# Analysis of Retinal Vessel Density and Macular Flow Area in Diabetic and Healthy Participants Using Optical Coherence Tomography Angiography

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## ABSTRACT

**Purpose:** To inspect the macular flow area, superficial and deep retinal vessel density measurements of optical coherence tomography (OCT) angiography (OCTA) in diabetic patients and healthy subjects.

**Methods:** This retrospectively reviewed, and the cross-sectional study included 64 right eyes of 64 diabetic patients (Diabetic group) and 60 right eyes of 60 healthy (Control group) subjects. The diabetic group included two subgroups of patients with proliferative diabetic retinopathy (PDR) and patients with non-proliferative diabetic retinopathy (NPDR). The groups and subgroups were compared in terms of the best-corrected visual acuity (BCVA), intraocular pressure and OCT/OCTA measurements, including central macular thickness (CMT, um), macular flow area ($mm^2$), foveal and parafoveal vessel density (VD, %) in the superficial and deep retinal layers.

**Results:** The mean values of BCVA and CMT were 0.42±0.32 and 0.86±0.17 ($p<0.001$), and 313.33±119.54 and 250.44±26.70 µm ($p=0.002$) in the diabetic and control groups, respectively. The mean macular flow area values were 1.29±0.20 and 1.36±0.16 $mm^2$ ($p=0.044$), the mean superficial retinal parafoveal VD measurements were 48.38±5.2 and 51.83±5.22 ($p=0.002$), and the mean deep retinal parafoveal VD measurements were 42.82±6.29 and 46.38±4.74 ($p=0.019$) in the diabetic and control groups, respectively. Excluding a lower mean CMT value, the mean values of BCVA, macular flow area, and all VD measurements were higher in the NPDR group than the PDR group ($p<0.05$ for all).

**Conclusion:** OCTA imaging enables the analysis of superficial and deep retinal vessel density in diabetic patients. Thus, it is possible to assess the association of retinal vasculature with visual acuity and macular flow area. Worsened visual acuity, impaired macular flow area and a tendency of decreased vessel density were observed in diabetic patients.


**Keywords:** Optical coherence tomography angiography, Vessel density, Macular flow area

## INTRODUCTION

Diabetes mellitus is a chronic systemic disease that affects over 400 million people worldwide.[1] Diabetic retinopathy (DR) is a microangiopathic complication of DM leading to visual impairment.[2, 3] Diabetic macular edema (DME) is a common cause of vision loss associated with DR despite the advances in the treatment modalities including pan-retinal or grid laser photocoagulation and intravitreal injections.[4]

Fluorescein angiography (FA) is frequently used for the diagnosis and treatment follow-up of DR.[5] However, as an invasive method, FA has some adverse effects including nausea, vomiting, itching, urticaria and rarely anaphylaxis due to the fluorescein.[6-8] Optical coherence tomography (OCT) has become widely accepted for the evaluation of retinal diseases as a noninvasive method enabling high-resolution images of the retina.[9-11] The development of OCT angiography (OCTA) which is also a noninvasive imaging technique, has provided the clinicians to obtain depth-resolved images of the retinal capillary plexus and macular flow area and choriocapillaris.[12-14] Compared to FA, it is an important advantage for OCTA images that no use of fluorescein dye is needed.[15, 16]

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OCTA works with time-related differences in erythrocyte reflective to render flow maps of retinal circulation with segmentation capabilities.[17] The purpose of this study is to inspect the macular flow area and vessel density in OCTA for diabetic patients and healthy subjects.

## METHODS

This cross-sectionally designed and retrospectively reviewed study was conducted in accordance with the tenets of the Declaration of Helsinki. All participants signed informed consent. The local ethics committee (Sisli Hamidiye Etfal Training and Research Hospital) approved the study.

