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Effect of Statin Therapy on Choroidal Structure in Patients with Hyperlipidemia: A Case–Control Study with Optical Coherence Tomography

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Abstract

Objective: To investigate the impact of statin therapy on choroidal structure.

Methods: A case–control study included otherwise healthy patients with hyperlipidemia. 12 patients with low-density lipoprotein (LDL) levels below 210 mg/dL were treated with lifestyle changes, while 12 patients with levels above 210 mg/dL were additionally treated with atorvastatin. Optical coherence tomography images were obtained in the third month.

Results: Choroidal thinning in the temporal region was observed in the statin group (P = .031, P = .033, P = .029 at different measuring points). Total choroidal and luminal areas were thinner in the statin group (P = .046 and P = .049), while the choroidal vascularity index remained the same (P = .853).

Conclusion: It is uncertain whether choroidal thinning is mediated by decreased LDL levels or by decreased inflammation and oxidative stress. It may be advantageous to investigate statins in the management of pachychoroid spectrum disorders or oxidative stress-related diseases such as age-related macular degeneration.

Keywords: Choroidal structure, choroidal vascularity index, hyperlipidemia, statin, optical coherence tomography

Introduction

The choroid is a dense circulatory network layer found between the retina and the sclera that nourishes the outer retina, retinal pigment epithelium, foveal avascular zone, and optic nerve with oxygen and nutrients.[1] The imaging of choroid, choroidal vascular flow, and density has been enhanced due to the advancements in optical coherence tomography (OCT) technology.[2]

Choroidal thickness increases in people with hyperlipidemia, according to studies in patients with risk factors for cardiovascular diseases.[3,4] In pachychoroid spectrum diseases, hyperreflective dots seen on OCT are thought to be intraretinal lipid deposits.[5] We also know that lipids are the main component of drusen in age-related macular degeneration (AMD).[6]

Statins are selective inhibitors of the enzyme 3-hydroxy-3-methyl-glutaryl-CoA reductase, which decreases cholesterol production and consequently serum cholesterol levels.[7] Statins not only lower cholesterol, but they also have pleiotropic effects, such as restoring endothelial function, stabilizing atherosclerotic plaque, or lowering oxidative stress and vascular inflammation.[8]

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The aim of this research is to look at the effect of statin treatment on choroidal structure in patients with hyperlipidemia.

Methods

Study Population

This prospective case–control study was conducted in Istanbul Medeniyet University Prof Dr Suleyman Yalcin City Hospital. The study protocol was approved by the Ethics Committee of Istanbul Medeniyet University Goztepe Training and Research Hospital (July 22, 2020, number: 2020/0465). Written informed consent was obtained from the participants. The study protocol adhered to the principles of the Declaration of Helsinki.

Patients who applied to the Cardiology Department between October 2020 and January 2021 with hyperlipidemia were included in the study. Patients with systemic diseases such as diabetes mellitus, hypertension, coronary artery disease, a history of chronic drug use, a history of intraocular surgery, retinal disease, uveitis, and glaucoma were excluded from the study. Patients with ocular media opacity that precluded high-quality OCT imaging of the retina and choroid were also excluded.

The participants were divided into 2 treatment groups based on low-density lipoprotein (LDL) levels. Patients with LDL levels below 210 mg/dL were followed up with lifestyle modification recommendations, particularly diet and exercise. Patients with

