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Choroidal vascular changes in non-alcoholic fatty liver disease

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Abstract

Introduction: The most common cause of death in nonalcoholic fatty liver disease (NAFLD) is cardiovascular disease. Choroidal microvascular structure in the eye may be a predictor of systemic vascular disease. We aimed to evaluate the effects of NAFLD on the choroidal microvascular structure using enhanced depth optical coherence tomography (EDI-OCT).

Material and methods: This prospective study was conducted by evaluating a total of 96 patients, 52 with steatosis and 44 without steatosis. After anthropometric measurements and ultrasonography were performed in the Gastroenterology Clinic, venous blood samples were taken for biochemical examinations. Then, all patients underwent an eye examination by an ophthalmologist. Subfoveolar choroidal thickness (SFCT) values of the cases were measured with EDI-OCT. Choroid vascular index (CVI) measurements were obtained by dividing the subfoveal choroidal area in the EDI-OCT images into luminal and stromal areas using the image binarization technique (ImageJ). In statistical analysis, the chi-square test was used to compare categorical data, and the independent t-test and Mann-Whitney U test were used to compare quantitative data.

Results: The mean age of those with fatty liver was 41±15.7 years, and of those without fatty liver it was 46 ± 10.7 years. There was no statistically significant difference between the groups in terms of age ($p = 0.064$). Body mass index (BMI), waist circumference (WC), glucose, uric acid, alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGT), total cholesterol (TC), ferritin, insulin, and Homestatic Model Assesment — Insuline Restistance (HOMA-IR) were statistically significantly higher in the NAFLD group. On the other hand, there was no statistically significant difference between the groups in terms of low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglyceride, and aspartate aminotransferase (AST) values. The mean SFCT was measured as 280.26 ± 23.68 microns in the NAFLD group, and 308.96 ± 18.57 microns in the control group. There was no statistically significant difference in SFCT between the groups ($p = 0.077$). CVI measurements were 0.63 and 0.65, respectively, and they were significantly lower in the group with NAFLD ($p = 0.045$).

Conclusions: This is the first study in the literature to compare patients with and without ultrasonographic fatty liver in terms of choroidal vascular changes. We found that the choroidal vascular index decreased in NAFLD. This result proves that NAFLD causes changes at the microvascular level and is a multisystemic disease. **(Endokrynol Pol 2023; 74 (4): 430–436)**

Key words: *NAFLD; EDI-OCT; choroidal vascular index*

Introduction

Nonalcoholic fatty liver disease (NAFLD) is identified by an abnormal accumulation of fat in the liver independent of alcohol consumption. Today, it is one of the most common causes of chronic liver disease in both children and adults [1]. NAFLD can be encountered in a wide clinical spectrum ranging from simple steatosis, steatohepatitis (SH), fibrosis, cirrhosis, and hepatocellular carcinoma [2–4]. Ultrasonography is the first choice in diagnosis because it is inexpensive, easily accessible, and noninvasive [5].

The leading cause of death in NAFLD patients is cardiovascular disease [6]. The available evidence indicates an increased risk of cardiovascular events in patients with fatty liver, independent of metabolic syndrome risk factors, compared with individuals without fatty liver. For instance, even patients with a body mass index < 25 kg/m^2 and a diagnosis of NAFLD have an increased incidence rate of cardiovascular events compared to patients without NAFLD [7, 8]. Compared to simple steatosis in NAFLD, the risk of cardiovascular disease increases significantly in more advanced histological conditions such as steatohepatitis or fibrosis [6, 9]. The reason for this is that patients with steatohepatitis have higher levels of small-particle LDL, which is more atherogenic than in patients with simple steatosis [10].