### *Study Design and Patient Selection*

Sixty-four right eyes of 64 naïve type 2 diabetic patients (Diabetic group) and 60 right eyes of 60 healthy (Control group) subjects were included in this retrospectively designed study. Diabetic patients were divided into two subgroups of patients with proliferative diabetic retinopathy (PDR, PDR group) and patients with non-proliferative diabetic retinopathy (NPDR, NPDR group) regardless of the existence of diabetic macular edema (DME). The measurements of best-corrected visual acuity (BCVA, in decimal), intraocular pressure (IOP, mmHg, pneumatic tonometry), slit-lamp ocular anterior segment and stereoscopic fundus examinations, colour fundus photo, fundus angiography (FA) and OCT/OCTA scans were performed in all participants. The diagnosis of PDR and NPDR was established clinically and confirmed with FA. Exclusion criteria included previous intravitreal injections, laser photocoagulation or vitreoretinal surgery, ischemic maculopathy (confirmed with FA), vitreus hemorrhage, vitro-retinal membrane or bands, cystic macular edema, star maculopathy, refractive errors (spheric equivalence >4 diopters), amblyopia, retinal vessel occlusion, glaucoma, optic atrophy and age-related macular degeneration.

### *Measurement Protocol*

The same experienced and masked technician performed all OCT/OCTA measurements. An Enhanced depth imaging and spectral-domain (SD) OCT/OCTA (AngioVue Avanti RTVue-XR, OptoVue, Fremont, CA, USA) was used for VD measurements. Images with significant artifacts and signal strength lower than 6/10 were excluded. The scans were capture over a 3 x 3 mm area centered on the fovea. The central macular thickness (CMT, µm), macular flow area and superficial and deep foveal and parafoveal vessel density (VD, %) parameters were measured using OCT/OCTA. VD was defined as the total number of pixels contributing to the blood flow signal identified by OCTA. Superficial retinal VD was measured between the inner limiting membrane (ILM) and the inner plexiform layer (IPL), and deep retinal VD was measured from the IPL to the outer plexiform layer (Figure 2). Since no vasculature exists above the RPE in healthy eyes, detect of blood flow at the level of the outer retinal layers is not expected in OCTA measurements.

### *Statistics*

The data of participants were evaluated using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). The independent samples t-test was used to compare the groups and subgroups. Pearson's correlation test was used to assess the correlations between the parameters. A $p < 0.05$ was accepted as a statistically significant level. The regression analysis of subgroups including sex, lens condition, systemic diseases was also considered on statistical evaluation.

## RESULTS

In this study, we evaluated 64 right eyes of 64 (34 females, 30 males) patients with diabetic retinopathy in the diabetic group and 60 right eyes of 60 (32 females, 28 males) healthy subjects in the control group. Twenty-nine eyes of 29 patients were in the PDR subgroup of the diabetic group. The remaining 35 eyes of 35 patients were in the NPDR subgroup of the diabetic group. The demographic and clinical features of the diabetic/control groups and PDR/NPDR subgroups were represented in tables 1 and 2, respectively. The diabetic and control groups had similar mean age values, similar gender and systemic disease proportions. However, the patients in the diabetic group were less phakic than the subjects in the control group ($p=0.024$). All demographic and clinical properties were similar in the PDR and NPDR subgroups.

The BCVA, IOP, CMT, macular flow area, superficial and deep retinal foveal and parafoveal VD measurements of the diabetic/control groups and PDR/NPDR subgroups were represented in tables 3 and 4, respectively. The diabetic group had worse mean BCVA, similar mean IOP, higher mean CMT, lower mean macular flow area values when compared with the control group ($p<0.05$ for all). While mean superficial and deep foveal VD measurements were similar between the groups, mean superficial and deep parafoveal VD measurements showed a reduction in the diabetic group ($p=0.002$ and $p=0.019$, respectively). The PDR subgroup had worse mean BCVA, similar mean IOP, higher mean CMT, lower mean macular flow area values when compared with the NPDR subgroup ($p<0.05$ for all). All mean superficial and deep foveal and parafoveal VD measurements were lower in the PDR subgroup than the NPDR group ($p<0.05$ for all).