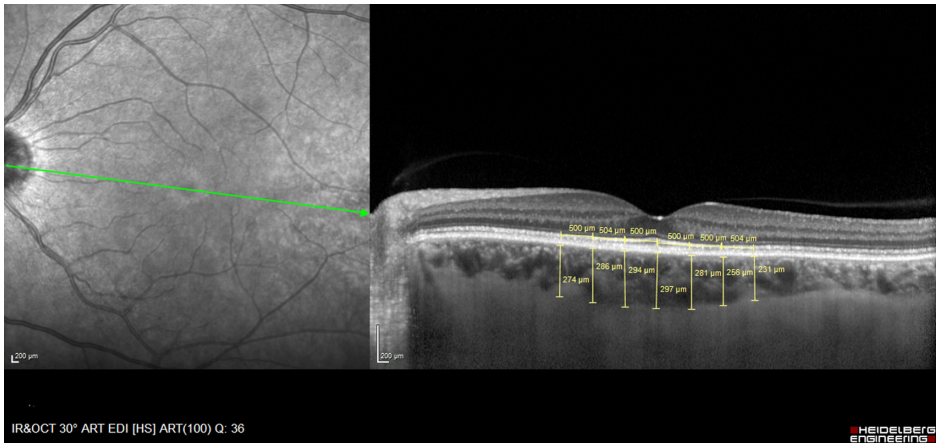

Figure 1. Subfoveal choroidal thickness. A line scan of the retina and choroid was captured. The thickness of the subfoveal choroidal layer was assessed at 7 different locations: just under the foveal center and 500, 1000, and 1500 µm away from the fovea on the nasal and temporal sides.

LDL levels above 210 mg/dL were treated with atorvastatin 20 mg/day in addition to lifestyle adjustments. After 3 months of follow-up, patients were referred to the Ophthalmology Department.

Data Collection and Image Analysis

All participants underwent a detailed ophthalmologic examination, including intraocular pressure, central corneal thickness, best corrected visual acuity measurement, slit-lamp examination, and dilated fundus examination. Following these examinations, a line scan of the retina and choroid was captured using the enhanced depth imaging (EDI) mode of OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany). The thickness of the subfoveal choroidal layer was assessed at 7 different locations: just under the foveal center and 500, 1000, and 1500 µm away from the fovea on the nasal and temporal sides (Figure 1).

In addition, a circular image with a diameter of 3.5 µm was obtained around the optic nerve head (in the retinal nerve fiber layer setup and EDI mode of the instrument), and peripapillary choroidal thickness was measured at 4 different locations: superior, temporal, inferior, and nasal (Figure 2).

All choroidal thickness measurements were recorded by the same researcher (MH) who was blind to the subjects' diagnoses. The posterior pole EDI-OCT scan was further studied using ImageJ software (National Institute of Mental Health, Bethesda, Md, USA) to calculate the total choroidal volume and choroidal vascularity index.[9] The foveal center was detected in the OCT analysis program, and 2 lines (each 1500 m) were formed in the temporal and nasal directions from the foveal center at the level of the retinal pigment epithelium (Figure 3).

The polygon tool in ImageJ software (National Institute of Mental Health, Bethesda, Md, USA) was used to define the choroidal area beneath this 3 mm section. The image has been binarized. The instrument's region of interest manager tool was used to calculate the total choroidal area (TCA) and total luminal area (TLA). The choroidal vascularity index (CVI) was calculated by dividing the TLA by the TCA.

Triglyceride (TG), high-density lipoprotein (HDL), and LDL levels were tested again in blood samples that were obtained on the same day as ocular examinations.

Statistical Analysis

The statistical analyses were performed using Statistical Package for the Social Sciences Statistics software for Windows, version 21 (IBM SPSS Corp.; Armonk, NY, USA). The Shapiro–Wilk test was used to evaluate the normal distribution of continuous data. The Student's *t*-test was used to compare 2 independent groups when the continuous variables were normally distributed; otherwise, the

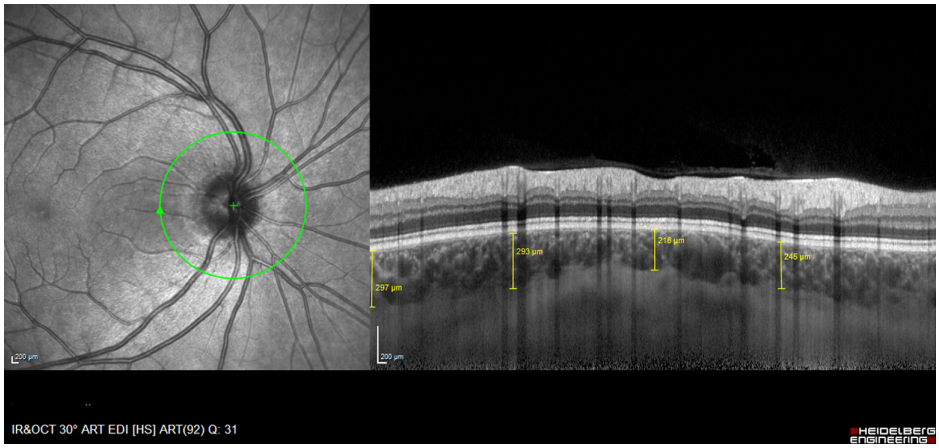

Figure 2. Peripapillary choroidal thickness. A circular image with a diameter of 3.5 µm was obtained around the optic nerve head, and peripapillary choroidal thickness was measured at 4 different locations: superior, temporal, inferior, and nasal.

