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Original Article

Evaluation of Choroidal Vascularity Index and Choroidal Thickness in Newly Diagnosed Fibromyalgia Patients

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ABSTRACT

Objective: This study aimed to analyze and compare the early choroiad vascularity index (CVI) and choroidal Thickness (CT) values of newly diagnosed fibromyalgia (FM) patients and healthy subjects.

Methods: The participants in this study consisted of 24 female FM patients (study group) and 30 similarly aged female healthy subjects (control group). Only newly diagnosed FM patients were included in the study group. FM was diagnosed according to the American College of Rheumatology (ACR) 2010 classification criteria.Fibromyalgia Impact Questionnaire (FIQ) was used to assess the disease severity. CT values were measured at five points: Subfoveal, 750 µm temporally, 1500 µm temporally, 750 µm nasally to the foveal center, 1500 µm nasally to the foveal center (1500-N). CVI values were measured using the public domain ImageJ software for subfoveal and total choroidal areas.

Results: CT values in 1500 µm nasal and temporal were statistically lower in the FM group ($p<0.05$). While 750 µm nasal and temporal, subfoveal CT values were no statistically significant different ($p>0.05$). There was no statistically significant difference between the groups in terms of subfoveal-CVI, ($p>0.05$) but total-CVI values were significantly higher in the FM group ($p<0.05$).

Conclusion: The thinner choroidal thickness in the nasal and temporal regions compared to the central area, preserved choroidal vascularity index in the subfoveal area, and overall increased CVI in these patients may indicate that choroidal vascular changes and thinning start from the peripheral choroidal area at early stages of FM.

INTRODUCTION

Fibromyalgia (FM) is a chronic pain syndrome that affects 2-8% of the world population, primarily women, and the age range is typically between 30 and 35 years.[1,2] FM is characterized by depression, anxiety, mood disorders, memory impairment, insomnia, fatigue, chronic musculoskeletal pain, muscle stiffness, joint stiffness, cognitive dysfunction, headaches, inability to carry out normal daily activities, and general sensitivity.[3,4] The central physiology changes in FM patients. It is known that FM leads to alterations in mono-aminergic neurotransmission, such as increased substance P and glutamate levels, and decreased norepinephrine and serotonin levels in the spinal cord. Altered activity of endogenous cerebral opioids and dopamine dysregulation has also been observed.[5] The pathophysiology of FM also involves genetic predisposition, autonomic nervous system abnormalities, neuroendocrine factors, oxidative stress, psychosocial and environmental changes.[6] Fibromyalgia persists due to central sensitization, characterized increased neuronal activity and changes in pain processing pathways. Neuroinflammation also plays a crucial role in this process. One of the main characteristics of neuroinflammation is the activation of glial cells, including microglia and astrocytes, in the central nervous system. These cells produce pro-inflammatory cytokines and chemokines. They contribute to increased pain sensitivity and the development of allodynia.[7] FM can be associated with many ocular symptoms such as blurred vision, foreign body sensation and irritation. Scleritis, including the necrotizing form, reduced corneal sensitivity, and dry eye syndrome, has been reported accompanying fibromyalgia. In addition, researches have shown that FM patients have decreased retinal nerve fiber layer (RNFL), ganglion cell layer (GCL) thicknesses, and thinner corneal stromal nerves with diminished sub-basal plexus nerve

density.[8] Regarding choroidal thickness (CT) there are three conflicting studies in the literature. Ulusoy et al.[9] and Sevimli et al.[10] found decreased CT in FM patients, but Boquete et al.[11] found no significant difference in CT in FM patients.