The choroid in the human eye is the region of the body where vascularity is most intense. There is a growing understanding that changes in choroidal microvascularity may be indicative of systemic diseases

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affecting blood vessels [11, 12]. Today, modalities such as enhanced-depth imaging optical coherence tomography (EDI-OCT) have the potential to detect microvascular changes and can provide high-resolution cross-sectional imaging of the eye with almost histological detail [13, 14]. The choroidal vascular index (CVI), which expresses the ratio of the choroidal vascular area to the total choroidal area, is a relatively newly defined marker that provides an opportunity to evaluate choroidal vascularity in various retinal and choroidal problems and systemic diseases affecting vascular tissue. CVI is considered a more stable marker in the examination of choroidal changes because it is less affected by physiological parameters such as axial length, age, intraocular pressure, and systolic blood pressure compared to subfoveal choroidal thickness (SFCT) [15, 16].

In our study, we aimed to evaluate the effect of NAFLD on the choroidal microvascular structure by using EDI-OCT-based SFCT and CVI measurements, because there has been no research on this subject in the literature.

Material and methods

This study was conducted prospectively between July 2020 and June 2022. It was performed in accordance with the principles of the Declaration of Helsinki with the ethical approval of the local Clinical Studies Ethics Committee. Informed consent form was obtained from the patients.

Study population

The patients who were eligible for the study were referred to the Ophthalmology Clinic for OCT after being examined in the Gastroenterology Clinic. Gastroenterological exclusion criteria were as follows: known chronic liver disease, diabetes mellitus, hypertension, coronary artery disease, heart failure, malignancy, inflammatory systemic disease, chronic renal failure, excessive alcohol use (over 20 g/day in women, over 30 g/day in men), smoking, systemic corticosteroid, and a history of using drugs (methotrexate, amiodarone, tetracycline, tamoxifen, etc.) that may cause fatty liver. In addition, people with history of ocular disease (including active or inactive central serous chorioretinopathy), history of ocular surgery, trauma or tumour, best corrected visual acuity (BCVA) less than 20/20, spherical 5 dioptres and cylindrical more than 2 dioptres refraction, patients with visual impairment, media opacities that make imaging difficult, and intraocular pressure > 21 mmHg were excluded from the study.

Physical examination

The patients were weighed between 9 and 10 a.m. after 6–8 hours of fasting, and height and waist circumference measurements were taken. Body mass index (BMI) was calculated by dividing the weight by the square of the height. A waist circumference (WC) measurement was made on the skin at the midpoint between the lower rib edge and the anterior superior iliac wing using a tape measure.

Measurement of biochemical parameters

Venous blood samples were taken from the antecubital vein for biochemical parameters from all patients in the sitting position after at least 8 hours of fasting. Glucose, uric acid, total cholesterol (TC), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), triglyceride, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), ferritin, and insulin were evaluated. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as follows: the fasting glucose and fasting insulin levels were multiplied and then divided by 405 (17).

Evaluation of hepatosteatosis

Hepatosteatosis was evaluated with 4.5 MHz convex probe ultrasonography (Siemens, Acuson X700 Ultrasounds, Siemens Medical Solutions, United States, Inc.) by a single gastroenterologist after fasting for 6–8 hours. Hepatosteatosis grade evaluation with ultrasonography was performed as follows: Grade 0: no steatosis; Grade 1: minimal diffuse increase in hepatic echogenicity, intrahepatic vein borders and diaphragm are clearly seen; Grade 2: moderate diffuse increase in hepatic echogenicity, intrahepatic views vessels and diaphragm slightly impaired; Grade 3: severe diffuse increase in hepatic echogenicity, with the increase in echogenicity at a level that prevents the visualization of the intrahepatic vessels and diaphragm.