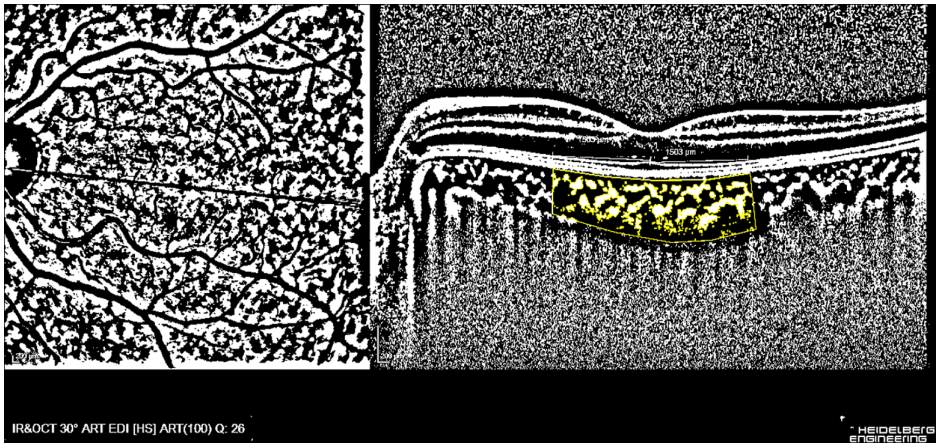

Figure 3. Choroidal vascularity index. The foveal center was detected in the OCT analysis program, and 2 lines (each 1500 µm) were formed in the temporal and nasal directions from the foveal center at the level of the retinal pigment epithelium. ImageJ software was used to define the choroidal area beneath this 3 mm section. The image has been binarized.

Mann–Whitney *U*-test was employed. Continuous variables were defined using the mean and standard deviation. To compare categorical values, the chi-square test was used. Statistical significance was defined as *P* values less than .05.

Results

A total of 613 patients were examined in the cardiology department between October 2020 and January 2021. About 92 patients had hyperlipidemia. After excluding patients with systemic comorbidities, 33 patients in total who completed the 3-month treatment period were referred to the ophthalmology department. Four patients with LDL levels greater than 210 mg/dL had refused initial statin therapy and were assigned to the first group. Therefore, 17 patients had been followed up with lifestyle changes, whereas 16 patients had been followed up with atorvastatin treatment. Due to the presence of ocular comorbidities such as cataract, glaucoma, or age-related macular degeneration, 5 patients from the first group and 4 patients from the second group were excluded. Eventually, 24 eyes of 12 patients in both groups were enrolled in the study.

The mean age was 51.6 ± 11.8 years in the hyperlipidemia group not receiving statin therapy and 51.8 ± 12.1 years in the group receiving statin therapy. The 2 groups were similar in terms of age and gender (*P* = .954 and *P* = .386, respectively). The demographic characteristics and lipid profiles of the patients were shown in Table 1.

The TG and HDL levels were not statistically different between the 2 groups. Pre-treatment LDL levels were significantly higher in the statin-initiated group, as expected. At the end of the treatment period, LDL levels were lower in patients who used statins compared to the first group. In terms of visual acuity, intraocular pressure, and central corneal thickness, there was no marked difference between groups.

Choroidal thickness measurements are shown in Table 2. In the choroidal thickness assessment, choroidal thinning was identified in the subfoveal area (*P* = .058), significantly in the temporal region (*P* = .031, *P* = .033, *P* = .029 at different measuring points) in the statin therapy group compared to the control group. Nasal quadrant measurements were also thinner but were not statistically significant. Peripapillary choroidal thickness also did not show a statistically significant difference between the 2 groups.

The choroidal vascular parameters of the patients were represented in Table 3. The TCA and TLA were thinner in the group that underwent statin treatment compared to the group that did not. The CVI, calculated by dividing TLA by TCA, remained unchanged.