The choroid is the pigmented and highly vascularized layer of the posterior segment, providing seventy percent blood supply of the retina. However, due to its anatomic location, it is challenging to obtain clear images of the choroid. The novel optical coherence tomography (OCT) technology, used with enhanced depth imaging (EDI) mode has enabled ophthalmologists to visualize the choroidal anatomy with accurate cross-sectional images of high quality.[12,13] Although CT is commonly used to determine choroidal changes, many factors such as blood pressure, age, diurnal variation, gender, axial length of the eye can affect the CT results. Therefore, the choroid vascularity index (CVI), which represents the ratio of the luminal/total choroidal area (LA/TCA ratio), is widely preferred as a more reliable assessment method of choroid. CVI is not influenced by physiologic factors, and provides the opportunity to evaluate both LA and (SA) separately.[14]

The choroidal effect of fibromyalgia remains controversial. But it is known that neuroinflammation, an important mechanism in the pathogenesis of fibromyalgia, involves vascular changes.[7] Our goal is to contribute to the literature by analyzing the CVI and CT values of newly diagnosed FM patients before receiving treatment, and comparing with healthy subjects.

MATERIALS AND METHODS

This cross-sectional, prospective study was performed between January 2023-December 2023, and approved by the Ethics Committee of Biruni University Hospital (No: 2022/71-04, Date: 24/06/2022) and it complies with the Declaration of Helsinki. The participants in this study consisted of 24 female FM patients (study group) and 30 similarly aged female healthy subjects (control group). Control group consists of healthy individuals without FM. Only newly diagnosed FM patients were included in the study group. Written consent was obtained from all participants. FM was diagnosed according to the American College of Rheumatology (ACR) 2010 classification criteria at the Physical Therapy and Rehabilitation clinic of our hospital. Widespread pain index (WPI) 3 – 6 and severity score (SS) ≥9 or WPI ≥7 and a SS≥5 was defined as FM.[15-17]

Fibromyalgia Impact Questionnaire (FIQ) was used to assess the disease severity of FM patients.[18] The FIQ was preferred for its good sensitivity in demonstrating therapeutic effects, credible construct validity, and reliable test-retest reliability in FM patients.[19] The FIQ evaluates 10 areas: Sleep, stiffness, pain, occupational status, physical impairment, general well-being, work, fatigue/tiredness, depression, and anxiety on a scale of 0 to 100 points. Higher scores indicate a greater impact on the patient's life. We utilized the reliable and validated Turkish version of the FIQ.[20] In this study, the FM patients were divided in two subgroups: Those with FIQ≥60 were considered as severe FM group and those with FIQ<60 were considered as mild-moderate FM group. Severe FM group consist of 14 patients, and mild moderate FM group consist of 10 patients.

Participants with a history of medical treatment, cognitive impairment, other rheumatological diseases, best-corrected visual acuity (BCVA) worse than 20/20, any ocular diseases (uveitis, trauma, cataract, glaucoma, retinal diseases, etc.), a refractive error of ≥ ±2.00D to avoid the effect of axial length on CT, previous laser or intravitreal injections, history of ocular surgery, systemic diseases (hypertension, vasculitis, heart disease, diabetes, neurological diseases, etc.) were excluded. Neurodegenerative diseases and obstructive sleep apnea syndrome (OSAS) were also excluded due to their potential effect on the visual system

