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Original Research

# Evaluation of Peripapillary and Macular Vascular Flow Changes with OCT-A in Patients with Superficial Optic Disk Drusen

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## Abstract

**Objectives:** The purpose of this study was to compare the peripapillary and macular vascular flow changes between healthy adults and adult patients with superficial optic disk drusen (ODD), as evaluated by optical coherence tomography angiography (OCT-A).

**Methods:** In this retrospective study, 44 eyes of 22 patients with superficial ODD followed-up in our neuro-ophthalmology unit and 54 eyes of 27 healthy individuals admitted to our clinic for routine ophthalmological examination were included in the study. The superior, inferior, nasal, and temporal radial peripapillary capillary plexus (RPC) vessel density (VD) values; superior, inferior, nasal, and temporal parafoveal and foveal region superficial capillary plexus (SCP) and deep capillary plexus (DCP) VD values; and choriocapillaris flow (CCF) area and foveal avascular zone area were evaluated by OCT-A.

**Results:** There was no statistically significant difference between groups in terms of age and sex. While there was a significant decrease in the temporal RPC VD values in cases with ODD (p=0.02), no significant difference was observed in other quadrants. No significant differences in either parafoveal zone four quadrant, foveal SCP and DCP VD values, or foveal avascular zone measurements were found between groups, while CCF area values were significantly higher in the study group (p=0.012).

**Conclusion:** Compared to healthy controls, our results showed a decrease in the RPC temporal quadrant VD values, and an increase in CCF area in cases with superficial ODD. To evaluate the effects of ODD on optic nerve head and macular perfusion, and to understand its underlying mechanisms and secondary complications, longer follow-up studies with larger case series are needed.

**Keywords:** Macular vascular flow, neuro-ophthalmology, optic disk drusen, optical coherence tomography angiography, peripapillary vascular flow, retina

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Optic disk drusen (ODD) was first characterized histologically as crystalline, fatty-appearing granules located at the head of the optic nerve in 1858.[1] While the incidence of ODD was reported to be 3.4/1,000 in adults, in postmortem histological studies, it was found to be higher.[1] Although the reported rates of bilaterality differ, in a study conducted using ultrasonography (USG), it was reported to be 91.2%.[1,2]

ODD can lead to changes in vascular structures in the optic nerve head and the peripapillary area. In cases with ODD, large diameter arteries and arteries without branching, the branching in arteries, and veins that start before normal disks, more common cilioretinal arteries and retinochoroidal collaterals have been shown by optical coherence tomography (OCT).[3] Abnormal vascularization due to ODD is assumed to allow plasma protein leak out

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of the cell, and these extracellular proteins serve in the creation of ODD as a nucleation point.[4] However, it has been theorized that axon metabolism is a secondary impairment due them to narrow scleral canal and small optic disk in eyes with ODD.[1]

ODDs are typically located in front of the lamina cribrosa, as recorded in postmortem studies, and may rarely display retrolaminar or anterior expansion toward the vitreous.[5] Typically, ODD is asymptomatic, and its superficial form can be detected at a routine ophthalmologic examination. Visual field defects with a slow and benign path, especially affecting the peripheral areas, can be observed due to nerve fiber damage during lesion growth.[6-8] However, in patients with an unusual superficial form, visual field defects have been documented most frequently in the inferonasal and inferotemporal regions.[9,10] Rarely, a severe reduction in visual acuity may occur as a result of vascular complications. In these situations, secondary vascular complications such as central retinal artery or vein occlusion, anterior ischemic optic neuropathy, or choroidal neovascular membrane formation, as a consequence of the impact of mechanical pressure on vascular structures, may occur.[8,11]

Scanning methods, such as USG, fundus autofluorescence (FAF), fluorescein angiography (FA), or OCT, are used for the differential diagnosis of the ODD and its form. OCT-angiography (OCT-A) which is a current, noninvasive scanning technique provides information of microvascular structures better than others. With its development, optic disk, macula, and choroid blood flow can be rapidly and noninvasively imaged at high resolution. Further, papillary and peripapillary microvascular changes were documented in various studies, where drusen-induced vascular changes were evaluated with OCT-A.[8,12-14]

In consideration of the vascular complications that may endanger vision and require a rapid treatment implementation, the examination of retinal vascular structures in case of ODD is critical.

OCT-A can be used in the diagnosis and follow-up of neuro-ophthalmological diseases such as optic neuropathies, papilledema, ODD, or papillitis; it is also an up-to-date technology that can be used to evaluate the effects of these pathologies on peripapillary and macular vascular density.