Discussion

In hyperlipidemic patients taking statin medication, choroidal thickness in the subfoveal area, notably in the temporal region, was found to be reduced in our study. This reduction affected both choroidal stroma and blood vessels, while the choroidal vascularity index in these patients remained similar. No thinning was observed in the peripapillary choroidal area. We assessed low LDL in the statin group as an expected outcome of statin therapy. However, it is unclear whether the choroidal thinning is caused by the drop in LDL levels or other effects of statins, such as decreasing inflammation or reducing oxidative stress.[8]

Table 1. Demographic Characteristics and Lipid Profile of the Study groups

	Hyperlipidemia Without Statin Treatment (n = 24)	Hyperlipidemia with Statin Treatment (n = 24)	*P*
Age	51.6 ± 11.8	51.8 ± 12.1	.954*
Gender (M/F)	5/7	3/9	.386‡
Vision (decimal)	0.94 ± 0.09	0.80 ± 0.26	.052*
IOP (mmHg)	18.08 ± 1.61	17.87 ± 2.02	.696†
CCT (µm)	528.37 ± 25.43	543.12 ± 17.70	.150*
TG (mg/dL)	171.00 ±7 2.93	121.83 ± 48.24	.064†
HDL (mg/dL)	53.16 ± 14.36	50.00 ± 11.66	.369*
LDL (mg/dL) (pretreatment)	214.58 ± 35.61	262.58 ± 62.62	**.015***
LDL (mg/dL) (posttreatment)	220.00 ± 38.45	146.00 ± 39.14	**.001***

CCT, central corneal thickness; HDL, high-density lipoprotein; IOP, intraocular pressure; LDL, low-density lipoprotein; TG, triglyceride. *Mann–Whitney *U*-test. †*t*-test. ‡Chi-square test. Significant p values were written in bold.

Table 2. Subfoveal Choroidal Thickness of the Study Groups

	Hyperlipidemia Without Statin Treatment	Hyperlipidemia with Statin Treatment	*P*
Subfoveal choroidal thickness			
N_{1500}	283.25 ± 104.66	251.70 ± 98.47	.288†
N_{1000}	314.41 ± 108.17	268.29 ± 105.17	.141†
N_{500}	330.16 ± 101.43	273.66 ± 107.75	.068†
SFCT	340.20 ± 102.77	281.75 ± 105.45	.058†
T_{500}	329.66 ± 95.68	266.79 ± 100.52	**.031†**
T_{1000}	310.83 ± 93.63	252.12 ± 90.93	**.033†**
T_{1500}	284.66 ± 88.60	229.12 ± 82.52	**.029†**
Peripapillary choroidal thickness			
Superior	207.37 ± 70.02	188.45 ± 68.14	.348†
Temporal	200.41 ± 83.69	181.91 ± 83.11	.446†
Inferior	151.54 ± 60.61	147.50 ± 58.70	.816†
Nasal	182.45 ± 55.11	171.12 ± 70.54	.538†

N_{500}, 500 µm nasal from the subfoveal line; N_{1000}, 1000 µm nasal from the subfoveal line; N_{1500}, 1500 µm nasal from the subfoveal line; SFCT, subfoveal choroidal thickness; T_{500}, 500 µm temporal from the subfoveal line; T_{1000}, 1000 µm temporal from the subfoveal line; T_{1500}, 1500 µm temporal from the subfoveal line.
*Mann–Whitney *U*-test. †*t*-test. Significant p values were written in bold.

Table 3. Choroidal Structure of the Study Groups

	Hyperlipidemia Without Statin Treatment	Hyperlipidemia with Statin Treatment	*P*
TCA	22842.62 ± 7144.13	18816.54 ± 6469.42	**.046†**
TLA	16426.41 ± 4801.87	13705.62 ± 4533.45	**.049†**
CV	0.72 ± 0.05	0.73 ± 0.03	.853*

CVI, choroidal vascularity index; TCA, total choroidal area; TLA, total luminal area.
*Mann–Whitney *U*-test. †*t*-test. Significant p values were written in bold.

