International Journal of Medical Ophthalmology

E-ISSN: 2663-8274
P-ISSN: 2663-8266
www.ophthalmoljournal.com
IJMO 2023; 5(1): 30-37
Received: 25-11-2022
Accepted: 30-12-2022

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Evaluation of peripapillary area and retinal nerve fiber layer thickness using OCT angiography in diabetic retinopathy

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DOI: https://doi.org/10.33545/26638266.2023.v5.i1a.137

Abstract
Background: It has been believed that diabetic retinopathy (DR) is a microvascular disorder. Recent research has linked DR to both neuronal and microvascular processes. The purpose of this research was to use optical coherence tomography angiography (OCTA) to compare the thickness of the peripapillary area and the retinal nerve fiber layer (pRNFL) in DR different stages.
Methods: This cross-sectional controlled research was carried out on 40 subjects Cases were subdivided into four equal groups: diabetes mellitus (DM) group (having no DR) non-proliferative DR (NPDR) group, proliferative DR (PDR) group, controls: healthy persons (Healthy eyes with no evidence of diseases affecting macula or optic nerve. Duration of diabetics was not less than 5 years with controlled HbA1c level (5-6%).
Results: Significant difference was observed regarding disease duration, Vessel density (VD) between the NPDR, PDR and controls, Thickness of the PRNFL (overall or segmental) between the Diabetes mellitus (DM) groups (DM-NPDR-PDR) and controls. A significant decrease in VD and Thickness of the PRNFL was observed in the optic disc and pRNFL among the DM groups compared to controls. Insignificant difference was observed regarding age, sex, side. A significant negative correlation was observed between disease severity and VD in the pRNFL.
Conclusions: As DR worsened, the number of radial peripapillary capillaries in the peripapillary area of the retina dropped. Cases with DM, NPDR, and PDR had thinner PRNFL in the peripapillary area compared to those in the controls.

Keywords: Peripapillary area, retinal nerve fiber layer thickness, OCT angiography, diabetic retinopathy

Introduction
It has been hypothesized that diabetic retinopathy (DR) is a microvascular disorder. Recently, variables related to both nerves and the blood vessels have been linked to DR [1]. Retinal neurodegeneration, involving death of retinal neuronal cells and weakening of the peripapillary retinal nerve fiber layer (pRNFL), has also been revealed to play a key part in the etiology of DR. The pRNFL is the inner neural layer of the retina and is made up of axons from retinal neural axons [2]. It has been demonstrated that radial peripapillary capillaries (RPCs) are likely to partially supply the nutrient requirements of the pRNFL [3].
Histological and clinical evidence indicates a significant function for RPCs in the pRNFL area [4]. The distribution of RPCs is consistent with the nerve fiber abnormalities seen in several clinical conditions, including the Bjerrum scotoma, cotton wool spot, intraretinal bleeds, and ischemic optic neuropathy [5].
Clinical understanding of DR neurodegeneration can be enhanced by analyzing alterations in the PRNFL and RPCs at various time points. RPC microcirculation in diabetic cases is an important topic, but there is a lack of quantitative data.
Measurements of RPC vessel density (VD) and Thickness of the PRNFL using optical coherence tomography angiography (OCTA), a relatively new noninvasive imaging technology, have been shown to be consistent and reliable [6]. The present research used optical coherence tomography angiography (OCTA) to quantitatively assess the changes in VD of RPCs and p Thickness of the PRNFL in the optic nerve head of DR cases over stages, and to determine whether or not these variables were correlated with DR severity.

Patients and Methods

This cross sectional, observational, selective, controlled research was carried out on 40 subjects at the department of ophthalmology, Tanta University Hospitals, Egypt starting from 1st of January 2021 to 31st December of 2021. The research was done after approval from the Ethical Committee Tanta University Hospitals. An informed written consent was obtained from the cases.

Fundus examination was not performed on eyes with opaque media and cases with poor quality OCTA, high error of refraction (>6 diobter, glaucoma, uveitis, other retinal diseases, ocular trauma, previous intraocular surgeries, laser, intravitreal injection, proliferative diabetic retinopathy cases with significant neovascularization of optic disc.

