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Changes in Peripapillary Perfusion and Retinal Nerve Fiber Layer in Diabetic Iraqi Patients

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ABSTRACT:

BACKGROUND:

Diabetic retinopathy (DR) is a leading cause of acquired blindness through retinal microvascular and neurodegenerative changes. Studying peripapillary vascular density (PPVD) through Optical coherence tomography and angiography (OCT & OCTA) imaging can offer insight into the effect of these changes and aid in management.

OBJECTIVE:

To assess the correlation between peripapillary retinal nerve fiber layer (PRNFL) thickness and peripapillary region perfusion through vascular density in various stages of diabetic retinopathy.

PATIENTS AND METHODS:

This is a comparative cross-sectional study. Participants underwent an optic nerve head OCT and OCTA to measure PRNFL thickness, and peripapillary vascular density (PPVD) using the Triton ® Topcon device. Patients' DR was classified according to the Early Treatment Diabetic Retinopathy Study (EDTRS) classification.

RESULTS:

This study enrolled 95 participants: 28 controls (56 eyes) and 67 diabetic patients (123 eyes), a total of 179 eyes. The PRNFL thickness showed no statistically significant differences among study groups. The average PPVD was significantly lower in severe non-proliferative DR / neovascularization elsewhere (NPDR/ NVE) group compared to all other groups.

CONCLUSION:

Peripapillary vascular density correlated significantly with DR severity, decreasing with increasing DR severity. The PRNFL thickness showed no significant decrease neither correlating with DR severity nor PPVD.

KEYWORDS: Diabetic retinopathy, Optical coherence tomography angiography, peripapillary vascular density.

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Iraqi Postgraduate Medical Journal, 2025; Vol. 25(1): 20-27
DOI: 10.52573/ipmj.2025.155402 Received: March 12, 2025 Accepted: May 5, 2025

INTRODUCTION:

Diabetes is growing as a pandemic anticipated to affect 700 million people by 2045, resulting in a corresponding increase in the prevalence of diabetic retinopathy worldwide. [(1)] The prevalence of diabetic retinopathy (DR) varies greatly among studies but is estimated to be 27% globally. [(2)]

The pathogenesis of DR at the microvascular level involves mainly endothelial cell loss ultimately leading to capillary dropout and changes of the retinal-blood barrier leading to leakage and retinal edema, In later stages neovascularization occurs as retinal ischemia becomes prominent. [(3)] At the neurological level there are microglial cell activation and cellular apoptosis affecting the ganglion cell complex and the retinal nerve fiber layer (RNFL). [(4)]

The peripapillary retinal nerve fiber layer (PRNFL) receives its blood supply mainly from the radial peripapillary capillary plexus (RPC) that is unique to this location and plays a very important role in neuronal health. [(5,6)]

There is limited information about the relationship between microvascular and neurodegenerative changes in the peripapillary region in diabetic patients. This can be changed with the employment of OCT as a noninvasive, no contact imaging modality that produces micrometer-resolution images of a tissue allowing tissue thickness determination and OCT angiography that can map out blood movement in all capillary layers through the technique of motion contrast helping the study of retinal vasculature. [(7)]

Diabetic retinopathy is classified according to the severity and extent of the diabetic lesions found. In non-proliferative diabetic retinopathy (NPDR), intraretinal vascular changes are present, but no extraretinal fibrovascular tissue. NPDR has a spectrum of being mild, moderate, or severe. Proliferative diabetic retinopathy (PDR) is defined as the presence of retinal neovascularization due to ischemia. It represents an advanced level of diabetic retinopathy. Clinically, PDR is staged as either early disease or PDR with high-risk characteristics. [8]

AIMS OF THE STUDY:

1. To measure peripapillary retinal nerve fiber layer thickness (PRNFLT), and peripapillary region perfusion through vascular density (VD) in diabetic retinopathy (DR) using optical coherence tomography angiography (OCTA).
2. To assess the correlation between the changes in peripapillary vascular density (PPVD) and PRNFL thickness in various stages of DR.

PATIENTS AND METHODS:

Study design: comparative cross-section study.

