.4 µm; at subfoveal region were 230.9 ± 58.4 µm and 332.4 ± 91.3 µm; at 500 µm temporally 227.5 ± 58.1 µm and 318.15 ± 92.3 µm; at 1000 µm temporally 224.5 ± 57.07 µm and 315.1 ± 84.2 µm; at 1500 µm temporally 212.5 ± 56.08 µm and 312.9 ± 87.8 µm in the FM and control groups, respectively ($P < 0.001$). Choroidal thicknesses were thinner at all measurement location, except temporal 1000 and 1500 in patients with FIQ score ≥50 than in FIQ score <50. **Conclusion:** The results of this study demonstrated that choroidal thickness decreases in patients with FM and correlated with disease activity. This choroidal changes might be related with the alterations in autonomic nervous system functioning. Further studies are needed to evaluate the etiopathologic relationship between choroidal thickness and FM.

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Fibromyalgia (FM) is a chronic disorder characterized by widespread pain with tenderness at specific sites on digital palpation that affects 3% of the population of developed countries.[1,2] This illness is also associated with insomnia, fatigue, headaches, memory impairment, mood disorders, joint stiffness, and cognitive difficulties.[3,4] The pathogenesis of FM is unclear but involves genetic factors, neuroendocrine and autonomic nervous system abnormalities, psychosocial variables, and environmental stressors. In particular, the autonomic nervous system alterations can affect the vascular system.[5] Based on a perfusion magnetic resonance imaging study, Foerster *et al.* reported baseline changes in brain perfusion in patients with FM, especially in the thalami.[6] Another study by Ozcan *et al.* recorded impaired elastic properties of the aorta in severely symptomatic FM patients.[7]

The choroid is a vascularized and pigmented tissue extending from the ora serrata anteriorly to the optic nerve posteriorly, and it plays a vital role in the pathophysiology of many conditions.[8] It has a rich blood flow and provides the vasculature supplying blood to the outer retina, retinal pigment epithelium, and possibly a portion of the optic nerve; it is the only source of metabolic exchange for the avascular fovea.[9,10] Choroidal vessels are capable of blood flow autoregulation in response to changes in blood pressure and intraocular pressure (IOP). However, as shown in a recent study, choroid can become thinner due to vasoconstriction as a result of chronic hypertension.[11] In addition, a rich autonomic vasoactive nerve supplies the choroid with the activation of sympathetic adrenergic and parasympathetic muscarinic receptors.[12] The parasympathetic nerves derived from the pterygopalatine ganglion, via the facial nerve, form a dense perivascular plexus around the choroidal vessels and a dense sympathetic innervation originates from the ipsilateral superior cervical ganglion, activating α1-adrenergic receptors in the smooth muscle cells of the vessels.[13,14] These rich autonomic innervations to various choroidal structures suggest a potential involvement of the autonomic system in the regulation of choroidal thickness; therefore, autonomic nervous system dysfunction may affect the choroid and lead to perfusion changes.[14] Although visualization of the choroid is difficult due to its localization between the rigid sclera and retinal pigment epithelium, imaging of this layer using spectral-domain optical coherence tomography (SD-OCT) is an easy, reproducible,

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noninvasive, and effective tool for understanding choroidal changes.[15]

Based on reported studies which show the effect of FM on vascular structures, we aimed to evaluate the possible changes of choroidal thickness in patients with FM using SD-OCT.