Ophthalmological examination

All participants underwent a complete ophthalmologic examination including visual acuity with Snellen chart, intraocular pressure with Goldmann applanation tonometry, biomicroscopy, and dilated fundus examination by the same ophthalmologist (AK). SFCT and CVI measurements were obtained on images taken with spectral-field optical coherence tomography (SD-OCT) (Spectralis, Heidelberg Engineering, Heidelberg, Germany) enhanced depth imaging (EDI) mode (Fig. 1). To minimize diurnal variations, all measurements were taken between 9 and 10 a.m. The images obtained by this method were processed in open-access ImageJ software, and the CVI was calculated. SFCT was measured using an internal calliper tool embedded in the OCT device. For measurement, the instrument is manually placed at the level of the fovea from the outer edge of the retinal pigment epithelium perpendicular to the choroid-sclera border. Measurements were made repeatedly and the average of 2 separate values for each participant was used. For CVI measurements, the same researcher binarized and segmented the Advanced HD line images using publicly available ImageJ 1.51s software. After the OCT image was opened in the ImageJ program, the polygon tool was used to select the region to be evaluated along the scan area. The total choroidal area (TCA) was determined by marking the upper border of the relevant region along the choroid-retinal pigment epithelium junction and the lower border along the choroidal-sclera junction. After the scan was converted to an 8-bit image, Niblack's automatic local threshold was applied to binarize the image and separate the lumen area (LA) and stromal area (SA). To select the dark pixels representing the LA, the image was converted back to a red, green, and blue image, and the colour threshold tool was used (Fig. 2). After measuring TCA and LA as mentioned above, the SA value was obtained by subtracting LA from TCA. Finally, the ratio of LA to TCA (CVI) was calculated. Calculation of all parameters was done by the investigator blind to patient characteristics (AK), and the mean value of each calculated parameter was used for statistical analysis.

Statistical analysis

The statistical analyses were performed using SPPS v.27.0 (SPSS, Chicago, IL, United States) software. While categorical data were expressed as frequency and percentage, quantitative data were expressed as mean and standard deviation. In the comparison of categorical data, the chi-square test was used. The independent t-test and Mann-Whitney U test were used for comparison of quantitative data. p-value < 0.05 was considered significant.

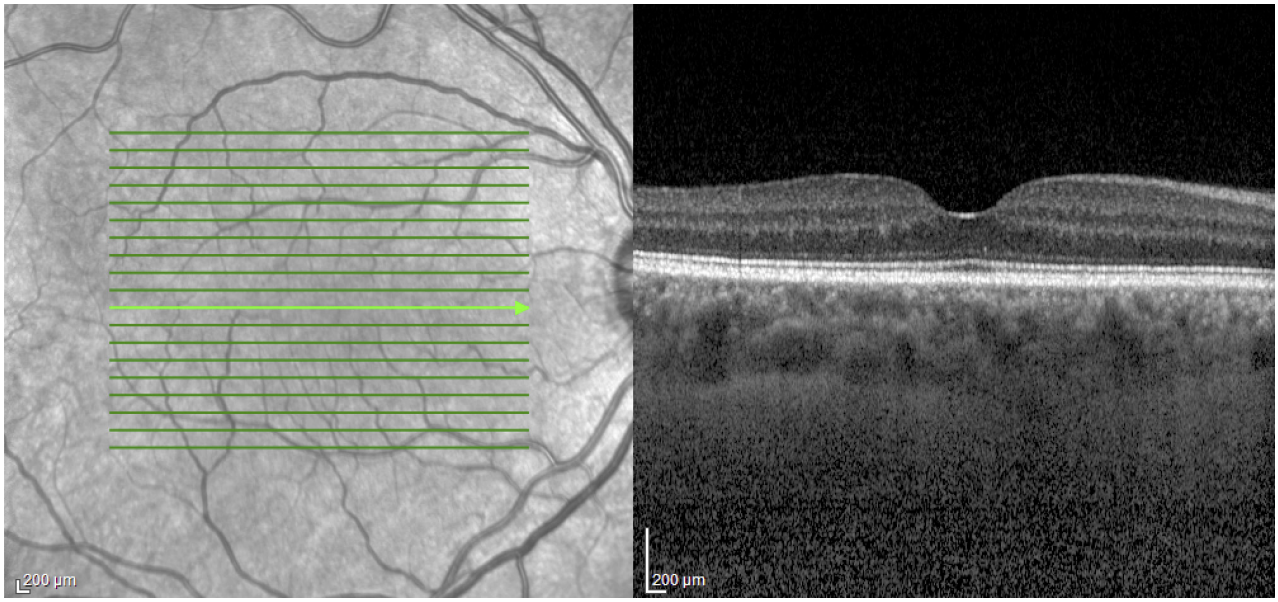

Figure 1. *Horizontal section enhanced depth optical coherence tomography (EDI-OCT) image of the central foveal region in a case of nonalcoholic fatty liver disease (NAFLD)*