Cases were further subdivided into 4 equal groups: diabetes mellitus (DM) group (having no DR) non-proliferative DR (NPDR) group, proliferative DR (PDR) group, controls: healthy persons (Healthy eyes with no evidence of diseases affecting macula or optic nerve. Duration of diabetics was not less than 5 years with controlled HbA1c level (5-6%).

All cases were subjected to: history taking, comprehensive ophthalmic examination.

Fundus examination

By slit lamp Biomicroscopy using+78 non-contact Volk lens and indirect ophthalmoscope using +20 condensing lens. Dilatation of the pupils for all cases was done using tropicamide 1% eye drops (Mydriacyl 1%, by Alcon pharmaceuticals) to facilitate imaging. Eyes with diabetic retinopathy were graded according to criteria of Early Treatment Diabetic Retinopathy research classification (ETDRS) [6].

Investigational studies

Color Fundus Photography, The traditional fundus camera (Zeiss FF, Carl Zeiss Meditec, Dublin, CA, USA) had a magnification of 2.5 and a field of vision of 30 degrees. Different stages of DR, from minimal retinopathy to significant vitreous hemorrhage, were identified and labeled.

Fluorescein angiography

The procedure was done on diabetic cases for staging of diabetic cases according to ETDRS classification (72) into, diabetic without retinopathy, non-proliferative or proliferative diabetic retinopathy. Dilatation of the pupils for all cases was done to facilitate imaging. FA was done using intravenous injection of sodium fluorescein dye 10%.

The OCT and OCTA imaging

OCT and OCT-A were obtained using the DRI OCT Triton device (Topcon Corporation, Tokyo, Japan). Its swept source OCT (SS-OCT) uses long wavelength (1050 nm) with band width of 100 nm which allows better penetration into tissue with imaging through optical opacities and is invisible to the subject [7].

Conventional OCT imaging

The DRI Triton SS-OCT instrument (Topcon, Tokyo, Japan) was used to acquire structural measurements of the retina. This instrument is a multi-modal swept source OCT with a non-mydriatic color fundus camera, and it operates at a wavelength of 1,050 nm, with a scanning speed of 100,000 A-scans per second and an axial resolution of 8 m and a transverse resolution of 20 m in tissue. Retinal nerve fiber layer (RNFL) thickness is measured separately from the inner limiting membrane (ILM) and the ganglion cell layer boundaries thanks to this scan. Peripapillary Thickness of the RNFL were determined in four sectors (superior, nasal, inferior, and temporal quadrants) by OCT [8].

OCT-A imaging

Imaging the disc was done using DRI_OCT Triton swept source OCT(SS_OCT&OCTA) (Topcon corp Japan) OCTA was scanned using (4.5 X 4.5) mm centered on the disc using an active eye tracker to reduce motion and blinking artifacts.

The OCTA scans of optic disc were manually segmented into 4 face slabs: Epsipapillary slap, from the top to internal limiting membrane to detect neo vessels. The superficial papillary slap, from below the internal limiting membrane to the outer border of the inner plexiform layer. The deep papillary slap: from the outer border of the inner plexiform layer to the Bruch's membrane (BM). The choriocapillary slap: from Bruch's membrane (BM) to 60 μm below it.

Slaps (1, 2) represent retinal flow. Slaps (3,4) represent ciliary flow [9].

Color coded VD map images were taken that gave qualitative data in which the more flow the more the hot colors and vice versa. Vascular density (VD) is the fraction of the disc's segmented area (4.5x4.5 mm squares) that is taken up by blood vessels. Image J computer program thresholding parameters and particle analysis were then used to quantify the result (National Institutes of Health Image J 1.48v; Bethesda, Maryland, USA) [9].