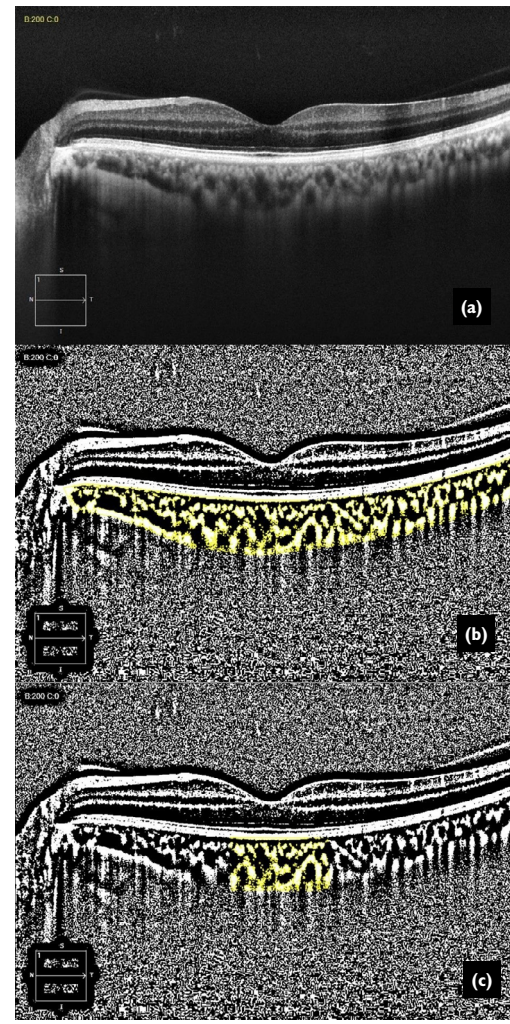

Figure 1. The original and binarized macular enhanced depth imaging optic coherence tomography (EDI- OCT). Original EDI-OCT image **(a)**; The binarized image used for calculating total CVI; dark pixels represent luminal area (LA), coloured pixels represent stromal area (SA)**(b)**; subfoveal binarized image used for calculating subfoveal CVI: Dark pixels represent luminal area (LA), coloured pixels represent stromal area (SA) **(c)**.

and choroid. Smoking was not taken into account in this study. However, participants who smoked, or consumed coffee or tea, were asked to wait for at least half an hour before the measurements were taken.

All participants underwent a detailed examination, including BCVA, slit lamp biomicroscope, applanation tonometry, and fundus examination. Subsequently, spectral domain optical coherence tomography (SD-OCT) was performed by the same experienced investigator between 08:00 and 10:00 a.m. to avoid diurnal variability. The investigator was blind to the FM diagnosis. The eye with the higher scan score index was chosen for OCT, and was used for statistical analyses.

Cirrus HD OCT-5000 device (Carl Zeiss, Jena, Germany) was used to measure the CT and CVI, with a single 9-mm horizontal EDI SD-OCT scan, based on an average of 100 images (Fig. 1). CT was measured manually measures from the outer edge of the retina pigment epithelium to the sclero-choroid interface. Measurements were taken at five points: Subfoveal, 750 µm temporally to the foveal center (750-T), 1500 µm temporally to the foveal center (1500-T), 750 µm nasally to the foveal center (750-N), 1500 µm nasally to the foveal center (1500-N). SA, LA, TCA and CVI were measured using the public domain ImageJ software by Fiji (http://fiji.sc./Fiji) as previously described by Agrawal et al.[21] for both subfoveal (the choroid area between the nasal and temporal 750 microns from foveal center, subfoveal CVI) and total choroidal areas (full – length scan (total CVI)).[19] CT and CVI measurements were conducted by the same trained ophthalmologist.

The effect on optical parameters was determined by using the power analysis with the G*Power program. When the value is taken as 1.0, it is detected for power: 0.85 (real power: 0.8507439) and type I error: 0.05. The minimum number of samples was determined n:23 for each group. Data analyze was performed using the IBM SPSS Statistics Version 21 Package Program in this study. The normal distribution of the variables was analyzed by Shapiro Wilk's Test, which indicated that the variables followed a normal distribution. Therefore, Independent T Test was used to analyze the differences between the groups. A p-value less than 0.05 was considered statistically significant. Pearson's correlation coefficient was used to establish the correlation between variables.

RESULTS

There was no statistically significant difference in terms of age between the two groups (p=0.18) (Table 1). 1500 – N

Table 1. Age comparison between groups

	n	Mean±SD	Minimum age	Maximum age	p value
Fibromyalgia group	24	41.58±11.45	21	60	0.188*
Control group	30	37.36±11.61	18	59	

SDX Standard Deviation; n: number. *Independent student's t test.

