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Optical coherence tomography angiography in non-alcoholic fatty liver disease: is it a disease affecting the microvascular system??

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Abstract

Purpose To investigate retinal thickness and vascular structure in patients with non-alcoholic fatty liver disease (NAFLD) using optical coherence tomography (OCT) and OCT angiography (OCTA) and to compare the results with healthy controls.

Method The medical records of NAFLD patients were retrospectively reviewed. Macular thickness (MT) and peripapillary retinal nerve fibre layer (pRNFL) thickness were assessed. The vessel density (VD) of Superficial Capillary Plexus (SCP), Deep Capillary Plexus (DCP), foveal avascular zone (FAZ) area, FAZ circularity index (CI), and FAZ perimeter were also recorded.

Results The study included 64 patients with NAFLD and 64 healthy controls. Mean MT and pRNFLT were similar between groups. The study group showed a significant reduction in VD-DCP compared to the control group (36.0 ± 5.2 vs. 38.5 ± 4.1, $p < 0.001$). Total FAZ area was greater in the study group than in the control group (0.42 ± 0.10 vs. 0.33 ± 0.12mm2, $p < 0.001$). FAZ CI also differed between groups (0.47 ± 0.08 vs. 0.53 ± 0.08, $p < 0.001$). Enlarged FAZ area and decreased VD-DCP were significantly associated with NAFLD severity.

Conclusion Individuals with NAFLD have certain changes in the retinal microvasculature, including reduced VD-DCP, an increased FAZ area, and a decreased of FAZ CI. The variations in VD-DCP and FAZ area exhibit discrepancies according to the disease grade. There are some limitations, including its retrospective nature, the small number of participants, the lack of analysis of the peripapillary area, and the lack of examination of longitudinal changes.

Keywords Non-alcoholic fatty liver disease, OCT, OCTA, FAZ area, FAZ circularity index

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterized by the accumulation of fat in the liver, known as hepatic steatosis (HS). This condition is diagnosed through imaging or histology, after ruling out other causes of liver fat buildup, such as excessive alcohol consumption, the use of medication that promotes fat accumulation, and hereditary disorders [1].

In our age, it remains among the most prevalent factors contributing to long-term liver damage in individuals of any decade [1]. From a histological perspective, NAFLD can be classified into two distinct types: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). The NAFL (non-alcoholic fatty liver) is a kind of NASH that does not worsen with time. NASH, on the other hand, is characterized by liver damage and inflammation, and has the potential to develop into liver fibrosis and cirrhosis. Ultrasonography is the preferred noninvasive and accessible technique for diagnosis [2]. Recent studies have indicated that NAFLD shares similar epidemiological and pathophysiological characteristics with type 2 diabetes and metabolic syndrome [2,3]. There is growing evidence that NAFLD is linked to a higher occurrence of both small and large blood vessel problems in individuals with diabetes [4]. Nevertheless, there is still ongoing debate concerning the correlation between NAFLD and retinopathy.

Optical coherence tomography angiography (OCTA) is a relatively novel technology that allows for evaluation of the blood flow in retina, without the need for any contrast agents.

There is scarce literature data regarding association between retinal morphological changes and NAFLD [5–7]. Studies have shown that NAFLD is associated with vascular changes such as retinal venous dilatation, narrowed retinal arteriolar diameter, low arterial/venous ratio, and decreased choroidal vascular index [5–7]. In addition, to the best of our knowledge, there is no study in the literature evaluating vessel density (VD) with OCTA in patients with NAFLD. This study aimed to investigate retinal thickness and vascular structure in NAFLD patients by using OCTA and compare the results with those of healthy controls.

Methods

In this cros-sectional study, the medical records of patients who were followed up with the diagnosis of NAFLD at a tertiary center between July 2020 and April 2021 were reviewed retrospectively. The protocol of the present study conformed to the Declaration of Helsinki. The study was approved by the Erzincan Binali Yıldırım University Hospital, College of Medicine Ethics Committee on Clinical Resarch (99-77968). Due to the retrospective design, informed consent was not obtained. The diagnosis of NAFLD was made by an internal specialist based on the diagnostic criteria already established in the literature. Individuals attending the clinic for routine eye examinations were selected as healthy subjects. An age and sex-matched control group consisting of healthy subjects without any ocular and/or systemic disorder were also enrolled. Only right eye from each subject was included in the study.

