ARAŞTIRMA MAKALESİ/ORIGINAL RESEARCH

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Evaluation of Posterior Ocular Structures in Patients with Familial Hypercholesterolemia

Ailevi Hiperkolesterolemili Hastalarda Posterior Oküler Yapıların Değerlendirilmesi

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ABSTRACT

INTRODUCTION: We aimed to investigate and compare the subfoveal choroidal thickness (SFCT) and peripapillary retinal nerve fiber layer thickness (pRNFLT) in patients with familial hypercholesterolemia (FH) and healthy controls.
METHODS: Forty-six consecutive patients with FH and 40 age and sex-matched controls were enrolled. SFCT, average pRNFLT and four quadrants of pRNFLT were measured by spectral domain- optical coherence tomography (SD-OCT).
RESULTS: The mean SFCT in patients with FH (372.56±51.24 µm) was significantly thicker than control (334.27±45.62 µm) (p=0.036). Patients with FH had thinner global, superior, and inferior pRNFLT compared to controls (p<0.001, p<0.001, and p=0.018, respectively) while there were no significant differences in nasal and temporal quadrant of pRNFLT between two groups.
DISCUSSION AND CONCLUSION: Patients with FH had thicker SFCT, and thinner global, superior, and inferior PRNFLT. All clinicians must be aware that patients with FH might have an additional risk for retinal vascular diseases and glaucoma.

Keywords: familial hypercholesterolemia, spectral domain optical coherence tomography, retinal nerve fibre layer thickness, subfoveal choroidal thickness.

ÖZ

GİRİŞ ve AMAÇ: Ailesel hiperkolesterolemi (AH) hastalarında subfoveal koroidal kalınlık (SFKK) ve peripapiller retina sinir lifi tabakası kalınlığını (pRSLTK) araştırmayı ve sağlıklı kontrollerle karşılaştırmayı amaçladık.
YÖNTEM ve GEREÇLER: AH'li 46 hasta ve yaş ve cinsiyet uyumlu 40 kişi control grubu olarak çalışmaya dahiledildi. SFKK, ortalama pRSLTK ve pRSLTK'nin dört kadranı spektral domain-optik koherens tomografi (SD-OKT) ile ölçüldü.
BULGULAR: AH'li hastalarda ortalama SFKK (372,56±51,24 µm), control grubundan (334,27 ± 45,62 µm) daha kalındı (p = 0,036). AH olan hastalarda kontrollere kıyasla daha ince global, superior ve inferior pRSLTK vardı (sırasıyla p <0.001, p <0. 001 ve p = 0.018), iki grup arasında pRSLTK'nin nazal ve temporal kadranında istatistiksel olarak anlamlı fark yoktu.
TARTIŞMA ve SONUÇ: AH olan hastalarda daha kalın SFKK ve daha ince global, superior ve inferior pRSLTK vardı, bu sonuçlar hiperkolesterolemi ile ilişkili bir iskeminin varlığını düşündürebilir.

Anahtar Kelimeler: Ailesel hiperkolesterolemi, retina sinir lifi tabakası kalınlığı, spektral domain optik koherans tomografi, subfoveal koroidal kalınlık.

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INTRODUCTION

Familial Hypercholesterolemia (FH) is the one of the most common genetic disorders which is affecting one out of every 250 people according to recent studies (1, 2). FH is transmitted by autosomal dominant inheritance of pathogenic variants in genes encoding proteins involved in LDL receptor (LDLR) metabolism (3). Diagnostic criteria of FH includes both increased blood LDL-c levels and clinical findings such as xanthomas, corneal arcus or early cardiovascular disease in the patient and their relatives (2). The FH causes atherosclerosis mostly seen in coronary vessels, but also affects other arteries such as carotid arteries, abdominal aorta, and lower limb vessels.

Due to its high metabolic rate, the retina has a dual arterial blood supply. The central retinal artery supplies the inner retina and the choriocapillaris supplies the retinal pigment epithelium and the outer retina which consists of mainly pigment epithelium and photoreceptors. The retinal vascular bed is an end-arterial system (4). Cholesterol metabolism plays a great role in all neuroretina and choroid metabolism. Significant expression of LDLRs provides the retina pigment epithelium a high affinity for LDLs, mediating uptake of blood lipids to the retina (5). It has been reported in animal studies that the atherosclerotic changes in retina-choroidal tissues reveal in the presence of hypercholesterolemia (6, 7). In addition, it has been suspected that hypercholesterolemia may be responsible for the pathophysiology of many ocular diseases such as age-related macular degeneration (AMD), glaucoma, cataract and ocular neuropathy. (4).