Table 2. Comparison of choroidal vascularity indexes and choroidal thicknesses between fibromyalgia and control group

	FM group (n=24)	Control group (n=30)	
	Mean±SD (µm)	Mean±SD (µm)	p value
1500 nasal-CT	262.20±66.83	297.56±44.72	0.032*
750 nasal-CT	311.87±56.20	336.53±49.67	0.098*
Subfoveal CT	366.58±63.94	399.23±55.13	0.054*
750 temporal-CT	331.33±64.01	360.26±44.65	0.076*
1500 temporal-CT	303.79±64.73	336.36±44.38	0.042*
Subfoveal-CVI	0.66±0.01	0.65±0.02	0.621*
Total-CVI	0.65±0.01	0.63±0.01	0.022*
Subfoveal-LA	0.34±0.06	0.34±0.08	0.945*
Subfoveal-SA	0.17±0.03	0.17±0.04	0.902*
Subfoveal-TCA	0.52±0.10	0.52±0.13	1.000*
Total-LA	1.48±0.24	1.65±0.29	0.020*
Total-SA	0.78±0.12	0.9±0.16	0.002*
Total-TCA	2.26±0.35	2.53±0.43	0.016*

SD: Standard Deviation; n: Number; CT: Choroidal thickness; CVI: Choroidal vascularity index; LA: Luminal area; SA: Stromal area; TCA: Total choroidal area. *Independent student's t test.

Table 3. Comparison of choroidal vascularity indexes and choroidal thicknesses between severe FM and mild-moderate FM group

	Severe FM Group (n=14)	Mild-moderate FM Group (n=10)	
	Mean±SD (µm)	Mean±SD (µm)	p value
1500 nasal-CT	260.64±62.39	264.40±76.03	0.899*
750 nasal-CT	308.14±53.38	317.10±62.48	0.718*
Subfoveal CT	368.35±65.54	364.10±65.05	0.876*
750 temporal-CT	335.35±63.50	325.70±67.73	0.660*
1500 temporal-CT	307.35±55.60	298.80±78.71	0.772*
Subfoveal-CVI	0.65±0.01	0.66±0.02	0.158*
Total-CVI	0.65±0.01	0.64±0.01	0.102*
Subfoveal-LA	0.33±0.06	0.35±0.07	0.489*
Subfoveal-SA	0.17±0.03	0.17±0.03	0.900*
Subfoveal-TCA	0.51±0.10	0.53±0.10	0.607*
Total-LA	1.47±0.23	1.49±0.26	0.875*
Total-SA	0.76±0.13	0.81±0.11	0.390*
Total-TCA	2.24±0.36	2.30±0.36	0.689*

SD: Standard Deviation; n: Number; CT: Choroidal thickness; CVI: Choroidal vascularity index; LA: Luminal area; SA: Stromal area; TCA: Total choroidal area. *Independent student's t test.

CT and 1500 – T CT values were statistically lower in the FM group than in the control group ($p<0.05$). While 750 – N CT, subfoveal CT and 750 – T CT values were lower in the fibromyalgia group, there was no statistically significant difference between the groups ($p>0.05$). There was no statistically significant difference between the groups in terms of subfoveal-CVI, subfoveal TCA, subfoveal LA, and subfoveal SA ($p>0.05$).

Total-CVI values were significantly higher in the FM group than in the control group ($p<0.05$). However, Total-LA, Total-SA, and Total-TCA values were lower in the FM group than in the control group, and these differences were statistically significant ($p<0.05$). The comparison of all these values is presented in (Table 2).

The evaluation of choroidal measurements between severe (n:14) and mild-moderate (n:10) FM patients is detailed in (Table 3). No statistical difference was found in terms of the CV and CVI values between these two subgroups. There was no correlation observed between FIQ score and choroidal variables in FM group.