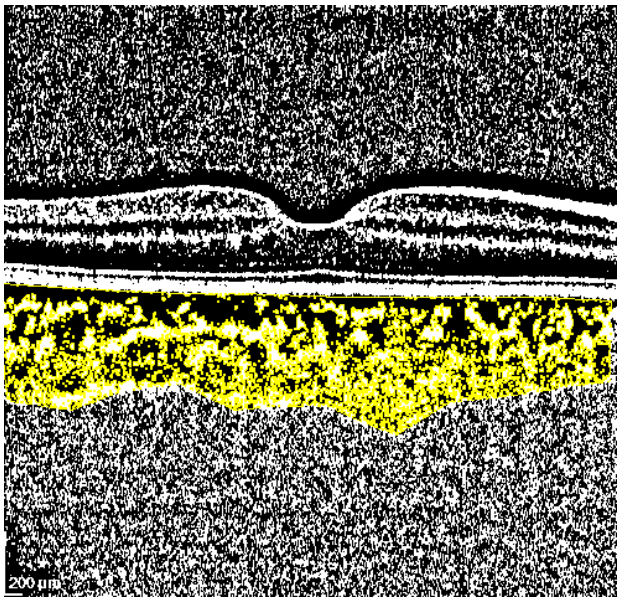

Figure 2. *Choroidal vascular index measurement of the same subject using ImageJ software. The luminal area (dark pixels) is seen as yellow dots with the colour threshold tool. The stromal area is observed as bright pixels*

Results

A total of 104 eyes of 52 patients with fatty liver and 88 eyes 44 patients without fatty liver were analysed in the study. Of the patients with fatty liver, 24 were women, 28 were men, and those without fatty liver comprised 32 women and 12 men (Tab. 1). The mean age of those with fatty liver was 41 ± 15.7 years and those without fatty liver was 46 ± 10.7 years. There was no statistically significant difference between the groups in terms of age ($p = 0.064$). The groups were compared in terms of BMI and WC. BMI and WC were statistically significantly higher in the group with fatty liver than in the control group ($p < 0.001$ and $p < 0.001$, respectively). When the groups were compared in terms of biochemical values, glucose, uric acid, TC, ALT, GGT, ferritin, insulin, and HOMA-IR values were statistically significantly higher in the group with fatty liver than the control group ($p < 0.05$). There was no statistically significant difference between the groups in terms of LDL-C, HDL-C, triglyceride, and AST values ($p > 0.05$) (Tab. 2).

Table.1: Gender ***distribution of the groups***

Gender	Fatty liver (+)	Fatty liver
Male	28	12
Female	24	32

The mean SFCT was measured as 280.26 ± 23.68 microns in the NAFLD group and 308.96 ± 18.57 microns in the control group. There was no statistically significant difference in SFCT between the groups ($p = 0.077$). In the evaluation made in terms of CVI, the mean CVI was 0.63 in those with fatty liver and 0.65 in those without fatty liver. In the analysis, CVI was statistically significantly lower in the fatty liver group than in the non-fatty liver group ($p = 0.045$) (Tab. 3).