We compared the peripapillary and macular vascular flow changes assessed by OCT-A imaging in adult patients with superficial ODD and healthy adult individuals in our study.

## Methods

The study protocol was approved by the Local Ethics Committee (Ethics Committee for Clinical Studies of University of Health Sciences, Sisli Hamidiye Etfal Training and Research Hospital, Department of Ophthalmology, Istanbul, Turkey date: 01/12/2020; no: 3021). Written informed consent was obtained from all patients.

This retrospective cross-sectional study was performed between January 2019 and July 2020 in the neuro-ophthalmology unit of our hospital's ophthalmology department, including patients >18 years old with an superficial ODD diagnosis and healthy controls. Forty four eyes of 22 patients who were followed-up for ODD in our neuro-ophthalmology unit and 54 eyes of 27 healthy controls who came to our clinic for a routine eye examination as a control group were included in the study.

In this study, patients with a systemic disease that may cause vascular changes in the retina or optic disk, anterior or posterior segment pathologies, ocular trauma or surgery history, dense cataract, ocular hypertension, amblyopia, or uveitis disease that may affect the OCT-A assessment including refractive errors (myopia > 2 diopters or hypermetropia/astigmatism > 1.50 diopters) were excluded from the study.

A thorough ophthalmological review of all patients provided their best visual acuity, intraocular pressure, pachymetry measurements, and anterior segment and posterior segment findings.

Patients diagnosed with fundus examination, B scan USG, FAF, and OCT and were evaluated with OCT-A for microvascular changes. OCT-A images were obtained after pupilla dilatation with the AngioVue (software version 2017.1, Optovue, Inc., Fremont, CA, USA) unit. The 6 × 6 mm macula and the 4.5 × 4.5 optical disk scanning protocol were tested for high quality and accurate shots. A single physician acquired all images (between 10.30 a.m. and 2.30 p.m.). Only images with a quality ≥7/10 were included in the study.

Peripapillary capillary plexus (RPC) four quadrants (superior, inferior, nasal, and temporal), foveal superficial capillary plexus (SCP) and deep capillary plexus (DCP), parafoveal four quadrants (superior, inferior, nasal, and temporal) SCP and DCP vessel density (VD), choriocapillaris flow (CCF) area, and foveal avascular zone (FAZ) area were evaluated by OCT-A.

OCT-A separates optic nerve head scans into two layers: The inner limiting membrane (ILM) and the 2000 µm area below were accepted as the inner limit, while the outer limit was accepted as the 150 µm below the inner plexiform layer. The RPC segment was considered as the area from the ILM to the retinal nerve fiber layer (RNFL) posterior border. Capillary VD was defined as the percentage density created by the microvascular system in the optic disk and peripapillary area. The peripapillary areas were automatically divided into four quadrants (superior, inferior, nasal,

and temporal) by the software.

Automatic software predefined retinal and choroidal layers were employed. Namely, there were 3 µm below the ILM and 15 µm below the ILM, at the upper and lower borders of the SCP, respectively. The DCP was defined as the region between 15 and 70 µm below the ILM. The upper and lower edges of the choriocapillaris layer were between 30 and 60 µm under the retina pigment epithelium. While the vascular density of the foveal region was defined as the VD (%) within a 1 mm diameter area, 3 mm diameter area excluding the foveal area was defined vascular density of the parafoveal region.[15] The FAZ and the CCF area was also automatically calculated. 6 × 6 mm macular area within the choriocapillaris layer was defined the CCF.

### Statistical Analysis

Number Cruncher Statistical System 2007 Statistical Software (Utah, USA) program was used for statistical analysis. In addition to descriptive statistical methods (mean, standard deviation), the Shapiro–Wilk normality test was used to analyze the distribution of variables, the independent t-test was used to compare variables with normal distribution, and the Chi-square test to analyze qualitative data. P<0.05 was considered as the threshold for statistical significance.

## Results

Forty-nine individuals were included in our study. Twenty two patients and 27 healthy individuals were included in the study. There were four men and 18 women with an average age of 26.5±7.33 years in the study group, and 10 men and 17 women with an average age of 28.56±3.6 years in the control group. There was no difference between the groups in terms of age and gender distribution (p=0.206; and p=0.146) (Table 1).

On ophthalmologic examination, all patients had complete visual acuity and biomicroscopic anterior segment evaluation was normal. There was no sign of strabismus or ocular movement disorder in the patient.

While no pathology in the anterior segment was found in biomicroscopy, a yellow accumulation on the optic disk surface and swelling and indistinctness at the optic disk margins was observed in the study group, consistent with superficial type ODD.