The inclusion criteria for the study group are as follows: a diagnosis of NAFLD, age above 18 years, and a refractive error within the range of ± 3 diopters (D).

The exclusion criteria were as follows: Presence of diabetes mellitus and systemic hypertension, Body Mass Index (BMI) greater than 30 kg/m2, presence of ocular and retinal diseases (i.e.; glaucoma, retinal vascular occlusion), media opacities or instability in fixation, previous intraocular surgery.

Optical coherence tomography angiography analysis

Retinal structural and microvascular imaging was performed using OCT (RS-3000 Advance, Nidek Co., Tokyo, Japan) and OCTA (Nidek RS-3000 Advance, Nidek Co., Tokyo, Japan) following pupillary dilatation. All OCT and OCTA measurements were taken by the same technician. The macular and peripapillary retinal nerve fiber layer (pRNFL) thicknesses were measured using device's software. The resolution of the transverse and axial scans was 20 μm and 7 μm, respectively. Macular thickness (MT) was assessed by measuring the thickness within a 1-mm radius circle centered at the macula, and then measuring the thickness in four quadrants located 3 mm apart from the center (superior, nasal, inferior, temporal) (ETDRS chart) (Fig. 1). The pRNFL thickness was measured mean value and at four distinct quadrants (superior, nasal, inferior, temporal) (Fig. 2). All OCTA images comprised a 3 × 3 mm2 region that was positioned at the center of the fovea. The macula's saturated in color VD maps (ETDRS chart) were utilized for the quantitative examination of VDs. The VDs of Superficial Capillary Plexus (SCP) and Deep Capillary Plexus (DCP) were also recorded (Figs. 3 and 4). Automated segmentation was used to determine the en face slab for the superficial and deep retinal layers. NIDEK recently launched an updated version (ver. 1.1.5) of its OCTA analysis software. The updated version is capable of determining the boundaries of the foveal avascular zone (FAZ) and automatically calculating its area. The macular OCTA scans were utilized to record the measurements of the FAZ area, perimeter, and circularity index (CI) at the level of SCP (Fig. 3). The circularity index values closer to "1" indicate a higher level of circularity. The OCT and OCTA scans of poor quality have been excluded.

Ultrasonography for hepatosteatosis diagnosis was done by using a 4.5 MHz convex probe (Siemens, Acuson