Methods

This cross-sectional study adhered to the tenets of the Declaration of Helsinki and was approved by our university's Institutional Review Board and Ethics Committee. Informed consent was obtained from all patients. The study group comprised 40 newly diagnosed FM patients. FM was diagnosed at the rheumatology clinic of our hospital according to the American College of Rheumatology criteria. Widespread pain index (WPI) and symptom severity scale (SSS) scores of the patients were recorded.[3] The results of these two scales are used for establishing the diagnoses of FM as well as for evaluating severity. The WPI results in an overall score of 0–19 points, given by the number of up to 19 specific areas where the patient experienced pain over the previous week, including left shoulder girdle, right shoulder girdle, right upper arm, left upper arm, right lower arm, left lower arm, right hip (gluteal region), left hip (gluteal region), right upper leg, left upper leg, right lower leg, left lower leg, right jaw, left jaw, chest, abdomen, upper back, lower back, and neck. SSS assesses fatigue, waking unrefreshed, cognitive functions, and somatic symptoms, which include muscle pain, tiredness, irritable bowel syndrome, thinking or remembering problems, headache, abdominal pain, numbness/tingling, dizziness, insomnia, depression, constipation, and a dry mouth. The four items were each rated as 0–3 (0, none; 1, mild; 2, moderate; 3, severe), resulting in an overall score of 0–12 points. The validity and reliability of the Turkish version of the WPI and SSS have been evaluated[16] (access at site https://www.fmmgmt.com/sites/default/files/pdfs/ACR.pdf).

The fibromyalgia impact questionnaire (FIQ) was administered to the patients by the Psychiatry Department.[17] The FIQ was used to assess functional status, disease progression, and outcomes. The questionnaire includes 20 items covering physical function, occupation, depression, anxiety, sleep, pain, stiffness, fatigue, and well-being. It assesses the impact of FM on patients for the previous 7 days. The maximum score is 100; higher scores indicate a greater impact of the disease on the patient. FM patients were subdivided into two groups based on the sum of the FIQ score: group 1 – more symptomatic group, FIQ ≥50; Group 2 – less symptomatic group, FIQ <50. The validity and reliability of the Turkish version of the FIQ have been evaluated[18] (access at site http://www.fiqr.info/FIQR%20FORM.pdf). Age- and sex-matched 40 control subjects were enrolled the study.

Patients with a history of ocular surgery, ocular trauma, glaucoma, uveitis, systemic hypertension, diabetes mellitus, neurodegenerative disease, or any other rheumatological disease and patients having any systemic and topical medication were excluded from the study. In addition, to obtain clear images and minimize the effect of axial length on choroidal thickness, patients with best-corrected visual acuity worse than 20/20 and ≥ ±1.00D refractive error were excluded from the study.

All patients underwent a detailed ophthalmic examination, including visual acuity testing using the Snellen chart, refraction assessment, anterior segment examination using slit lamp biomicroscopy, IOP measurement using noncontact tonometry, axial length measurement with IOLMaster 500 (Carl Zeiss Meditec AG, Jena, Germany, Software Version 5.4), dilated fundus examination using 90 D lens, and choroidal thickness measurement using SD-OCT. Only measurements of the right eye were used for statistical analyses. All basal OCT scans were performed at the same time of the day (in the morning) to avoid diurnal fluctuations.[19] The interexaminer reproducibility of the choroidal thickness measurements was assessed by measuring the intraclass correlation coefficient (ICC).

Choroidal thickness measurements were obtained by the same experienced technician using a high-speed, high-resolution SD-OCT device Optovue RTVue (Optovue Inc., Fremont, CA, USA) (λ = 840 nm, 26000 A-scans/s, and 5 μm axial resolution), and the results were analyzed using Optovue RTVue software version 3.5 (Optovue Inc., Fremont, CA, USA). The scan pattern was the retina cross line, consisting of two orthogonally oriented 6-mm lines that contained 1024 A-scans. After the patient's chin and forehead were correctly positioned, the instrument pushed toward the eye while the patient maintained fixation on the internal fixation light until the retinal image was inverted. Only the nasal temporally oriented line was used for the measurement. By automatically inverting the image, the chorioretinal interface became adjacent to the zero delay. The retina cross line scan had 32 frames on an average, 16 per direction, without tracking.[15]

Choroidal thickness was measured perpendicularly from the outer edge of the retinal pigment epithelium to the choroid–sclera boundary at the fovea and at six more points located at the fovea, 500 μm nasal to the fovea, 1000 μm nasal to the fovea, 1500 μm nasal to the fovea; 500 μm temporal to the fovea, 1000 μm temporal to the fovea, and 1500 μm temporal to the fovea [Fig. 1]. Choroidal thickness measurements were obtained by two masked physicians (UMO and KA). The average of the two measurements was taken; the differences between readings of the masked physicians were found to be within 10% of the mean.