**Table 1.** Demographic data of the patients

| | Control Group n=27 | | Study Group n=22 | | p |
|---|---|---|---|---|---|
| Age | 28.56±3.6 | | 26.5±7.33 | | 0.206* |
| Gender | | | | | |
| Male | 10 | 37% | 4 | 18.18% | 0.146⁺ |
| Female | 17 | 63% | 18 | 81.82% | |

*Independent t-test; ⁺Chi-square test.

When OCT-A data were evaluated; there was no statistical difference in the parafoveal region SCP superior, inferior, nasal, and temporal quadrants VD values (p=0.895, p=0.578, p=0.718, and p=0.425), and DCP superior, inferior, nasal, and temporal quadrants VD values (p=0.760, p=0.978, p=0.436, and p=0.126), or in foveal region SCP and DCP VD values (p=0,113, p=0.333) between the study group and healthy control group (Table 2).

When the RPC superior, inferior, nasal, and temporal quadrant VD values of the study group were compared with the healthy control group, a significant VD decrease in the temporal quadrant was detected (p=0.569, p=0.071, p=0.888, and p=0.020) (Table 2).

Although the CCF area values in the study group were significantly higher than in the control group (p=0.012), there was no significant difference in FAZ area values between the groups (p=0.740).

## Discussion

In our study, we compared the RPC VD percentages, foveal and parafoveal SCP and DCP VD percentages, CCF area, and FAZ area values of adult patients with a diagnosis of superficial ODD and a healthy control group. The value of RPC VD in the temporal quadrant in the study group was found to be lower than the control group in accordance with both groups. Although there was no statistically significant difference between the SCP and DCP VD values of the parafoveal and foveal regions and the FAZ area values between the groups, the CCF area was significantly in the higher in the study group.

Despite the formation mechanism of ODD not being fully understood, a small disk and narrow scleral canal can lead to ODD development, leading to decreased axoplasmic flow and ganglion cell axon death. ODD with scotomas in the visual field or visual loss secondary to transient ischemia, secondary to progressive neural tissue loss caused by growing, is often diagnosed in the second life decade.[16,17]

While the diagnosis of superficial ODD can only be reached by direct ophthalmoscopic examination, in cases with buried ODD, both definitive diagnosis and detection of complications can be achieved with scanning methods such as USG, FA, FAF, OCT, and OCT-A (Figs. 1-3). The importance of these methods has been emphasized in the follow-up of vascular complications secondary to ODD.[18]

**Table 2.** Parafoveal, foveal, radial peripapillary capillary plexus VD percentages in different quadrants and CC flow area, and FAZ measurement of both groups

| | Control group | | Study group | | P[t] |
|---|---|---|---|---|---|
| | Mean±SD | Median | Mean±SD | Median | |
| Parafoveal superficial superior VD (%) | 51.82±3.37 | | 51.73±3.46 | | 0.895 |
| Parafoveal superficial inferior VD (%) | 51.52±4.00 | | 51.94±3.40 | | 0.578 |
| Parafoveal superficial nasal VD (%) | 49.99±4.01 | | 50.27±3.64 | | 0.718 |
| Parafoveal superficial Temporal VD (%) | 48.80±4.18 | | 49.40±2.91 | | 0.425 |
| Parafoveal deep superior VD (%) | 55.16±3.70 | | 54.91±4.52 | | 0.760 |
| Parafoveal deep inferior VD (%) | 54.44±3.73 | | 54.42±4.38 | | 0.978 |
| Parafoveal deep nasal VD(%) | 55.08±3.89 | | 55.67±3.55 | | 0.436 |
| Parafoveal deep temporal VD (%) | 54.78±3.73 | | 55.93±3.61 | | 0.126 |
| Fovea superficial VD (%) | 17.64±5.51 | | 19.35±4.94 | | 0.113 |
| Fovea deep VD (%) | 33.92±7.03 | | 35.23±6.15 | | 0.333 |
| RPC superior VD (%) | 52.54±1.40 | | 52.07±5.84 | | 0.569 |
| RPC inferior VD (%) | 53.67±1.24 | | 52.25±5.55 | | 0.071 |
| RPC nasal VD (%) | 53.44±1.11 | | 53.30±7.65 | | 0.888 |
| RPC temporal VD (%) | 53.33±1.18 | | 51.59±5.25 | | 0.02 |
| CC flow area ($mm^2$) | 2.084±0.112 | | 2.157±0.170 | | 0.012 |
| FAZ ($mm^2$) | 0.288±0.110 | | 0.280±0.119 | | 0.740 |

The average of the right and left eye of each subject was used for the analyses. [t]Student's t-test for independent samples. SD: Standard deviation; VD: Vessel density; CC: Choriocapillaris; FAZ: Foveal avascular zone; RPC: Radial peripapillary capillary plexus.