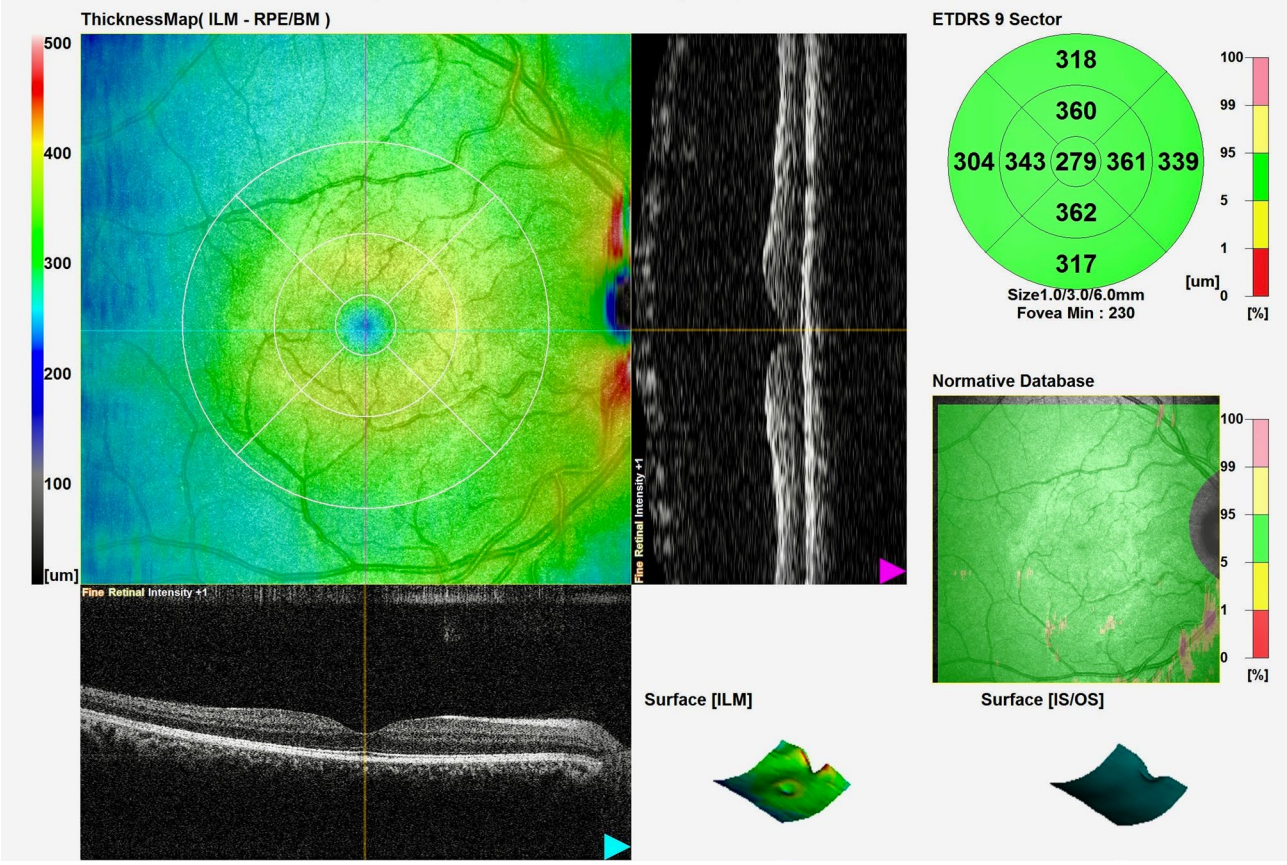

Fig. 1 Measurement of macular thickness profile

X700 Ultrasounds, Siemens Medical Solutions, United States, Inc.). The evaluation of hepatosteatosis grade was conducted using ultrasonography in the following manner: Grade 1: There is a little overall rise in liver brightness, with clear visibility of the margins of the veins inside the liver and the diaphragm. Grade 2: There is a modest diffuse rise in the liver's brightness on ultrasound, with slightly decreased visualization of the blood vessels within the liver and the diaphragm. Grade 3: There is a significant and widespread rise in the liver's brightness on ultrasound, to the extent that it hinders the ability to see the blood veins within the liver and the diaphragm.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM Corp., Chicago, IL, USA). Descriptive statistics were presented as mean ± standard deviation (SD). The chi-squared test (χ^2) was used to compare categorical variables between groups. The distribution of continuous variables was assessed using the Kolmogorov-Smirnov test or the Shapiro-Wilk test. For group comparisons, the Student's t-test was used for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. The Kruskal-Wallis test was used for comparisons between more than two independent groups. A post-hoc power analysis was performed. Based on the FAZ area the result of power (1 - β) was shown to be 0.99, α = 0.05, 2 - tailed. A p-value of less than 0.05 was considered statistically significant.

Results

The study included a total of 128 participants [(64 NAFLD (grade 1 = 23, grade 2 = 23, grade 3 = 18 and 64 healthy controls)]. The mean age was 47.0 ± 14.2 years and 47.2 ± 13.3 years in study and control groups, respectively. The age and sex distributions were similar between the groups ($p = 0.88$ and $p = 1.0$, respectively).

The mean MT, and pRNFLT values were similar between the groups ($p > 0.05$) (Table 1).

Total FAZ area was greater in the study group than in control group (0.42 ± 0.10 vs. 0.33 ± 0.12mm^2, $p < 0.001$). The FAZ CI also differed between the groups (0.47 ± 0.08 vs. 0.53 ± 0.08, $p < 0.001$). The study group exhibited a significant reduction in VD-DCP as compared to the control group (36.0 ± 5.2 vs. 38.5 ± 4.1, $p < 0.001$). The VD-SCP and FAZ perimeter were similar between the groups ($p < 0.05$). (Table 2)