Statistical analysis

Microsoft Excel was used for data entry and analysis. The information was then analyzed using SPSS 20.0, the Statistical Package for the Social Sciences. The significance of differences was tested using either the Pearson or the Spearman correlation coefficient, depending on whether the data was represented as numbers and percentages or as a continuous group's mean and standard deviation. The cutoff chosen to denote statistical significance was < 0.05.

Results

There were no significant differences between groups regarding to age, sex, and side. Table 1

Table 1: Case Characteristics (N = 40)

		Control n= (10)	DM n= (10)	NPDR n= (10)	PDR n= (10)	P value
No. Eyes		10	10	10	10	
Age (years)		56.4±5.6	54.5±6.7	52±7.8	53.2±7.1	.195*
Sex	Male	7 (70%)	6 (60%)	7 (70%)	5 (50%)	.759**
	Female	3 (30%)	4 (40%)	3 (30%)	5 (50%)	
Side	Right	7 (70%)	6 (60%)	5 (50%)	6 (60%)	.841**
	Left	3 (30%)	4 (40%)	5 (50%)	4 (40%)	
DM Duration (years)			7.3 ± 1.1	10.7 ± 0.8	13 ± 0.7	.000*

Data are presented as mean ± SD or frequency (%) * One way ANOVA; ** Chi-square test.

Significant negative correlation was observed between disease severity and Best Corrected

Visual Acuity (BCVA), more severe cases were associated with decreased BCVA using the Spearman correlation coefficient analysis. (r = -0.927, P =.000) Figure 1

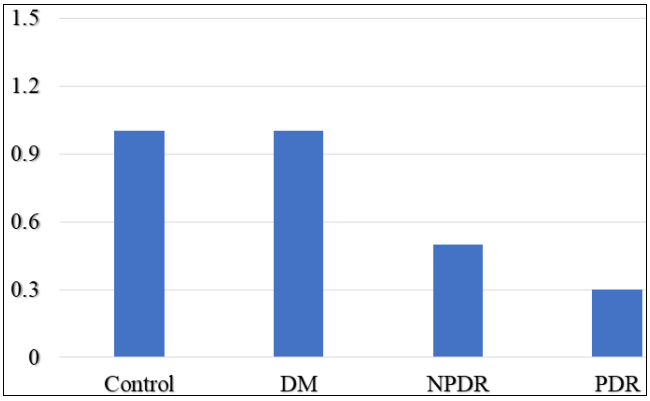

Fig 1: BCVA

A significant difference in VD was observed in the optic disc and peripapillary area, the Thickness of the PRNFL among the DM groups (DM-NPDR-PDR) compared to controls, and in the overall or segmental (inferior, superior, nasal, and temporal quadrants) Thickness of the PRNFL was observed between the DM, NPDR, and DPR groups.

Table 2: VD of Superficial plexus of papillary & peripapillary Area and Retinal Nerve Fiber Layer Thickness of Peripapillary Area:

	Control n= (10)	DM n= (10)	NPDR n= (10)	PDR n= (10)	P value*
VD (%)	53.2±1.1	52.1±1.2	51.1±1.3	49.9±1.4	<0.001*
Thickness of the RNFL (µm)	116.5±6.1	105.6±2.5	104.9±2.5	103.3±3.2	<0.001*
Inferior Quadrant	129.5±4.9	113.6±10	112±7.2	111±9.4	<0.001*
Superior Quadrant	120±6.1	108±5.8	107.8±6.3	106.8±6.5	<0.001*
Nasal	70±6.5	50.6±8	48±9.8	45±9.7	<0.001*
Temporal	57.8±5	51.6±7.6	48.2±7.5	43.9±7.4	<0.001*

Data are presented as mean ± SD or frequency (%) * One-way ANOVA

Case presentation

Female case 50 yrs old, no history for any systemic nor ocular disease No past history for medication no surgery and BCVA is 1.0. Figure 2