Study setting: This study was carried out at the Ophthalmology department/ Medical City Complex in Baghdad during the period April 2022 - February 2023.

Participants: 95 participants (28 controls, 56 eyes and 67 patients, 123 eyes) meeting the inclusion criteria mentioned below were examined in the outpatient clinic.

Inclusion criteria:

1. **Controls**: healthy adults between 40-75 years of age with documented normal HbA1C (4%-5.6%).
2. **Patients:** adults between 40-75 years of age with type 2 DM as confirmed by an internist.

Exclusion criteria:

1. Eyes with opaque media (corneal opacity, cataract, etc.) that precluded fundus examination.
2. Glaucoma, uveitis, other retinal diseases, and history of ocular trauma.
3. High refractive error (>6 diopters).
4. Evidence of optic disc neovascularization and/or optic disc edema.
5. History of cataract surgery in the last 6 months.
6. History of pan retinal photocoagulation (PRP) and/or vitreoretinal surgery.
7. Strabismus or any condition affecting proper central fixation.
8. OCTA images with a scan quality index (SQI) of less than 5.

Information including duration of diabetes was collected and an HbA_1C test was ordered for each participant.

Each participant underwent a series of ocular examinations, including Visual Acuity (Log Mar VA), Slit- Lamp biomicroscopic examination of the fundus, OCT optic disc, OCTA and intraocular pressure measurement using a noncontact (air puff) tonometer.

Each eye was graded using the Early Treatment Diabetic Retinopathy Study classification [8] as confirmed by the clinical assessment of a retinal specialist, then divided into the following three groups: Diabetes mellitus without DR (No DR), a mild-to-moderate NPDR, and a severe NPDR to NVE. Patients were classified according to the eye with the more severe stage of DR.

Mild and moderate DR were included in the same group for the present study because the classification of Mild NPDR is characterized by the presence of at least one retinal microaneurysm or hemorrhage. Moderate NPDR is characterized by increased hemorrhages and microaneurysms as well as other signs for the diagnosis of DR while still not meeting the clear cut off 4-2-1 rule of Severe NPDR, which makes it challenging to differentiate them clinically.

Optical Coherence Tomography Angiography Imaging and Image Processing

The Triton® Topcon OCTA device was used. The device's working conditions were: Central wavelength 1,050 nm, axial resolution 8 µm, transverse resolution 20 µm, and scan speed 100,000 A-scans/s. The OCTA measurements were made after pupil dilation by a well-trained examiner with the participant sitting and looking at a fixed point.

The algorithm used by the Triton® device was OCTA-ratio analysis (OCTARA, full-spectrum ratio-based amplitude ratio analysis). Vessel density was defined as the percentage of vessel area showing blood flow out of the total area measured. The mode used was "Angio Macula," a 6 × 6 mm scan was centered manually at the optic nerve head (ONH) and VD measurements were made in four peripapillary quadrants: superior, inferior, nasal, and temporal. These quadrants were identified by an ETDRS grid overlay. [9]

The Triton® swept source OCT (3D scan centered at the ONH) was used to measure the RNFL thickness (PRNFLT) at the peripapillary region.

Statistical analysis

Data input and handling was done using Statistical Package for Social Sciences version 23 software. Chi-square test was used to test the significance of association among categorical variables. Analysis of Variances (ANOVA) test was used for examining the differences of numerical variables among the study groups, namely (Duration of disease, HbA1c, PRNFLT, and PPVD), then Tukey post hoc test was used for in-group multiple comparisons. Spearman rho (RS) was used to study the correlation between PRNFLT and average PPVD.

RESULTS:

This study enrolled 95 participants: 28 controls (56 eyes) and 67 diabetic patients (123 eyes), yielding a total of 179 eyes. The mean age of control group was 60.8± 8.7 years, and of diabetic patients was 61.2± 7.9 years. As for sex distribution, 48 (50.5%) were males and 47 (49.5%) were females (table-1).

There was no statistically significant difference in age nor gender among study groups (Table 1).

Table 1: Distribution of basic characteristics according to study groups (patients' number= 95).