DISCUSSION

This study demonstrates the early changes of CT and CVI in newly diagnosed FM patients, and compares the results with the literature.

Ulusoy et al.[9] concluded that CT values decrease in FM patients due to alterations in autonomic nervous system functioning and correlated with disease activity. Sevimli et al.[10] also found thinner CT in FM patients, in their study based on the average CT at subfoveal 1500 µm. In contrast, Boquete et al.[11] found no significant differences in any part of the choroid in FM patients and observed no correlation with disease severity. Boquete et al.[11] calculated CT in nine areas and obtained 64 measurements around the macula measured using the artificial intelligence. Therefore, they asserted that their results were more reliable. In our study, we observed that CT values were thinner in FM patients compared to healthy subjects in the areas 1500 µm temporally to the foveal center and 1500 µm nasally to the foveal center. Subfoveal, 750 µm nasally, and 750 µm temporally CT were also thinner in the fibromyalgia group, but this was not statistically significant. Additionally, CT values did not differ with FİQ score. Our sample group comprises fibromyalgia patients in the early stages of the disease. We speculate that CT thinning may start at the peripheral area in FM patients. Choroid is supplied by a rich vasoactive autonomic nerve with the parasympathetic muscarinic and sympathetic adrenergic receptors. Sympathetic hyperactivity leads to vasoconstriction and endothelial dysfunction via alpha-1 receptor stimulation. Studies showed that chronic hypertension, chronic heart failure and coronary artery disease patients have thinner choroid due to vasoconstriction. Autonomic nervous system fluctuations such as increased sympathetic hyperactivity may result with endothelial dysfunction and choroidal thinning in FM.[22-25]

Sevimli et al.[10] significantly higher total CVI values in FM patients. In their study, it is not specified from which area of the subfoveal region of OCT section the CVI measurement was taken. We also found higher total-CVI values in FM patients compared to healthy subjects. Differently we evaluated subfoveal-SA, subfoveal-LA, subfoveal-TCA, and subfoveal-CVI. These findings did not differ between FM

group and control subjects. However, we observed lower total-SA, total-LA, and total-TCA values in FM patients, along with higher total-CVI values compared to healthy subjects. Also, choroidal thinning might initially manifest in the peripheral region in in early stages of FM. However, the decrease in SA is more pronounced than LA. This results in higher CVI values in the total area. Bambo et al.[26] examined the optic nerve head by colorimetric analysis software in FM patients, and revealed decreased hemoglobin levels. But they did not assess the macular area. In their OCT angiography study Garcia-Martin et al.[27] suggested that FM patients and healthy individuals has similar blood vessel density in the macular area. But superior sector vascular density had an inverse correlation with disease duration. Likewise, Öztürk et al.[28] found no significant differences in terms of superficial and deep capillary plexus densities, foveal avascular zone characteristics and, choriocapillaris flow area between FM patients and healthy controls. Sympathetic and neurotransmitter dysregulations such as acetylcholine and dopamine, and neurodegeneration may contribute to CVI changes in FM patients. Oxidative stress and neurodegeneration may be responsible of decrease in SA.[10,29] These findings are particularly consistent with the decrease in SA observed in our study.

Our participants are newly diagnosed FM patients, and exclusion criteria is very strict. Therefore, it is an opportunity to observe the early changes on choroid in FM patients. We assert that choroidal changes start at the peripheral area of the choroid in FM patients, and these changes are mostly about SA.

We did not find any significant difference in CT and CVI values between the severe FM and mild-moderate FM groups. Longitudinal studies or studies with larger sample sizes may reveal predictive associations between choroidal structural changes and FM severity.

The first limitation of our study is the inclusion of only female subjects. FM is more common in women than in men due to the altered responses to pain, menstrual cycle-related central nervous system input and higher levels of depression and anxiety.[29] Additionally, there are several studies in the literature that focus on female subjects with FM.[30-32] The second limitation is the relatively small sample size. We only included newly diagnosed FM patients before their treatment started, and our exclusion criteria were broad.