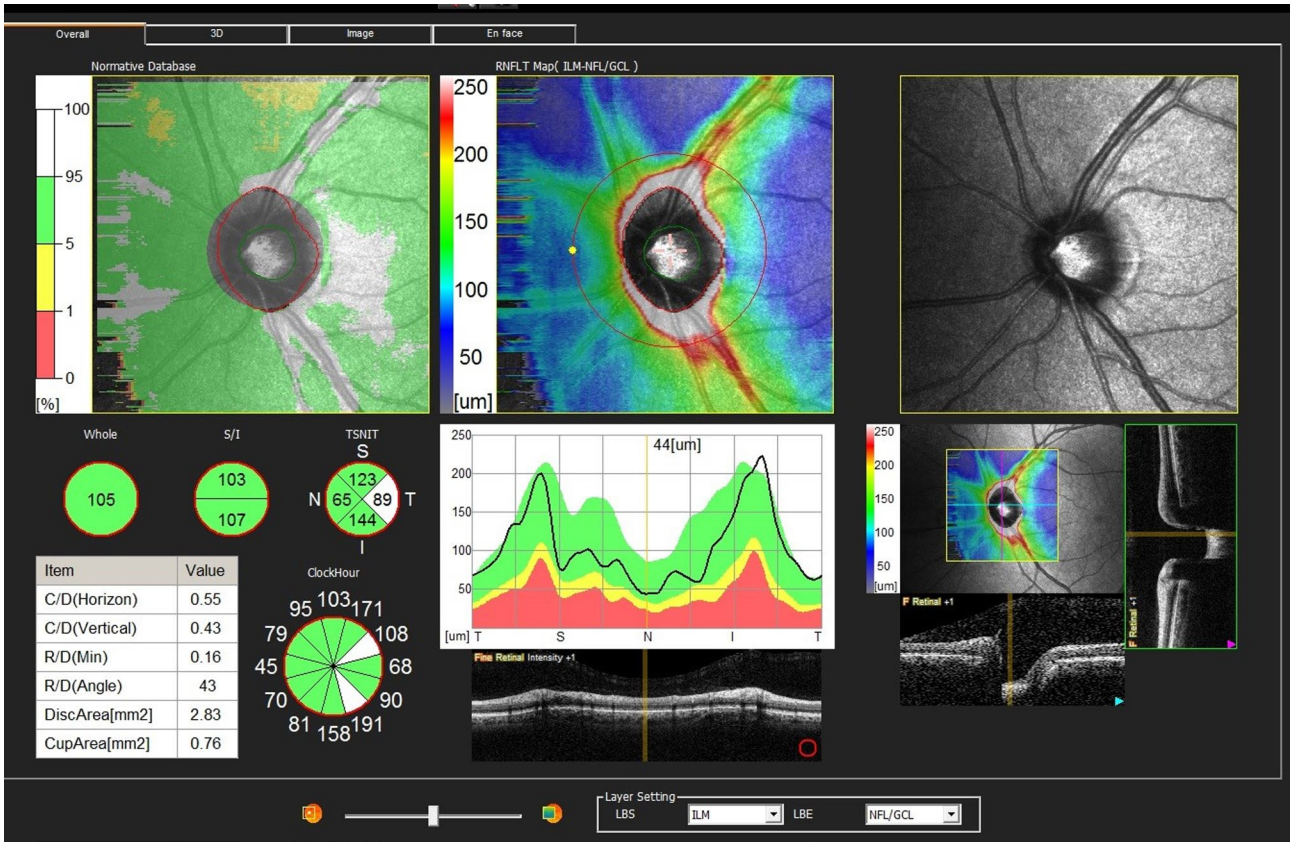

Fig. 2 Measurement of peripapillary retinal nerve fibre layer thickness profile

Enlarged FAZ area and decreased VD-DCP were significantly associated with NAFLD severity ($p < 0.05$). FAZ area and VD-DCP did not differ between stage 1 and stage 2 disease, whereas FAZ area was significantly larger and VD-DCP was significantly lower in stage 3 disease compared to both stage 1 and stage 2 disease. (Table 3)

Discussion

The present study revealed that there was no statistically significant difference in either the MT or the pRNFL between the patients with NAFLD and the control group. However, OCTA data revealed a reduction in VD-DCP of the macular region, as well as an enlargement of the FAZ area and a decrease in the FAZ CI. Furthermore, there were notable variations in the VD-DCP and the FAZ area based on the severity of the illness grades. Specifically, grade 3 disease exhibited more pronounced effects compared to the other grades.