The spectral domain optical coherence tomography (SD-OCT) has gained increasingly important role in chorioretinal diseases in recent decades. It is a non-invasive method that allows us to objectively evaluate retinal layers and detect changes in choroidal thickness. Many studies evaluated the choroidal thickness and retinal layer thickness changes in various systemic and ocular diseases (8). Also, some SD-OCT parameter has become an indicator and/or early diagnose marker in some disorders (8, 9). In this study, we aimed to compare the subfoveal choroidal thickness (SFCT) and peripapillary retinal nerve fiber layer thickness (pRNFLT) of patients with FH and age-sex matched healthy controls.

METHODS

This prospective and comparative study was conducted in accordance with the Declaration of Helsinki. The protocol for this study was approved by the institutional review board. Written informed consent was obtained from all the participants.

The sample size was calculated using G Power 3.1.9. Forty-six patients diagnosed with FH according to Dutch Lipid Clinic Network criteria were included to

study between May 2018 to January 2021. Patients with definite or probable FH (Dutch Lipid Clinic Network score ≥6) according to Dutch Lipid Clinic Network criteria were included in the study. All patients with FH were diagnosed by a cardiologist and were referred to ophthalmologist. Forty healthy participants were included the study as control.

The individuals aged ≥ 18 years with a previous diagnosis of FH were included. Those with a previous history of antihyperlipidemic drug usage were excluded from the study. Further criteria included (1) best-corrected visual acuity (BCVA) of at least 0.8 Snellen, (2) a refractive error (RE) between +3D and -4D, (3) no history of any intraocular surgery and (4) no history of systemic or ocular diseases, such as diabetes mellitus, systemic hypertension, glaucoma, or trauma, that could affect the retina and choroid blood flow.

All participants underwent a comprehensive ophthalmic examination, including RE measurements with autorefracto-keratometry, BCVA, intraocular pressure measurements with Goldman applanation tonometry, a slit-lamp examination, dilated fundoscopy and SD-OCT-imaging. As SFCT can be affected by axial length (AL), AL was measured using an IOL Master 500 (Carl Zeiss Meditec Inc., Jena, Germany). The ocular findings of hypercholesterolemia such as, xanthelasma, corneal arch, retinal vascular cholesterol emboli were recorded.

The SFCTs and pRNFLT were measured using an SD-OCT (Nikon RS-3000, Japan). All SD-OCT assessments were done between 09:00-12:00 am by the same technician. Both eyes were examined in all patients. Only the scans that had a minimum signal strength of 6 or above with good reliability were included in the analysis. All SFCT images were evaluated by the same ophthalmologist (HSK) using enhanced-depth imaging (EDI) scans. The SFCT data included establishing the axial distance from the RPE to the outer choroid/sclera interface at the foveal area. A software program was performed for automated measurements of the pRNFL. The pRNFLT measurements were evaluated using SD-OCT with a 3.46 mm in diameter scan circle centred on the optic disc. This method provided the pRNFLT for four quadrants (N – nasal, T – temporal, S – superior and I – inferior), six sectors and the global mean values (360 degrees). Average values for all quadrants were used for statistical analyses.

Statistical analyses

Statistical analysis was performed using the SPSS software version 21 (SPSS Inc., Chicago, IL, USA). The Kolmogorov Smirnov test was used to test the normality of distribution of continuous variables. Continuous variables with normal distributions were expressed as mean±standard deviation. Group means for continuous variables with normal distributions were compared with the use of independent samples t-test. Two tailed p values of less than 0.05 were

considered to indicate statistical significance.

RESULTS

The mean age of the patients with FH and the healthy subjects in the control group were 39.78 ± 12.27 years and 37.98 ± 8.47 years respectively (p=0.37). There were no statistically significant differences between the two groups with respect to the gender distribution, RE, IOP and AL. Table 1 shows the clinical and demographic data of the study groups. The mean Dutch Lipid Clinic Network score was 8.7±1.9. Table 2 shows the Dutch Lipid Clinic Network criteria summary of the study group.

The mean SFCT of patients with FH and and the control group was 372.56±51.24 µm and 334.27±45.62 µm, respectively (p=0.036).