**Table 1:** *Demographic and clinical features of the patients in the diabetic and control groups.*

| Characteristics | Diabetic Group (n=64) | Control Group (n=60) | p* |
|---|---|---|---|
| Age (years) | 60.82±8.13 (55-72) | 59.86±11.10 (50-68) | 0.382 |
| Gender (n) | | | |
| Female | 34 (53.12%) | 32 (53.33%) | 0.732 |
| Male | 30 (46.87%) | 28 (46.66%) | |
| Lens Status (n) | | | |
| Phakic | 38 (59.37%) | 46 (76.66%) | *0.024 |
| Pseudo-phakic | 26 (40.62%) | 14 (23.335%) | |
| Systemic Disease (n) | | | |
| Hypertension | 9 (14.06%) | 6 (10%) | 0.107 |
| Hypercholesterolemia | 7 (10.94%) | 5 (8.33%) | 0.138 |

*CNV: Choroidal neovascular membrane, AMD: Age-related macular degeneration, *The Chi-Square and Independent samples student's t-tests were used, n: Number*

**Table 2:** *Demographic and clinical features of the patients in the PDR and NPDR subgroups.*

| Characteristics | PDR Subgroup (n=29) | NPDR Subgroup (n=35) | p* |
|---|---|---|---|
| Age (years) | 61.96±11.71 (57-72) | 60.03±6.98 (55-70) | 0.245 |
| Gender (n) | | | |
| Female | 16 (55.17%) | 18 (51.42%) | 0.665 |
| Male | 13 (44.82%) | 17 (48.57%) | |
| Lens Status (n) | | | |
| Phakic | 17 (58.62%) | 21 (60%) | 0.194 |
| Pseudo-phakic | 12 (41.37%) | 14 (40%) | |
| Systemic Disease (n) | | | |
| Hypertension | 5 (17.24%) | 4 (11.43%) | 0.388 |
| Hypercholesterolemia | 4 (13.79%) | 3 (8.57%) | 0.235 |

*PDR: Proliferative diabetic retinopathy, NPDR: Non-proliferative diabetic retinopathy, *The Chi-Square and Independent samples student's t-tests were used, n: Number*

**Table 3:** *The Comparison of the BCVA, IOP, CMT, superficial and deep retinal vessel density measurements between the diabetic and control groups.*

| Measurements | Diabetic Group (n=64) | Control Group (n=60) | p* |
|---|---|---|---|
| BCVA (decimal) | 0.42±0.32 | 0.86±0.17 | *<0.001 |
| IOP (mmHg) | 15.92±3.84 | 16.25±2.81 | 0.366 |
| CMT (um) | 313.33±119.54 | 250.44±26.70 | *0.002 |
| Macular flow area ($mm^2$) | 1.29±0.20 | 1.36±0.16 | *0.044 |
| Superficial Foveal VD (%) | 23.62±6.91 | 25.20±5.98 | 0.054 |
| Superficial Parafoveal VD (%) | 48.38±5.42 | 51.83±5.22 | *0.002 |
| Deep Foveal VD (%) | 19.94±8.56 | 21.11±6.32 | 0.154 |
| Deep Parafoveal VD (%) | 42.82±6.29 | 46.38±4.74 | *0.019 |

*BCVA: Best-corrected visual acuity, IOP: Intraocular pressure, CMT: Central macular thickness, VD: Vessel density, *The Independent samples student's t-test was used*

The correlation values of BCVA with CMT, macular flow area, superficial and deep parafoveal VD were r=-0.357, p=0.001; r= +0.234, p=0.014; r=+0.242, p=0.008 and r=+0.230, p=0.022 in the diabetic group, respectively. The correlation values of macular flow area with deep foveal and parafoveal VD were r=+0.417, p=0.001 and r=+0.862, p<0.001 in the diabetic group, respectively. The BCVA showed significant correlations with CMT, macular flow area, superficial foveal and deep parafoveal VD in the PDR subgroup (r=-0.588, p<0.001; r= +0.394, p=0.009;