Numerous studies have established a potential relationship between the eyes and liver through various etiological aspects, including metabolism, inflammation, oxidative stress, and immunology [8, 9]. NAFLD is considered to be the hepatic manifestation of the metabolic syndrome and shares pathophysiological characteristics with type 2 diabetes [6, 10, 11]. On a worldwide scale, the current estimate is that NAFLD impacts approximately 25% of the general population [10]. Pathophysiological processes, such as liver fat accumulation due to NAFLD, can lead to inappropriate liver function, which in turn can trigger insulin resistance and high liver gluconeogenesis, as well as other disruptions in blood glucose regulation. These factors may contribute to the development or worsening of diabetes [12]. Furthermore, there is a significant correlation between the existence of NAFLD and endothelial dysfunction, which arises in the initial phases of atherosclerosis [13]. It is not surprising that all pathological processes, such as insulin resistance, lipid oxidation, inflammation, mitochondrial, oxidative, and endoplasmic reticulum stress, may lead to micro- and macro-vascular complications in the eye as well as in the liver. All grades of NAFLD contribute to its clinical burden, with the more advanced stages predicted to have the greatest impact [11].

When evaluating studies on ocular findings in patients with NAFLD, it was discovered that several reports demonstrated the presence of macroscopic retinal vascular alterations in NAFLD patients [5]. Conversely, other studies reported no significant difference in macroscopic retinal vascular changes between NAFLD patients and normal controls [6]. Avcı et al. conducted OCT on

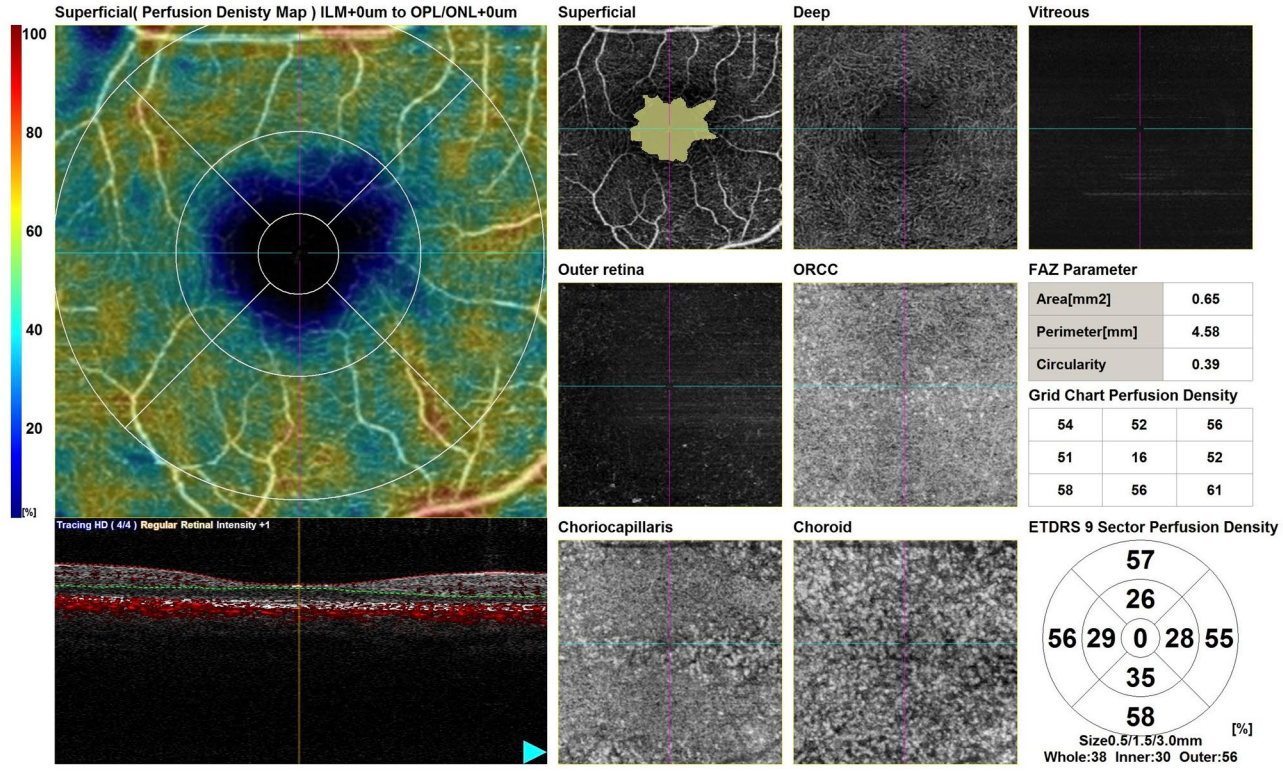

Fig. 3 Demonstration of the macula's saturated in color Superficial Capillary Plexus (SCP) vessel density (VD) maps (ETDRS chart), quantitative examination of VD-SCP, Foveal avascular zone (FAZ) area, FAZ perimeter, and FAZ circularity index