The mean global pRNFLT in patients with FH, 101.31±7.34 µm and 108.34±7.41 µm. The differences were statistically significant (p=<0.001). The mean superior and inferior quadrants of pRNFL in patients with FH were significantly thinner than controls (p<0.001 and p=0.018, respectively). There were no statistically significant differences between the two groups with respect to the temporal and nasal quadrants of pRNFLT (Table 3).

Table 1: Comparison of Clinical Characteristics of the Study Groups

	Patients with FH (n=46, eyes=92)	Controls (n=40, eyes=80)	P value
Mean age (year)	39.78±12.27	37.98±8.47	0.37
Gender (Female)	26 (56.5%)	22 (55%)	0.88
RE (D)	-0.68±-0.2	-0.74±-0.3	0.77
IOP (mm Hg)	15.4±3.4	16.8±2.41	0.84
AL (mm)	22.3±0.6	23.02±0.8	0.62
Total blood TC (mg/dl)	254.2±116.8	176.35±37.4	**<0.001**
Blood LDL-C (mg/dl)	188.6±94.7	89.97±22.9	**<0.001**
BMI (kg/m^2)	28.4±4.3	27.2±3.8	0.19
Presence of systemic HT	28 (60.8%)	-	
Presence of coronary artery diseases	22 (47.8%)	-	
Tendinous xanthomata	18 (39.1%)		
Corneal arch	11 (11.9%)	-	
Xanthelasma	13 (14.1%)	-	
Cholesterol emboli in retina	6 (6.5%)	-	

Data are presented as mean ± standard deviation. Abbreviations: AL: Axial length; BMI: Body mass index; D: diopter; FH: familial hypercholesterolemia; IOP: Intraocular pressure; LDL-C: low density lipoprotein cholesterol; RE: refractive equivalent; TC: total cholesterol.

Table 2. Dutch Lipid Clinic Network Criteria of the Study Group

	Study Group (n=46)
Mean score	8.7±1.9
Family history (n/%)	30 (67.3%)
Clinical history (n/%)	24 (52.1%)
Physical examination (n/%) • Tendinous xanthomata • Corneal arch	 18 (39.1%) 11 (11.9%)
LDL-cholesterol (n/%) • LDL-C ≥330 mg/dl • LDL-C 250-329 mg/dl • LDL-C 249–190 mg/dl • LDL-C 155-189 mg/dl	 4 (8.6%) 5 (8.9%) 16 (34.7%) 21 (45.6%)

Abbreviation: LDL-C: low density lipoprotein cholesterol

Table 3: Statistical Analyses of the Comparison of pRNFLT between Two Groups

	Patients with FH (n=46, eyes=92)	Controls (n=40, eyes=80)	P value
Global pRNFLT (µm)	101.31±7.34	108.34±7.41	< **0.001**
Superior pRNFLT	124.23±12.36	136.44±12.78	< **0.001**
Inferior pRNFLT	122.40±14.37	134.53±14.82	**0.018**
Nasal pRNFLT	82.83±10.73	84.66±9.23	0.085
Temporal pRNFLT	76.24±11.80	77.85±9.03	0.14

Data are presented as mean ± standard deviation. Abbreviations: FH: familial hypercholesterolemia; pRNFLT: peripapillary retinal nerve fiber layer thickness.

DISCUSSION

In this study, we aimed to assess the SFCT and pRNFLT in patients with FH and to compare the healthy controls. The following summarizes major findings of the current study: (1) the mean SFCT in patients with FH was statistically significant thinner than controls. (2) Patients with FH had significantly thinner global pRNFLT, superior and inferior pRNFLT compared to controls.

It is known that many retinal diseases originate from the choroid or retinal vascular diseases are affected by the choroid. The choroidal tissues have highly fenestrated vascular component therefor is responsible for blood supplying of outer retinal segments. Also, cholesterol plays particularly important role in choroidal tissues, Bruch

membrane that provides nutrient passage between choroid and retina, and photoreceptor functions. Due to the high blood flow, the choroid has been recognized as a potential area for the presence of atherosclerotic alterations. In animal studies, the hypercholesterolemia was found related with atherosclerotic changes in choroidal and retinal tissues. (6, 7) Salazar et al. found that rabbit with hypercholesterolemia had thicker choroidal thickness compared to rabbit with normal blood cholesterol levels, and they added that the choroidal alteration did not improve after the normalization of cholesterol level in rabbit with hypercholesterolemia. (6) In animal studies provided that building up of lipid at the suprachoroidal tissues, hypertrophy of the endothelial and vascular smooth muscle cells, and increasing the inflammatory cytokines such as, TNF-α and IL-6 in the sclera and choroid was found in histopathologic findings as results of hypercholesterolemia.