**Table 4:** *The Comparison of the BCVA, IOP, CMT, superficial and deep retinal vessel density measurements between the PDR and NPDR subgroups.*

| Measurements | PDR Subgroup (n=29) | NPDR Subgroup (n=35) | p* |
|---|---|---|---|
| BCVA (decimal) | 0.32±0.27 | 0.58±0.34 | *0.003 |
| IOP (mmHg) | 16.16±3.32 | 15.84±4.51 | 0.395 |
| CMT (um) | 336.29±137.12 | 274.21±68.22 | *0.016 |
| Macular flow area ($mm^2$) | 1.23±0.20 | 1.40±0.14 | *0.004 |
| Superficial Foveal VD (%) | 19.80±6.43 | 24.48±7.85 | *0.001 |
| Superficial Parafoveal VD (%) | 46.25±5.36 | 51.73±4.24 | *0.001 |
| Deep Foveal VD (%) | 17.48±6.72 | 20.52±5.38 | *0.028 |
| Deep Parafoveal VD (%) | 40.04±6.03 | 45.24±5.92 | *0.008 |

*BCVA: Best-corrected visual acuity, IOP: Intraocular pressure, CMT: Central macular thickness, PDR: Proliferative diabetic retinopathy, NPDR: Non-proliferative diabetic retinopathy, VD: Vessel density, *The Independent samples student's t-test was used*

r=+0.276, p=0.012 and r=+0.406, p=0.001, respectively). The macular flow area had a significant correlation with superficial foveal and deep parafoveal VD (r=+0.457, p=0.001; r=+0.844, p<0.001) in the PDR subgroup. Significant correlations were observed between the BCVA and deep parafoveal VD (r=+0.240, p=0.013), between the macular flow area and deep parafoveal VD (r=+0.204, p=0.034) in the NPDR subgroup. No remarkable results were noted on the confounding effects assessed by regression analysis according to sex, lens condition, and systemic diseases,

## DISCUSSION

This study compared the macular flow area, superficial and deep retinal foveal and parafoveal VD in diabetic and healthy subjects using OCTA, which can visualize macular perfusion, microaneurysms and retinal ischemic areas and is useful to evaluate retinal microvascular status and therapeutic effects of the treatment modalities for diabetic retinopathy.[18-20] BCVA was deteriorated in the diabetic group and PDR subgroup when compared to the control group and NPDR subgroup, respectively as well as the increase of the CMT. Macular flow area was also impaired in the diabetic patients and in the PDR subgroup when compared to controls and NPDR subgroup, respectively. VD in the superficial and deep parafoveal retina was lower in diabetic patients than in controls. All VD measurements were lower in the PDR subgroup than in the NPDR subgroup. From these results, it might be concluded that a decrease in the superficial and deep retinal VD was observed in diabetic patients based on the existence and severity of diabetic retinopathy.[21]

In accordance with the literature, this study showed that both superficial and deep retinal VD was affected, and macular flow area values were lower in the diabetic group and PDR subgroup suggesting the parallelity with the existence and severity of diabetic retinopathy.[22-28] Similar to previous studies, superficial and deep retinal VD showed a significant correlation with BCVA.[29, 30] The macular flow area showed a significant positive correlation with deep retinal foveal and parafoveal VD in the diabetic group and with superficial foveal and deep parafoveal VD in the PDR subgroup, which demonstrates retinal vascular perfusion impairment with the existence and severity of diabetic retinopathy.[22, 23] Meanwhile, as expected, the BCVA showed significant positive correlations with macular flow area, superficial and deep retinal foveal and parafoveal VD, but significant negative correlation with CMT in the diabetic group and PDR subgroup. The study has some limitations including cross-sectional nature, small sample size, absence of choriocapillaris VD measurements. Regarding these limitations, prospective studies with larger sample sizes including VD measurements in the choriocapillaris are warranted.

In conclusion, as a non-invasive, faster, safer and high-resolution technique, OCTA can be used to measure the macular flow area and retinal VD, especially preferable to FA in patients with a high risk of allergic reactions, in office conditions, children and patients with a feeling of nausea-vomiting. The mean values of macular flow area and retinal VD measurements were lower in the diabetic group and PDR subgroup, which may be related to the severity of diabetic retinopathy.

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