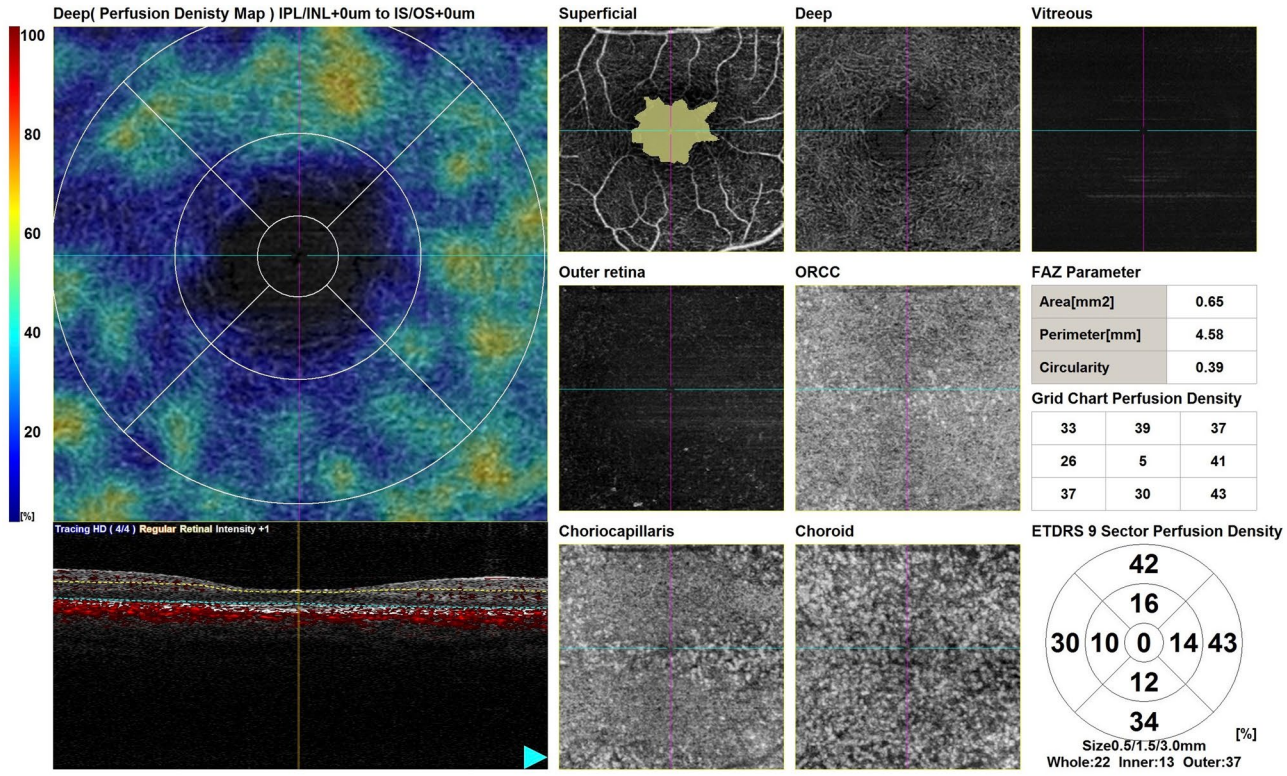

Fig. 4 Demonstration of the macula's saturated in color Deep Capillary Plexus (DCP) vessel density (VD) maps (ETDRS chart) and quantitative examination of VD-DCP. Foveal avascular zone (FAZ) area, FAZ perimeter, and FAZ circularity index at the level of Superficial Capillary Plexus