Until the development of SD-OCT, imaging of choroidal tissues is insufficient due to the many factors of choroid such as vascular tone. After SD-OCT, in vivo cross-sectional images of the anatomy of the RPE or choroidal layers and the actual choroidal thickness value became objectively evaluable. This simple, reproducible, and noninvasive technique has been used in many studies for evaluate the effects of systemic or ocular disorders on choroidal and retinal tissues. (8, 9) Also, there many studies which evaluated the choroidal thickness changes in cardiovascular disorders. Yeung et al. reported that choroidal thickness was affected by several cardiovascular diseases and the authors revealed that choroidal thickness alterations might be used as a noninvasive prognostic marker to screening for some cardiovascular pathologies. (10) In another study, authors showed that patients with coronary artery diseases had statistically significant thinner SCFT than healthy controls, even after correction for the presence of hypertension, hypercholesterolemia, and diabetes. (11)

There are few studies which have evaluated the choroidal thickness in patients with hypercholesterolemia. A recent study evaluated the SFCT in patients with FH treated with lipoprotein apheresis for at least two years using SD-OCT and OCT-angiography. While they did not observe differences in SFCT values between patients and healthy controls, there was foveal avascular zone enlargement, which is a sign of ischemia, in the patient group receiving treatment. But the authors did not include the blood cholesterol levels before the lipoprotein apheresis treatment. (12) Wong et al. assessed the relationship of hypercholesterolemia and choroidal thickness in healthy participants, and they reported that SFCT was significantly higher in subjects with hypercholesterolemia. (13) Similarly,

we found that patients with FH had significantly thicker SFCT compared to controls. Hypercholesterolemia with increasing choroidal thickness also affects RPE cells with high LDL receptors and Abnormal lipid metabolism and/or Apo-E deficiencies may affect the cholesterol balance in RPE and photoreceptors. Therefore, retinal, and choroidal changes in hypercholesterolemia were found to be similar to pathological changes of age-related macular degeneration in the human retina. So, patients with FH might have an earlier risk of macular degeneration than their peers.

The pRNFLT is a quantitative evaluation of the viable ganglion cells in the axonal mass, and alterations in the pRNFLT are now easy to identify with the advance of SD-OCT. In general ophthalmology practice, pRNFLT is generally used for the diagnosis and follow-up of glaucoma and optic disc disorders. Shin et al. found that localised pRNFLT damages were related with certain cardiovascular risk factors such as, systolic blood pressure, estimated glomerular filtration rate, and HbA1c and they added that concomitant cardiovascular risk factors should be considered when evaluating a patient with localized pRNFLT defects. (14) Hypercholesterolemia also was found related with glaucoma in animal studies. Kashiwagi et al reported the histological findings of glaucoma in a rabbit fed a high-cholesterol diet, in which the lesions caused by hypercholesterolemia might cause progression of the glaucoma. (15) Microvascular dysfunction in glaucomatous eyes has gained more attention in recent years as evidence has increased supporting its correlation with the development of glaucoma. In our study, patients with FH had significantly lower global pRNFLT, superior pRNFLT and inferior pRNFLT than controls. Similarly, Stefanutti et al. found the superior and inferior pRNFLT were significantly lower than controls. The pRNFLT thinning in the superior and inferior quadrants were proven to be associated with early stages of optic nerve damage in patients with glaucoma and progression of early glaucoma.

Our study has some limitations. The study groups were relatively small. We did not evaluate the effect of hypercholesterolemia treatments on SD-OCT parameters. Also, only SD-OCT was performed, and optic disc perfusion and vascular zones of retina were not evaluated. The use of ultrasound and/or optical coherence tomography angiography may provide additional information for evaluating the vascularity of retina and optic disc in future studies.

In conclusion, increase in SFCT and thinning of global pRNFLT, superior and inferior pRNFLT was found in patients with FH. In clinical practice, clinicians must be aware that patients with FH might have an additional risk for ocular diseases including retinal vascular diseases and glaucoma. Early diagnosis of some diseases can be provided

by regular follow-up of these patients by multidisciplinary approach by ophthalmologists and cardiologists.

Ethics Committee Approval: Kartal Dr. Lutfi Kirdar Training and Research Hospital ethics committee (04.01.2021; 1458/9/21)

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