Variables		Control	No DR	Mild/moderate NPDR	Severe NPDR/ NVE	P-value
No. of participants		28	22	23	22	
Age groups	40-49	4(14.3)	3(13.6)	2(8.7)	2(9.1)	0.975
	50-59	8(28.6)	9(40.9)	6(26.1)	8(36.4)	
	60-69	12(42.8)	7(31.8)	10(43.5)	8(36.4)	
	70-79	4(14.3)	3(13.6)	5(21.7)	4(18.1)	
Sex	Male	14(50)	10(45.5)	12(52.2)	12(54.5)	0.941
	Female	14(50)	12(54.5)	11(47.8)	10(45.5)	

The duration of disease among diabetic groups showed no statistically significant difference, also patients with severe NPDR/ NVE had significantly higher levels of HbA1c (9.06% ± 1.5%) in comparison to other groups (table 2).

Table 2: Disease duration and HbA1C according to study groups.

Variables	Control	No DR	Mild/moderate NPDR	Severe NPDR/ NVE	P-value
Duration of disease (years)	-	7.27±5.04	9.96±5.19	11.09±8	0.121
HbA1c	5.27±0.5	6.96±1.08	7.67±1.2	9.06±1.5	<0.001

The peripapillary retinal nerve fiber layer thickness showed no statistically significant differences among study groups (Table 3).

Table 3: Distribution of peripapillary retinal nerve fiber layer thickness according to study groups (eyes number= 179).

Variables	Control	No DR	Mild/ moderate NPDR	Severe NPDR/ NVE	P-value
Number of eyes	56	43	39	41	
PRNFLT µm	113.7±6.83	113.6±8.32	113.5±6.9	117.3±19.3	0.334

Eyes with severe NPDR/ NVE had the lowest peripapillary vascular density (PPVD) in all locations (P<0.001), it was lowest temporally with 46.05% ± 4.1%. The temporal PPVD was the lowest in controls and mild/ moderate NPDR measuring 53.3%±3.74% and 51.3%±4.6% respectively. The nasal PPVD was lowest in diabetic patients with no DR measuring 51.82%±3.93% (table 4).

Table 4: Distribution of peripapillary vascular density (PPVD) according to study groups (eyes' number= 179).

Variables	Control	No DR	Mild/ moderate NPDR	Severe NPDR/ NVE	P-value
Number of Eyes	56	43	39	41	
PPVD-superior %	56.3±4.86	56.08±4	54.67±4.5	50.03±3.9	<0.001
PPVD-inferior %	56.61±5.77	55.19±3.7	52.81±4.2	49.8±4.4	<0.001
PPVD-nasal %	53.37±4.04	51.82±3.93	51.3±4.6	46.22±3.6	<0.001
PPVD-temporal%	53.3±3.74	53.95±3.4	51.55±3	46.05±4.1	<0.001
Average PPVD %	53.89±1.87	53.53±1.66	51.65±2.3	47.07±2.1	<0.001

The superior PPVD was 56.3±4.86 percent in controls, 56.08±4 percent in diabetic patients without DR, 54.67±4.5 percent in mild/ moderate NPDR, and 50.03±3.9 percent in severe NPDR/ NVE, post hoc test revealed that it was significantly lower in the latter group compared to all other groups (figure 1, table 5).

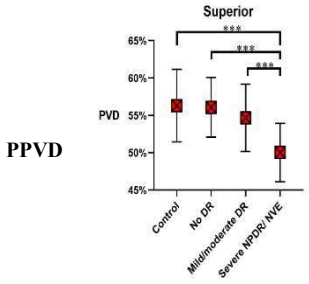

Figure 1: Distribution of superior peripapillary vascular density (PPVD) according to study groups (*P <0.05; ***P <0.001).

The inferior PPVD was 56.61±5.77 percent in controls, 55.19±3.7 percent in diabetic patients without DR, 52.81±4.2 percent in mild/ moderate NPDR, and 49.8±4.4 percent in severe NPDR/ NVE, post hoc test revealed it was significantly lower in the latter group compared to all other groups, also it was lower in eyes with mild/ moderate NPDR compared to controls, (Figure 2, table 4).