Table 1 Optical coherence tomography characteristics in study and control group

	Study Group (*n*:64)	Control Group (*n*:64)	*p**
pRNFL (μm)			
Mean	107.32 ± 12.62	105.62 ± 11.63	0.32
Superior	128.50 ± 16.69	131.78 ± 18.50	0.13
Nasal	76.15 ± 19.75	76.35 ± 16.68	0.058
İnferior	137.56 ± 20.62	139.06 ± 19.11	0.54
Temporal	75.50 ± 16.05	75.50 ± 16.05	1
MT(μm)			
1 mm central	262.96 ± 38.65	263.60 ± 22.12	0.87
3 mm superior	344.18 ± 17.16	346.71 ± 16.12	0.22
3 mm nasal	343.62 ± 15.83	344.18 ± 16.35	0.78
3 mm inferior	341.25 ± 16.72	342.11 ± 16.25	0.67
3 mm temporal	327.82 ± 15.78	328.64 ± 15.89	0.67

p*= Student T test

pRNFL: peripapillary retinal nerve fibre layer, MT: macular thickness

Table 2 Optical coherence tomography angiography characteristics in study and control group

	Study Group (*n*:64)	Control Group (*n*:64)	*p**
Superficial Capillary Plexus VD (mm^{-1})	41.98 ± 3.00	42.04 ± 2.62	0.85
Deep Capillary Plexus VD (mm^{-1})	36.07 ± 5.21	38.55 ± 4.19	**< 0.001**
FAZ Area (mm^2)	0.42 ± 0.10	0.33 ± 0.12	**< 0.001**
FAZ perimeter (mm)	2.99 ± 0.64	2.95 ± 0.61	0.56
FAZ Circularity Index (mm)	0.47 ± 0.08	0.53 ± 0.08	**< 0.001**

p*: Student T test

FAZ: Foveal avascular zone, VD: Vessel Density

patients with NAFLD and discovered that the choroidal vascularity index decreased significantly, although there was no notable alteration in choroidal thickness [7]. In the current study, retinal thickness around the macula and optic nerve were similar between patient and control groups.

The NAFLD causes substantial alterations in vessel functioning. Oguz et al. [14] have shown that patients with NAFLD exhibited a notable decrease in aortic flow propagation velocity. Other investigations have demonstrated a notable decline in coronary flow velocity reserve in patients with NAFLD [15]. The advantage of OCTA is that it is a non-invasive technique and provides detailed documentation of the superficial and deep layers of retinal vascular density in a way that fundus fluorescein angiography cannot. To the best of our knowledge, there has been no research conducted on the microvascular level in patients with NAFLD. Our results showed that VD-DCP was markedly reduced in NAFLD patients, whereas the VD-SCP was similar to that of normal healthy subjects. In addition, when vascular densities were evaluated based on the NAFLD grades, VD-DCP of individuals with grade 3 disease were found to be lower than those with grade 1 and grade 2 disease. It is known that oxidative stress and inflammation also increase the deterioration of capillaries and the development of vascular lesions [16]. The presence of distinct ischemia and inflammatory reactions in the SCP and DCP of the retina might be related to their unique structures and positions. The researchers hypothesized that DCP would be particularly vulnerable to tissue oxygen deprivation and increased levels of inflammatory cytokines [17]. The perfusion pressure in the SCP may be higher because of the earlier departure of its branches from the retinal artery compared to those in the DCP. Additionally, the DCP may exhibit increased sensitivity to changes in venous pressure and reduced oxygen levels because of its composition, which contains venous collecting channels, and its location in a watershed-like area relative to the SCP. The DCP, being the layer closest to the photoreceptors, is very vulnerable to oxidative stress. Alternatively, the diminished blood flow to the DCP may cause outer retinal ischemia. The outer retina, acting as a transitional area between the retinal capillary and choroidal circulations, is particularly susceptible to ischemia to the deep capillary layers. This creates a harmful loop where DCP ischemia and photoreceptor metabolic stress reinforce each other [18].