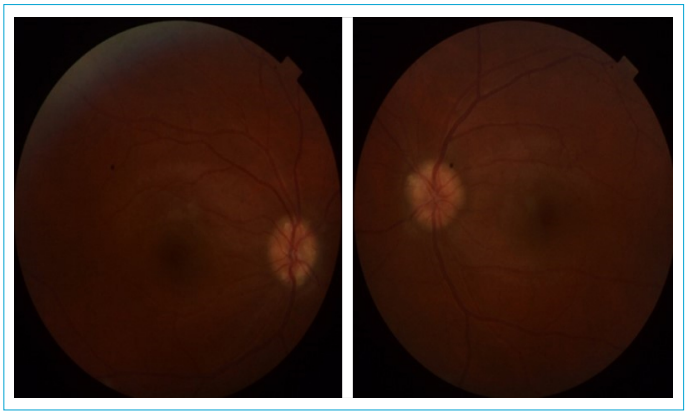

**Figure 1.** The color fundus photography of a patient with superficial optic disk drusen. The indistinct margins and mild swelling of the optic nerve head could be detected.

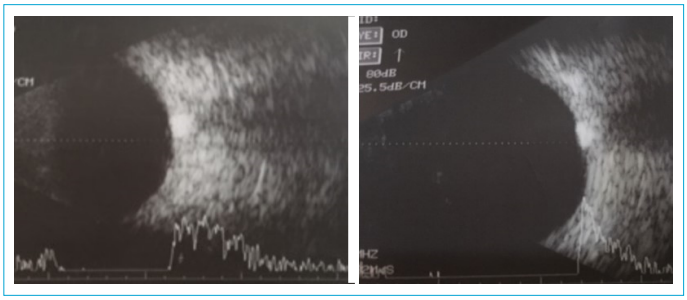

**Figure 2.** The fundus autofluorescence imaging of a patient with superficial optic disk drusen. The hyperautofluorescence representing the drusen formation could be detected in the optic nerve head.

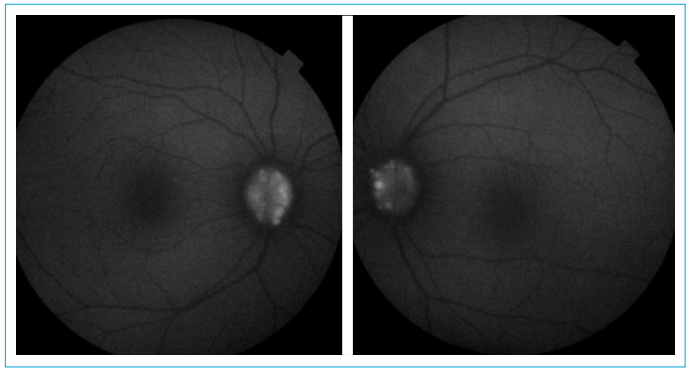

**Figure 3.** The B scan ultrasonography imaging of a patient with superficial optic disk drusen. The hyperreflective, calcific lesions representing the drusen formation, could be detected in the optic nerve head.

Visual field defects, which can be seen especially in buried ODD, are a complication that requires careful monitoring. Even though most patients are unaware of these defects, visual field defects such as blind spot enlargement, arcuate scotomas, and peripheral visual field narrowing may be observed.[19] Due to chronic visual field loss, ODD may be diagnosed late and produce sudden vision loss with anterior ischemic optic neuropathy.

Similar to its compression effect, ODD can cause axonal degeneration with a narrow scleral canal mechanism in surrounding tissues or indirectly affect on vascular structures

and cause perfusion impairment. ODD growth can compress the RNFL and vascular structures leading to visual field defects, retinal artery or vein occlusions, and retinal hemorrhages.[6,7]

While thinning was found to be most prevalent in the nasal quadrant, Gili et al. suggested that thinning occurred in the temporal quadrant.[20] Furthermore, in a study examining the flow changes that ODD can produce in the optic nerve head, a lower flow index and decreased vascular density in the optic nerve head were found.[12] Flores-Reyes et al. reported ischemia in the peripapillary region in OCT-A in a patient with reduced contrast sensitivity and visual field defect, and that this ischemic area may be related to ODD location.[13] Herein, we found a decrease in the RPC VD values in the temporal quadrant in the ODD group (Fig. 4). This may be due to the impact of ODD on the vascular structures of the peripapillary region, similar to the effect of the nerve fiber that can be generated in the peripapillary region in various quadrants.