Table 2. *Comparison of age, body measurements, and biochemical values of patients with and without fatty liver*

	Fatty liver (+)	Fatty liver (–)	p-value
Age	46 ± 10.8	41 ± 15.7	0.064
BMI	30.6 ± 4.4	23.4 ± 3.5	< 0.001
WC	105.4 ± 10.5	85.1 ± 11.08	< 0.001
Glucose	104.3 ± 16.5	94.45 ± 13	0.002
Uric acid	5.81 ± 1.22	3.84 ± 1.08	< 0.001
TC	222.8 ± 48.2	202.4 ± 50.8	0.048
LDL-C	133.6 ± 42.2	120.7 ± 42	0.130
HDL-C	56.4 ± 36.9	57.3 ± 15.3	0.880
Triglyceride	202.5 ± 181.5	150.9 ± 185.9	0.170
Ferritin	101.3 ± 116.3	51.8 ± 44.6	0.006
Insulin	12.03 ± 4.3	7.6 ± 3.5	< 0.001
ALT	27.5 ± 16.6	19.6 ± 10.2	0.006
AST	23.6 ± 9.6	21.9 ± 6.2	0.300
GGT	34.4 ± 21.8	20.3 ± 11.7	< 0.001
HOMA-IR	3.2 ± 1.45	1.73 ± 0.72	< 0.001

BMI — body mass index; WC — waist circumference; TC — total cholesterol; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; ALT — alanine aminotransferase; AST — aspartate aminotransferase; GGT — gamma glutamyl transpeptidase; HOMA-IR — homeostatic model assessment — insulin resistance

Table 3. *Comparison of groups in terms of choroid vascular index (CVI) and subfoveolar choroidal thickness (SCFT)*

	Fatty liver (+)	Fatty liver (–)	p-value
CVI	0.63	0.65	0.045
SFCT	280.26 ± 23.68	308.96 ± 18.57	0.077

Discussion

In this study, we found that patients with fatty liver had a lower CVI than those without fatty liver.

Over the years, it has been shown that NAFLD is not limited to liver-related morbidity and mortality, but is also a multisystem disease affecting many systems [18]. Especially in patients with NAFLD, the rate of cardiovascular diseases (CVD) is increased, and the major cause of death in these patients is CVD (6). It has been reported that there is a strong correlation between NAFLD and various subclinical atherosclerosis markers such as increased carotid intima-media thickness, coronary artery calcification, impaired vasodilation, and arterial stiffness [19]. In a cohort of over 11,000 adults, NAFLD was associated with an increased prevalence of CVD independent of multiple CVD risk factors [20]. In another study, it was determined that coronary artery calcification progressed more in those with NAFLD than in those without NAFLD [21]. Many factors such as genetic/epigenetic factors, endothelial dysfunction, atherogenic dyslipidaemia, systemic/vascular inflammation, insulin resistance, coagulation, and altered gut microbiome are responsible for the increased CVD in NAFLD [22]. In particular, insulin resistance seems to be the most important pathogenetic mechanism linking the 2 diseases. Both NAFLD and CVD are diseases caused by end organ damage of metabolic syndrome, and the main disorder of metabolic syndrome is insulin resistance [23–25]. As a result of insulin resistance, glucose utilization in peripheral tissues decreases and irregular lipolysis occurs in adipose tissue. This causes excess fatty acids in the liver. In the liver, fatty acids either undergo mitochondrial beta-oxidation or are re-esterified to form triglycerides. When the elimination of fatty acids through beta-oxidation or triglyceride formation is insufficient or inhibited, lipotoxic products begin to accumulate in hepatocytes and the NAFLD process begins [26, 27]. The dyslipidaemic environment caused by excessive production and secretion of very low-density lipoprotein (VLDL) particles and decreased high-density lipoprotein (HDL) levels predisposes to CVD [28]. In

addition, insulin resistance is closely associated with endothelial dysfunction, and endothelial dysfunction also plays an important role in the pathogenesis of atherosclerosis [29, 30]. As a result of these mechanisms, CVD occurs more commonly in patients with NAFLD than in the healthy population.