In an experimental study on New Zealand rabbits, Rojas et al[10] divided rabbits into 3 groups and began a standard diet in 1 group, a cholesterol-rich diet in another, and fluvastatin or pravastatin at a dose of 2 mg/kg/day in addition to a cholesterol-rich diet in the third group. They then used electron microscopy to examine the pleiotropic effects of statins on choroid morphology. The researchers reported that statins reduced lipid and macrophage buildup in the choroid while preserving the ultrastructural morphology of endothelial cells and smooth muscle cells in choroidal vessels.

Histological examination of the choroid in another hyperlipidemic animal model revealed choroidal thickening due to lipid accumulation in the extravascular choroidal space, as well as endothelial hypertrophy and vascular lumen narrowing due to compression.[11] In our study, the areas of choroidal stroma and choroidal vessels were both reduced. We suggest that statins may have reduced extravascular lipid build-up while also reversing endothelial hypertrophy.

Kanar et al[12] observed that choroidal thickness increased following 2 weeks of atorvastatin treatment in patients with abnormal coronary angiographic findings, and the authors hypothesized that this was due to enhanced microcirculation. Our study differs in that the endpoint was 3 months. There may have been an increase in choroidal thickness in the short term due to improved circulation, but the choroidal thickness may have decreased again in the long term as a result of reduced inflammation and reduced oxidative stress.

Pachychoroid spectrum diseases are thought to be caused by varying degrees of abnormalities in the retinal pigment epithelium and choroidal vessels, inflammation, and ischemia.[13] It has also been suggested that the hyperreflective dots seen in the OCT may represent intraretinal lipid deposits.[5] Moreover, it is well-known that lipids are the main component of the drusen seen in age-related macular degeneration and that genes related to cholesterol metabolism and cardiovascular risk factors are linked to the disease.[6] Despite the inconsistent findings regarding the effect of statin usage on AMD progression, it has been reported that it can prevent the formation of choroidal neovascularization.[14] It has lately been emphasized that statin therapy for AMD warrants additional investigation and attention.[15] Therefore, we believe it is important to investigate statin therapy as a potential treatment option for pachychoroid spectrum diseases such as central serous chorioretinopathy and polypoidal choroidal vasculopathy and for diseases such as age-related macular degeneration, which is thought to be related to oxidative stress and inflammation.

We would like to acknowledge the limitations of our study. Patients with hyperlipidemia without any systemic comorbidity were included in the study, and statin therapy was initiated for patients with an LDL level of at least 210 mg/dL. Diabetes mellitus or heart disease frequently co-occurred in people with increased LDL levels who needed statin therapy. We think that the fact that the study was conducted in a tertiary facility and in collaboration with the cardiology clinic may have contributed to this situation. Therefore, the overall number of patients who meet the criteria is low. Due to the small number of patients, both eyes of the patients were included in the study, which raises the likelihood of inter-eye correlation since each measurement does not represent a completely independent eye. On the other hand, the fact that the patients did not have any systemic disease despite the high LDL levels should be considered as the strength of the study.

Conclusion

Our study showed that choroidal thickness in the subfoveal area, particularly in the temporal region, decreased in hyperlipidemic patients using statin medication. This diminution had an effect on both the choroidal stroma and the blood vessels. However, it is uncertain whether the choroidal thinning is caused by the drop in LDL levels or by statin treatment. Further research is needed to elucidate the impact of statin therapy, with or without hyperlipidemia, on the choroidal structure.

Data availability: Data from this study are accessible upon request from the corresponding author.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Istanbul Medeniyet University (Approval no: 2020/0465, Date: July 22, 2020).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.H., A.Y.C., M.G.C., F.S., F.B.C., H.O.; Design – M.H., A.Y.C., M.G.C., F.S., F.B.C., H.O.; Supervision – M.H., A.Y.C.; Resources – M.H., A.Y.C., M.G.C., F.S., F.B.C.; Materials – M.H., A.Y.C., M.G.C., F.S., F.B.C.; Data Collection and/or Processing – M.H., A.Y.C., M.G.C., F.S., F.B.C.; Analysis and/or Interpretation – M.H., A.Y.C.; Literature Search – M.H., A.Y.C., H.O.; Writing Manuscript – M.H., A.Y.C., M.G.C., F.S., F.B.C., H.O.; Critical Review – M.H., A.Y.C., H.O.

Declaration of Interests: The authors have no conflict of interest to declare.

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