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Statistical analysis

Statistical data were analyzed using the SPSS software version 21.0 (SPSS, Chicago, IL, USA). Values were expressed

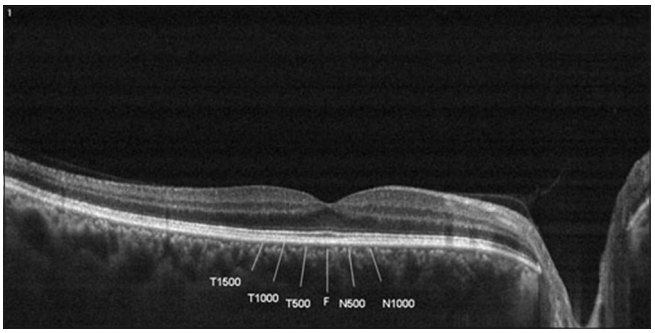

Figure 1: Spectral-domain optical coherence tomography scan showing the choroidal thickness of a patient

as mean ± standard deviation. The normality of the values was analyzed using the Kolmogorov–Smirnov test. Student's *t*-test was used according to the Kolmogorov–Smirnov test results. Differences were considered statistically significant at $P < 0.05$. Correlations between the WPI, SSS, and FIQ and choroidal thickness were determined based on the Pearson's or Spearman's correlation coefficient.

Results

The mean age of the patients was 39 ± 10.5 years (range: 24–64) and that of the controls was 37.1 ± 6.76 years (range 30–56). There were 16 (40%) men and 24 (60%) women in the FM group and 13 (32.5%) men and 27 (67.5%) women in the control group. We found no statistically significant differences in age or gender between the groups (P = 0.339 and 0.492, respectively). The IOP was 13.1 ± 2.3 mmHg (range 9–17) and 12.8 ± 2.1 mmHg (range 10–8) in the FM and control groups, respectively (P = 0.621). The axial lengths were 22.9 ± 0.8 mm (range: 22.60–23.15) and 23.1 ± 0.7 mm (range 22.75–23.20) in the FM and control groups, respectively (P = 0.468). The mean spherical equivalent of refractive error was –0.73 ± 0.68 D (range: –1.5 to + 1.0 D) in FM and –0.62 ± 0.58 D (range: –1.25 to + 0.75 D) in controls. We found no significant difference with respect to mean refractive error between patients with FM and controls (P = 0.687).

Choroidal thicknesses at 1500 µm nasally were 198.5 ± 46.7 µm and 306.3 ± 85.4 µm; at 1000 µm nasally were 211.7 ± 50.2 µm and 310.05 ± 87.26 µm; at 500 µm nasally were 216 ± 55.05 µm and 311.5 ± 83.4 µm; at subfoveal region were 230.9 ± 58.4 µm and 332.4 ± 91.3 µm; at 500 µm temporally 227.5 ± 58.1 µm and 318.15 ± 92.3 µm; at 1000 µm temporally 224.5 ± 57.07 µm and 315.1 ± 84.2 µm; at 1500 µm temporally 212.5 ± 56.08 µm and 312.9 ± 87.8 µm in the FM and control groups, respectively (all $P < 0.05$) [Table 1 and Fig. 2].