In the pathophysiology of ODD and the development of associated complications, vascular mechanisms may be as relevant as the evident compressive effect. In a Doppler study in cases with ODD, the blood flow in the posterior ciliary arteries was lower in cases with ODD compared than in individuals with glaucoma.[8] Biçer et al. found decreased VD in SCP and DCP in more than one quadrant in the macula and decrease in nasal peripapillary region VD values of an ODD case in OCT-A imaging. They related this change to the acute or chronic compressive effect of ODD development on nerve fibers or vascular structures.[14] Yan et al. found a positive correlation between visual acuity, RNFL, ganglion cell complex (GCC), and peripapillary VD measurements in cases with ODD; finding as well a negative correlation with macular flow measurements and reported it as a possible early biomarker. They highlighted that the response of autoregulation may cause increase in blood flow in the retina to compensate the changes that ODD causes to the vessels and other structures in the peripapillary region. Further, with the visual field and GCC loss progression, there may be a bigger decrease in RPC VD values, which may be a late biomarker.[11]

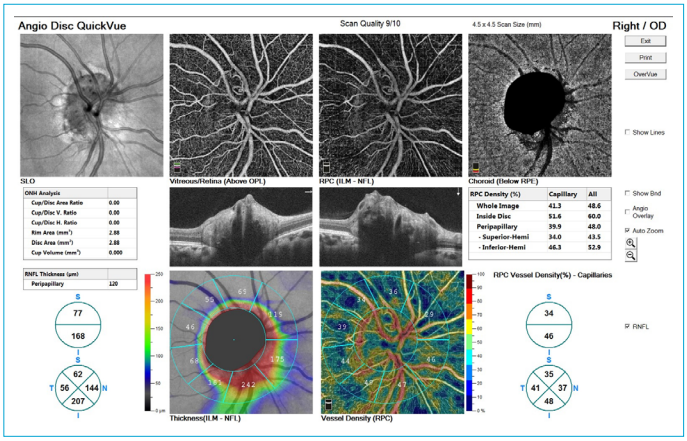


**Figure 4.** The optical coherence tomography and optical coherence tomography angiography images of a patient with superficial optic disk drusen. The drusen formation with hyporeflective core and hyperreflective halo could be detected in optical coherence tomography scans. Capillary drop out areas in blue color that refers to ischemia could be detected in peripapillary regions of both eyes in optical coherence tomography angiography images.

In our study, while there was no difference between the groups in all quadrants of the parafoveal region and foveal region SCP and DCP VD values and FAZ area measurements, the CCF area was found to be increased in patients with superficial ODD. It has been previously reported that blood flow may increase in the retina as a reactive response to perfusion disorder.[11] Perhaps the increase in the flow area in the choriocapillaris layer constitutes a very early hemodynamic shift that could occur before the changes of vascular structures. Although perfusion changes can be observed with Doppler USG, OCT-A may be a more effective and modern technology for early detection and tracking of ischemia and secondary changes in various locations and different layers of the retina.

There are aome limitations our study, including the small sample size. The ODD and its neuronal and vascular effects are still not fully elucidated. Although the effects of ODD on the peripapillary RNFL and GCC layers have been further clarified, its effects on the vascular structures in the macula and the flow area are still unclear, and large case series is needed in this regard. OCT-A may facilitate clarifying its effects on perfusion. Studies combining OCT-A results with microperimetry tests or multifocal electroretinography may reveal a correlation between decreased macular perfusion and CCF area. Absence of ODD size measurements and the determination of the ODD location is another limitation of our study. Furthermore, the most important advantage of our study is that it includes a group that is homogeneous in terms of age and gender with no additional systemic disease.

## Conclusion

We compared the RPC VD values, foveal and parafoveal region SCP and DCP VD values, CCF area, and FAZ area values in OCT-A images of adult patients with superficial ODD with those of a healthy control group. Compared to the control subjects, patients with ODD had lower RPC temporal quadrant VD values and higher CCF area values. OCT-A can be an effective and safe method for monitoring vascular changes caused by ODD. However, large case series and long follow-up studies are still warranted.

### Disclosures

**Ethics Committee Approval:** The study protocol was approved by the Local Ethics Committee (Ethics Committee for Clinical Studies of University of Health Sciences, Sisli Hamidiye Etfal Training and Research Hospital, Department of Ophthalmology, Istanbul, Turkey date: 01/12/2020; no: 3021).

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