There are various invasive and noninvasive techniques to diagnose systemic or coronary atherosclerotic plaques. For the diagnosis of atherosclerotic vascular disease, catheter-based invasive artery angiography is the gold standard test, but the procedure is invasive and has potential complications [31]. Therefore, various non-invasive modalities have been investigated, which specifically indicate the severity of coronary artery disease. Positron emission tomography, computed tomographic coronary angiography, and magnetic resonance imaging are among these modalities, each of which has its own advantages and disadvantages [32]. In the last decade, attempts have been made to find the relationship between retinal features and cardiovascular outcomes [33]. The choroid is a thin dense vascular network layer with high perfusion between the retina and the sclera, which supplies nutrients and oxygen to the retina and the outer nuclear layer of the retina [34]. Imaging of the choroid using non-invasive imaging methods is unique in that it allows direct visualization of the systemic vasculature. Thanks to this imaging, microstructural changes that occur before macrovascular diseases can be observed [35]. In the literature, many studies have been done in terms of the presence of choroidal thickness changes in atherosclerotic vascular diseases. In various studies, a decrease was found in SFCT in atherosclerotic vascular diseases, while a decrease was not shown in others [36–38]. Recently, it has been reported that changes in retinal microvasculature parameters despite changes in choroidal thickness are a potential biomarker for cardiovascular disease risk [15]. The change in choroidal thickness may originate from the stromal tissue as well as from the vascular system. The choroidal vascularity index (CVI) is a relatively new method that offers the opportunity to evaluate the choroid by dividing it into vascular and stromal areas. CVI is a more stable marker than choroidal thickness and is less affected by physiological factors [39]. Li et al. grouped the patients according to the degree of carotid stenosis compared with healthy patients, and found the CVI of patients with severe stenosis to be significantly lower than that of the normal group. They also stated that CVI is a more accurate parameter than SFCT for diagnosing and monitoring choroidal vascular changes in carotid stenosis [40]. In the study conducted by Asikgarip et al., 50 newly diagnosed, treatment-naïve, hypertensive eyes were compared with 50 healthy eyes. CVI was significantly lower in the hypertensive group than in the control group. [41]. Durusoy et al. examined early changes in the choroidal vascularity index before and after stenting in patients with severe carotid stenosis and observed a significant improvement in CVI after stenting [42]. Seo et al. determined that CVI was lower in the group with triple vessel disease than in the groups without coronary artery disease and with 1–2 vessel disease, and they reported that CVI could be useful in differentiating severe coronary artery disease from less severe coronary artery disease [43]. In our study, patients with a diagnosis of NAFLD had a statistically significantly lower CVI compared to the control group. Considering the NAFLD-CVD relationship, our result seems compatible with the existing literature. Prospective, larger, and longer follow-up studies are needed on this subject.

Limitations

The first of the limitations of our study is that study population is relatively small. Second, the presence of coronary artery disease in the groups was not demonstrated by invasive or non-invasive methods. Third is the use of manual measurements during CT measurements and CVI calculation, but the automation of these measurements has not yet been achieved.

Conclusion

This is the first study in the literature to compare patients with and without ultrasonographic fatty liver in terms of choroidal microvascular structural changes. We found that the choroidal vascular index (CVI) decreased in NAFLD. This result proves that NAFLD causes changes at the microvascular level and is a multisystemic disease. For this reason, we believe that physicians and patients should be made aware that NAFLD is not only limited to the liver, but may also pave the way for systemic atherosclerotic vascular diseases.

Ethics statement

The study protocol was approved by Konya Medicana Hospital Ethics Committee (Date: June 08, 2022; No: 2022/03).

Author contributions:

Concept — E.A., A.K.; design — E.A., A.K.; supervision — E.A., A.K.; resources — E.A., A.K.; materials — E.A, A.K.; data collection and/or processing — E.A., A.K.; analysis and/or interpretation — E.A.,A.K.; literature search — E.A., A.K.; writing manuscript — E.A., A.K.; critical review — E.A., A.K.

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Conflict of interest
The authors declare that they have no competing interest.

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