The mean WPI, SSS, and FIQ scores were 10.2 ± 2.92 (range: 5–17), 8.85 ± 1.64 (range: 7–12), and 59.6 ± 20.09 (range: 26–96), respectively. There were no significant correlations between choroidal thickness and WPI and SSS [Table 2]. Choroidal thicknesses were thinner at all measurement locations, except temporal 1000 and 1500 in FIQ Group 1 than in Group 2 (Group 1 was FIQ score ≥ 50; Group 2 was FIQ score < 50) [Table 3]. There were no differences between male and female gender in all choroidal thickness levels and WPI, SSS, or FIQ scores ($P > 0.05$).

The interexaminer ICC for the choroidal thickness was 0.956 (95% CI, 0.904–0.983) and ICC was > 0.90 for all measurement points.

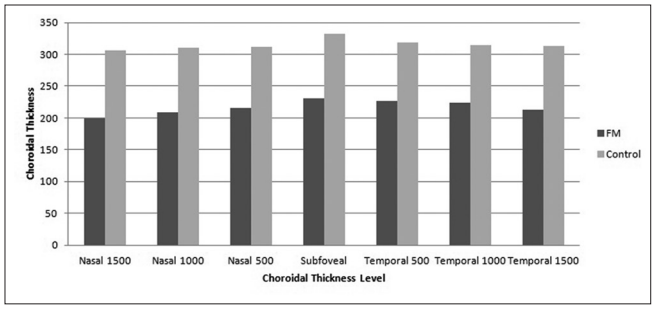

Figure 2: Choroidal thickness differences between the groups

Discussion

To the best of our knowledge, this is the first study evaluating choroidal thickness in patients with FM. We found the choroid

Table 1: Comparison of choroidal thicknesses between fibromyalgia and control group

Locations (µm)	Fibromyalgia	Controls	*P*
Nasal			
1500	198.5±46.7	306.3±85.4	<0.001
1000	211.7±50.2	310.05±87.26	<0.001
500	216±55.05	311.5±83.4	<0.001
Subfoveal	230.9±58.4	332.4±91.3	<0.001
Temporal			
500	227.5±58.1	318.15±92.3	<0.001
1000	224.5±57.07	315.1±84.2	<0.001
1500	212.5±56.08	312.9±87.8	<0.001

Table 2: Correlation analysis results between choroidal thickness and widespread pain index and symptom severity scale

Locations (µm)	WPI	SSS	Statistics
Nasal			
1500	0.953	0.165	*P*
	–0.001	–0.224	*r*
1000	0.980	0.138	*P*
	–0.004	–0.239	*r*
500	0.600	0.482	*P*
	–0.086	–0.114	*r*
Subfoveal	0.873	0.854	*P*
	–0.26	–0.03	*r*
Temporal			
500	0.574	0.626	*P*
	–0.092	–0.079	*r*
1000	0.559	0.610	*P*
	–0.095	–0.083	*r*
1500	0.674	0.720	*P*
	–0.069	–0.058	*r*

WPI: Widespread pain index, SSS: Symptom severity scale

Table 3: Comparison of choroidal thicknesses between fibromyalgia impact questionnaire subgroups

Locations (µm)	FIQ		*P*
	Group 1 (≥50)	Group 2 (<50)	
Nasal			
1500	183.4±31.6	233.7±58.2	0.001
1000	195.5±32.6	241.1±75.3	0.011
500	199.9±41.1	253.5±66.2	0.003
Subfoveal	215.1±45.4	267.7±70.9	0.007
Temporal			
500	215.1±50.1	254.8±67.8	0.046
1000	213.6±47.7	249.7±70.9	0.066
1500	201.4±44.9	238.3±71.7	0.055

FIQ: Fibromyalgia Impact Questionnaire

to be significantly thinner at all locations examined in patients with FM than that in controls. In the Beijing Eye study, Wei *et al.* reported a mean subfoveal choroidal thickness of 254 ± 107 μm in elderly subjects (mean age 64.3 ± 9.6 years, *n* = 3233). They also described an age-related decrease in subfoveal computed tomography of 3.3 μm per year that was similar across all ages.[20] Our control group's choroidal thicknesses were consistent with that study's results. Given the fact that FM is more severe in women, we had expected to see differences in choroidal thickness according to genders; however, we did not find any significant difference, due to the small study size.