Table 3 Nonalcoholic fatty liver disease severity and optical coherence tomography angiography characteristics

	Grade 1 (*n*:23)	Grade 2 (*n*:23)	Grade 3 (*n*:18)	*p**	p^a	p^b	p^c
Superficial Capillary Plexus VD (mm^{-1})	42.29 ± 3.14	42.11 ± 3.06	41.41 ± 2.72	0.338	0.747	0.155	0.269
Deep Capillary Plexus VD (mm^{-1})	37.00 ± 4.59	37.44 ± 4.77	33.16 ± 5.50	***0.003***	0.677	***0.005***	***0.001***
FAZ Area (mm^2)	0.41 ± 0.09	0.38 ± 0.09	0.48 ± 0.08	***< 0.001***	0.091	***0.006***	***< 0.001***
FAZ perimeter (mm)	2.86 ± 0.56	2.99 ± 0.66	3.17 ± 0.69	0.049	0.267	***0.014***	0.172
FAZ Circularity Index (mm)	0.47 ± 0.08	0.48 ± 0.07	0.47 ± 0.08	0.886	0.690	0.676	0.875

p*= Three group comparison, Krusskall Wallis test

p^a= Grade 1 and grade 2 comparison, Mann-Whitney U test with Bonferroni correction

p^b= Grade 1 and grade 3 comparison, Mann-Whitney U test with Bonferroni correction

p^c= Grade 2 and grade 3 comparison, Mann-Whitney U test with Bonferroni correction

FAZ: Foveal avascular zone, VD: Vessel Density

The FAZ is a specialized capillary-free area in the central macula and it is in proximity to the region of the highest cone photoreceptor density and oxygen consumption [19]. Studies have revealed specific retinal microvascular alterations in several chronic inflammatory conditions. Investigators have examined FAZ area in inflammatory bowel illness cases and found larger FAZ area in individuals with active disease compared to those in remission [20]. Another previous research has shown that patients with psoriasis exhibit an increase in the size of the FAZ area and a decrease in the DCP [21]. These findings along with those presented in the current study may imply a negative impact of NAFLD on retinal microvasculature. The development of ischemia in NAFLD may be attributed to chronic inflammatory processes, which lead to oxidative stress, lipid oxidation, endothelial dysfunction, and ultimately atherosclerosis. As mentioned earlier, the pathogenesis of NAFLD is similar to the pathogenesis of diabetes. In a study conducted in diabetic patients without diabetic retinopathy, enlargement of FAZ area and decrease in VD-DCP were shown similar to the present study [22, 23]. In addition, recent literature has demonstrated the importance of OCTA in other systemic vascular diseases [24, 25].

While the FAZ area is frequently used to characterize, the significant variance in its size may restrict its capacity to indicate pathology in cross-sectional screening applications. The regularity of the overall shape of the FAZ, as assessed by its roundness or circularity, may provide a more sensitive signal of disease due to reduced variation in normal individuals [26]. However, it is important to note that there are several restrictions associated with it, including variations in computation methods and algorithms. In current study, not only FAZ area was found to be larger but also FAZ CI was observed to be lower in NAFLD patients compared to controls. In accordance with these results, the literature shows the FAZ CI is lower for multiple systemic diseases such as diabetes and systemic lupus erythematosus [23, 27]. Reduced FAZ CI is a good indicator of vascular dropout and perifoveal microcirculation impairment. Possible reasons for the reduced FAZ CI may be disturbances of microcirculation, oxidative stress, which are also blamed in the pathophysiology of NAFLD.

The current study has several limitations, including its retrospective nature, a small number of participants, a lack of analysis of the peripapillary area, a lack of examination of longitudinal changes, and a failure to adjust the FAZ area for differences in retinal magnification. However, it is worth to note that including of subjects only with mild refractive errors might have minimized this flaw.

In conclusion, individuals with NAFLD have certain changes in the retinal microvasculature, including reduced VD-DCP, an increased area of the FAZ, and a decreased index of FAZ circularity. The variations in VD-DCP and FAZ area exhibit discrepancies according to the disease grade, with grade 3 being more significantly impacted compared to the other grades. These findings may suggest that NAFLD causes significant changes in the retinal microvascular system and these changes may be more pronounced with increasing disease severity. Prospective longitudinal studies are necessary to clarify the impact of NAFLD on retinal microvasculature and get a deeper understanding of the molecular pathways involved in NAFLD.

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Author contributions
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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate
All procedures performed in studies involving human participants followed the ethical standards of the institutional and/or national research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Erzincan Binali Yıldırım University Hospital, College of Medicine Ethics Committee on Clinical Resarch (Approval Number = 99-77968). Written informed consent was obtained from all the participants of the study.

Competing interests
The authors declare no competing interests.

Conflict of interest
The authors have no financial or proprietary interests in any material discussed in this article.

Consent for publication
Not applicable.

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