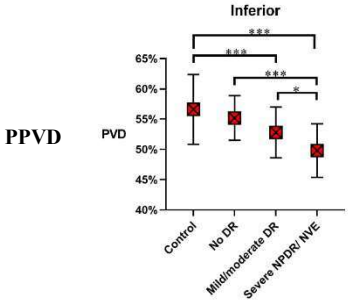

Figure 2: Distribution of inferior peripapillary vascular density (PPVD) according to study groups (*P <0.05; ***P <0.001).

The nasal PPVD was 53.37±4.04 percent in controls, 51.82±3.93 percent in diabetic patients without DR, 51.3±4.6 percent in mild/ moderate NPDR, and 46.22±3.6 percent in severe NPDR/ NVE, post hoc test revealed that it was significantly lower in the latter group compared to all other groups, (Figure 3 and table 4).

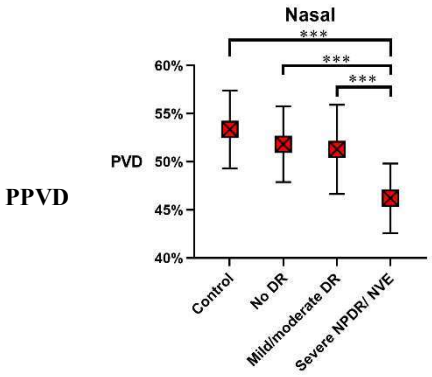

Figure 3: Distribution of nasal peripapillary vascular density (PPVD) according to study groups (*P <0.05; ***P <0.001).

The temporal PPVD was 53.3±3.74 percent in controls, 53.95±3.4 percent in diabetic patients without DR, 51.55±3 percent in mild/ moderate NPDR, and 46.05±4.1percent in severe NPDR/ NVE, post hoc test revealed that it was significantly lower in the latter group compared to all other groups, also it was lower in eyes with mild/ moderate NPDR compared to diabetic patients without DR, (Figure 4 and table 5).

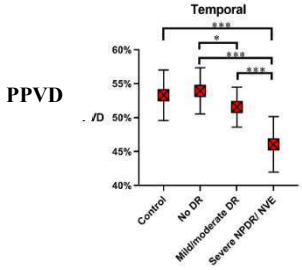

Figure 4: Distribution of temporal peripapillary vascular density (PPVD) according to study groups (*P <0.05; ***P <0.001).

The average PPVD was 53.89±1.87 percent in controls, 53.53±1.66 percent in diabetic patients without DR, 51.65±2.3 percent in mild/ moderate NPDR, and 47.07±2.1 percent in severe NPDR/ NVE, post hoc test revealed that it was significantly lower in the latter group compared to all other groups, also it was lower in eyes with mild/ moderate NPDR compared to controls and diabetic patients without DR, (Figure 5 and table 5).

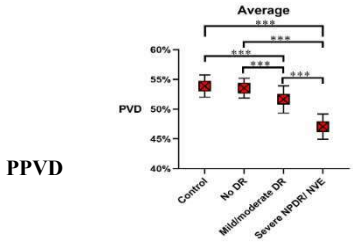

Figure 5: Distribution of average peripapillary vascular density (PPVD) according to study groups (*P <0.05; ***P <0.001).

There were no significant correlations between PRNFL and average PPVD in all study groups, as shown in Table 5.

Table 5: Correlation between RNFL thickness and average PPVD in each study group.

Variables	Control		No DR		Mild/ moderate NPDR		Severe NPDR/ NVE	
RNFL thickness versus average PPVD	r_s	P-value	r_s	P-value	r_s	P-value	r_s	P-value
	-0.134	0.325	0.083	0.599	0.103	0.538	-0.011	0.948

r_s: Spearman's rho

DISCUSSION:

In the current study, peripapillary retinal nerve fiber layer thickness (PRNFLT) showed no statistically significant differences among study groups. This was consistent with results of Liu al., (2019) who reported that PRNFLT showed no significant difference in correlation to DR severity. [10] However, Shin et al., (2019) [11] and Lee et al., (2022) [12] showed statistically significant decrease in PRNFLT. It was noticeable that the aforementioned studies had lower mean PRNFLT than what was seen in this study sample.