Despite the high prevalence of FM, increasing public awareness, and physicians' acceptance of the syndrome, the pathophysiology of this disease is still unclear.[21] Functional abnormalities of the autonomic nervous system, such as decreased microcirculatory vasoconstriction and orthostatic hypotension, may contribute to the clinical problems associated with FM.[5] Sympathetic hyperactivity affects the cardiovascular system and plays a major role in the development of endothelial dysfunction.[22] FM patients with higher FIQ scores are sensitized to endothelial dysfunction due to excessive activation of sympathetic nervous system.[23] Furthermore, according to another study, patients with higher FIQ scores have impaired elasticity of the ascending aorta.[7] Moreover, the breakdown of blood pressure regulation may trigger vascular wall sclerosis, leading to vasoconstriction and choroidal ischemia in the long term.[19] The choroid has been found to be thinner in situations with high sympathetic activity, such as chronic heart failure and coronary artery disease.[24,25] We believe that the significant decrease in choroidal thickness in patients with FM in our study may be explained by fluctuations in the autonomic nervous system of these patients.

Patients with FM experience sleep disturbances such as nonrestorative sleep, insomnia, early morning awakening, and poor quality of sleep, more often than unaffected individuals.[26,27] Moreover, they also present frequent obstructive sleep apnea syndrome (OSAS), a common medical condition associated with many systemic disorders.[28] Interestingly, the choroid has been reported to be thinner in patients with OSAS and researchers believe that irregularities between vasodilator and vasoconstrictor mediators are responsible for the choroidal changes.[29-32] We did not perform polysomnography (PSG) on our patients with FM; however, all of them reported poor sleep quality, during the FIQ. Thus, an association between the presence of sleep disturbances and choroidal thinning in patients with FM is possible.

WPI and SSS are severity scales and diagnostic criteria assessing characteristic FM symptoms as recommended by the American College of Rheumatology.[3] Although the scores on these scales were high (WPI: 10.2 ± 2.92 [must be ≥7], and SSS: 8.85 ± 1.64 [must be ≥5]), they were not significantly correlated with any level of choroidal thickness in our study. FIQ scores have been used for evaluating FM disease activity.[33] Moreover, we found thinner choroid in the group of patients with higher FIQ scores. Other studies have shown that patients with higher FIQ scores presenting worse endothelial function and arterial elastic properties.[7,25] Those results and ours suggest that choroidal changes may be due to cardiovascular system in our FM patients. More importantly, this correlation between FIQ scores and choroidal thickness can be used as an indicator of disease severity and can be useful to evaluate the course of disease and treatment.

The limitations of our study include the small sample size and it restricts our interpretation of the relationships between choroidal structural changes and FM. Although the patients we included in our study were newly diagnosed, it was very difficult for us to determine how long they had suffered from the disease. Another limitation might be due to the type of OCT used in this study. Although the effectiveness of SD-OCT and swept source-OCT (SS-OCT) for evaluating choroid was reported as equal in healthy eyes, SS-OCT was reported to be superior to SD-OCT in eyes with retinal disease.[34] Besides, if the probable sleep disorders of the patients were revealed by PSG, it could be helpful to comment about the pathophysiological relationship.

Conclusion

We found that the choroid was thinner and correlated with disease activity in patients with FM. Although the pathophysiology of FM is unclear, we suggest a role for the persistent activation of the autonomic nervous system and the resulting cardiovascular response in the thinning of the choroid seen in patients with FM. Studies with larger groups of patients are required to confirm our findings, but the possible association of choroid thinning with FM activity opens the door for a noninvasive technique to follow disease course and treatment.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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