CONCLUSION

Our study revealed that CT is thinner in FM patients at 1500 µm temporally and 1500 µm nasally to the foveal center, but no significant differences were observed at 750 µm temporally and 750 µm nasally to the foveal center, as well as in the subfoveal region. No significant difference was found in terms of subfoveal CVI between FM patients and healthy controls; however total CVI values were higher in FM group. Total LA, SA, and TCA values were lower in FM group. This suggests that the loss in stromal and vascular area begins in the peripheral region of the choroid. Moreover, the reduction in stromal area of the choroid is more pronounced than that in the vascular area. The subfoveal area does not appear to be affected in FM. Studies with larger sample sizes are necessary to establish a more accurate association between choroidal parameters and FM.

Ethics Committee Approval

The study was approved by the Ethics Committee of Biruni University Hospital (Date: 24.06.2022, Decision No: 2022/71-04).

Informed Consent

Written consent was obtained from all participants.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: B.I., M.G.E.; Design: B.I., O.K.; Supervision: B.I., M.G.E., M.S.; Fundings: M.G.E., B.I.; Materials: M.S., B.I.; Data collection &/or processing: B.I., O.K., M.G.E.; Analysis and/or interpretation: B.I., M.S.; Literature search: B.I., M.G.E.; Writing: B.I., M.S.; Critical review: B.I., M.G.E., O.K., E.B.S.

Conflict of Interest

None declared.

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Yeni Tanı Alan Fibromyalji Hastalarında Koroid Vaskülarite İndeksi ve Koroid Kalınlığının Değerlendirilmesi

Amaç: Bu çalışmada yeni tanı alan fibromiyalji (FM) hastaları ile sağlıklı bireylerin erken koroid vaskülarite indeksi (KVI) ve koroid kalınlığı (KK) değerlerinin analiz edilmesi ve karşılaştırılması amaçlandı.

Gereç ve Yöntem: Bu çalışmaya 24 kadın FM hastası (çalışma grubu) ve benzer yaştaki 30 sağlıklı kadın gönüllü (kontrol grubu) dahil edildi. Çalışma grubuna sadece yeni tanı almış FM hastaları dahil edildi. FM tanısı Amerikan Romatoloji Koleji'nin (ARK) 2010 sınıflandırma kriterlerine göre konuldu. Hastalığın şiddetini değerlendirmek için Fibromiyalji Etki Anketi (FEA) kullanıldı. KK değerleri beş noktada ölçüldü: Subfoveal, 750 µm foveal merkezin temporali, 1500 µm foveal merkezin temporali, 750 µm foveal merkezin nazali, 1500 µm nazal olarak foveal merkezin nazali. KVI değerleri, subfoveal ve toplam koroid alanları public domain ImageJ yazılımı kullanılarak ölçüldü.

Bulgular: 1500 µm nazal ve temporal KK değerleri FM grubunda istatistiksel olarak daha düşüktü ($p<0.05$). 750 µm nazal ve temporal, subfoveal KK değerlerinde ise istatistiksel olarak anlamlı fark yoktu ($p>0.05$). Subfoveal-KVI açısından gruplar arasında istatistiksel olarak anlamlı fark yoktu ($p>0.05$), ancak total-KVI değerleri FM grubunda anlamlı olarak yüksekti ($p<0.05$).

Sonuç: Nazal ve temporal bölgelerdeki koroid kalınlığının santral bölgeye göre daha ince olması, subfoveal bölgedeki koroid vaskülarite indeksinin korunmuş olması ve bu hastalarda genel olarak artmış KVI, koroidal vasküler değişikliklerin ve incelmenin erken dönemde FM hastalarında periferik koroid alanından başladığını gösterebilir.

Anahtar Sözcükler: Fibromiyalji; koroid kalınlığı; koroid vaskülarite indeksi.