Cao et al., (2019) reported that mean RNFLT was significantly less in diabetics with no DR vs. controls, [13] which can be attributed to the small sample size of this study involving 60 eyes of 60 patients.

Muraca et al., (2018) showed a decrease in RNFLT in patient with DR vs. no DR and healthy controls [14], the same goes for Vujosevic et al., (2018), [15] both with different age group than the current study (18 years and above) including patients with type 1 DM.

These studies imply that having diabetes alone might affect the RNFLT via microvascular alterations around the optic nerve head, even before more identifiable structural changes ensue. [11,12,13-15]

In this study, eyes with severe NPDR/ NVE had significantly the lowest PPVD in all locations, while those with mild/ moderate DR had significantly lower average and inferior PPVDs in comparison to controls and lower average and temporal PPVD in comparison to no DR.

There are increasing numbers of studies concerning blood supply to the optic nerve head and peripapillary region. [10-21]

Similar to this study when DR patients were compared to healthy controls, there was a substantial reduction in average peripapillary vascular density, indicating that the peripapillary area may be more vulnerable to diabetic damage. [10-12,15,17,21] It is uncertain if this is due to retinal nerve fiber layer thinning observed in some of these studies leading to decrease in metabolic requirement or solely because of microvascular changes.

Notably, as compared to normal controls, several researchers discovered a substantial reduction in peripapillary vessel volume in diabetics even before clinically visible indications of DR. [11,13,15,20,23] Lui et al. (2019), [10] though, did not notice any differences in the no DR group vs. controls as it is seen in this study.

However, when the bigger blood vessels were omitted from the assessment of peripapillary capillary networks by Rodrigues et al. (2019) there was no association between peripapillary vascular system and DR severity. [20]

In the current study, there was no correlation between RNFL thickness and average PPVD, which is in concordance to results of Lui et al. who reported that there were no significant associations between PPVD and RNFL thickness. [10]

In several other studies, a positive correlation between RNFL thinning and PPVD reduction in diabetic patients vs controls, was found, [11-15,18-20]

In addition to the causes mentioned above, another point to consider is that the differences in these studies are related to the type of OCTA device used to examine PPVD. Shin et al. [11] and Lee et al. [12] used "AngioPlex" mode available in Cirrus devices, Lui et al. used "Angiovue" new built-in software in Optovue device [10] and Ghassemi et al., used more specific "AngioDisc" mode in Optovue device. [21]

Like the current study, Muraca et al., (2018) used Triton OCTA to study PPVD via the "Angio Macula" mode that was made for macular area angiography, which was used for diabetic patients, [14] and by other investigators to study peripapillary PPVD in different subjects in ophthalmology. [22,23]

A limitation of this study is the absence of vessel skeletonization, which can remove the influence of vessel size on retinal perfusion measurements. Another limitation is the need to assess the

reliability of peripapillary retinal nerve fiber layer thickness using multiple OCTA systems, while identifying possible problems with processing and interpretation of OCTA images of optic nerve.

It is noteworthy that research in this area is still ongoing, heightening our understanding, and offering a new direction for further investigation into the relationship between microvascular changes and neurodegeneration in DR.

CONCLUSION:

1. Peripapillary vascular density correlated significantly with DR severity, decreasing with increasing DR severity.
2. There was no obvious correlation observed between RNFL thickness and DR severity.
3. There was no correlation between PPVD and RNFL thickness regardless of DR severity.

Recommendations

1. Vessel density in the peripapillary region, measured by OCTA technology, can be a predictive marker of DR severity in patients, hopefully through studies observing disease progression over time.
2. Further studies investigating the effect and efficiency of the currently available management options, such as the different types of Anti-VEGF injections on preventing and/or halting vascular loss are required to determine the best outcome.

- informed consent has been obtained from the involved patients for the participation in this thesis and their approval was given for the publication of the data.
- The authors have no affiliation with any organization with a direct or indirect conflict of interest in the subject matter discussed in the manuscript.

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