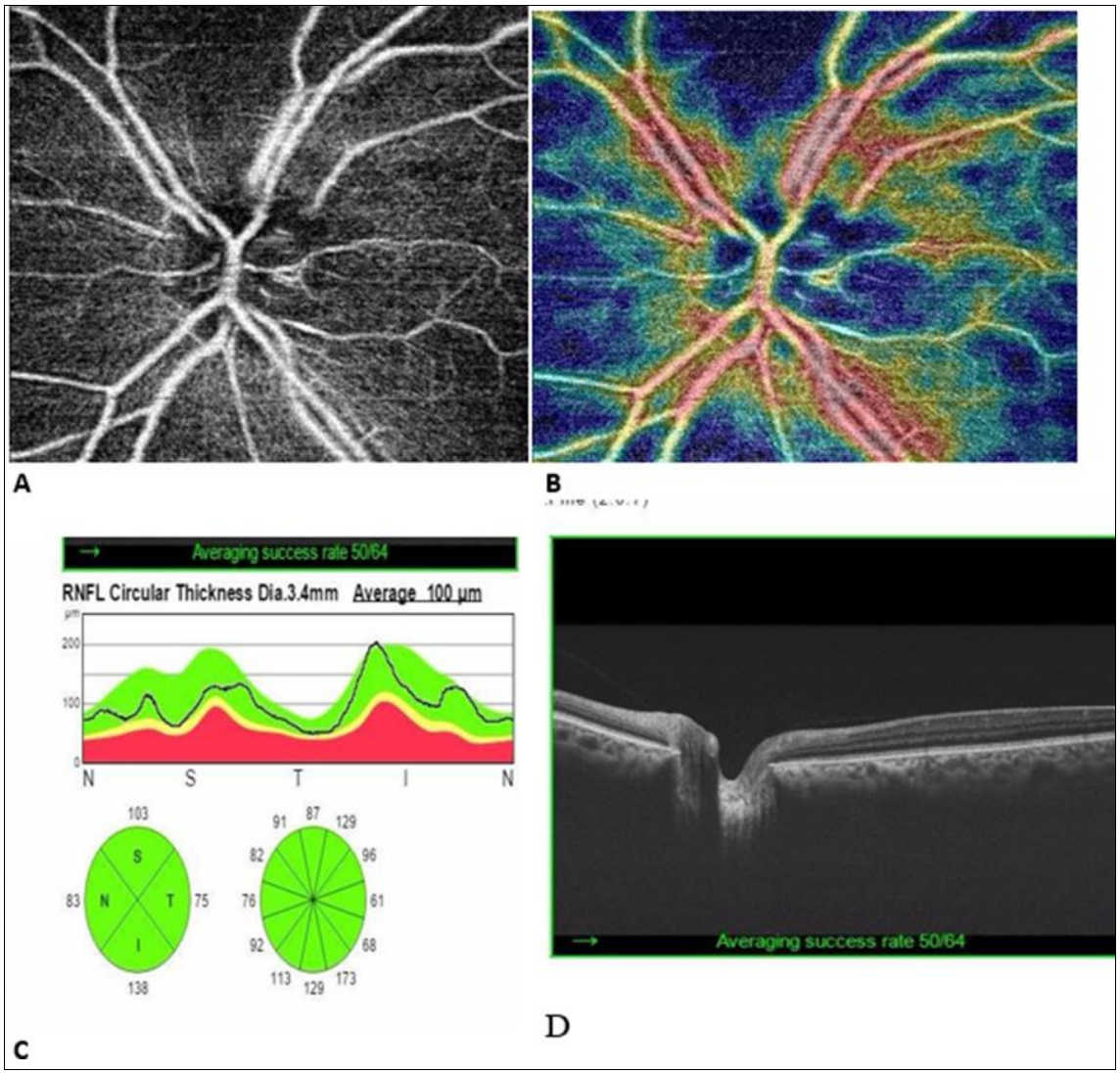

Fig 2: A: Superficial peripapillary plexus (SPP) B: spp color coded VD map with VD 55%. C, D: Retinal nerve fiber layer thickness of normal eye Thickness of the RNFL is within the accepted normal range

Cases without diabetic retinopathy showed decreased VD of the disc and peri papillary area and Thickness of the RNFL compared to normal subjects. Figure 3

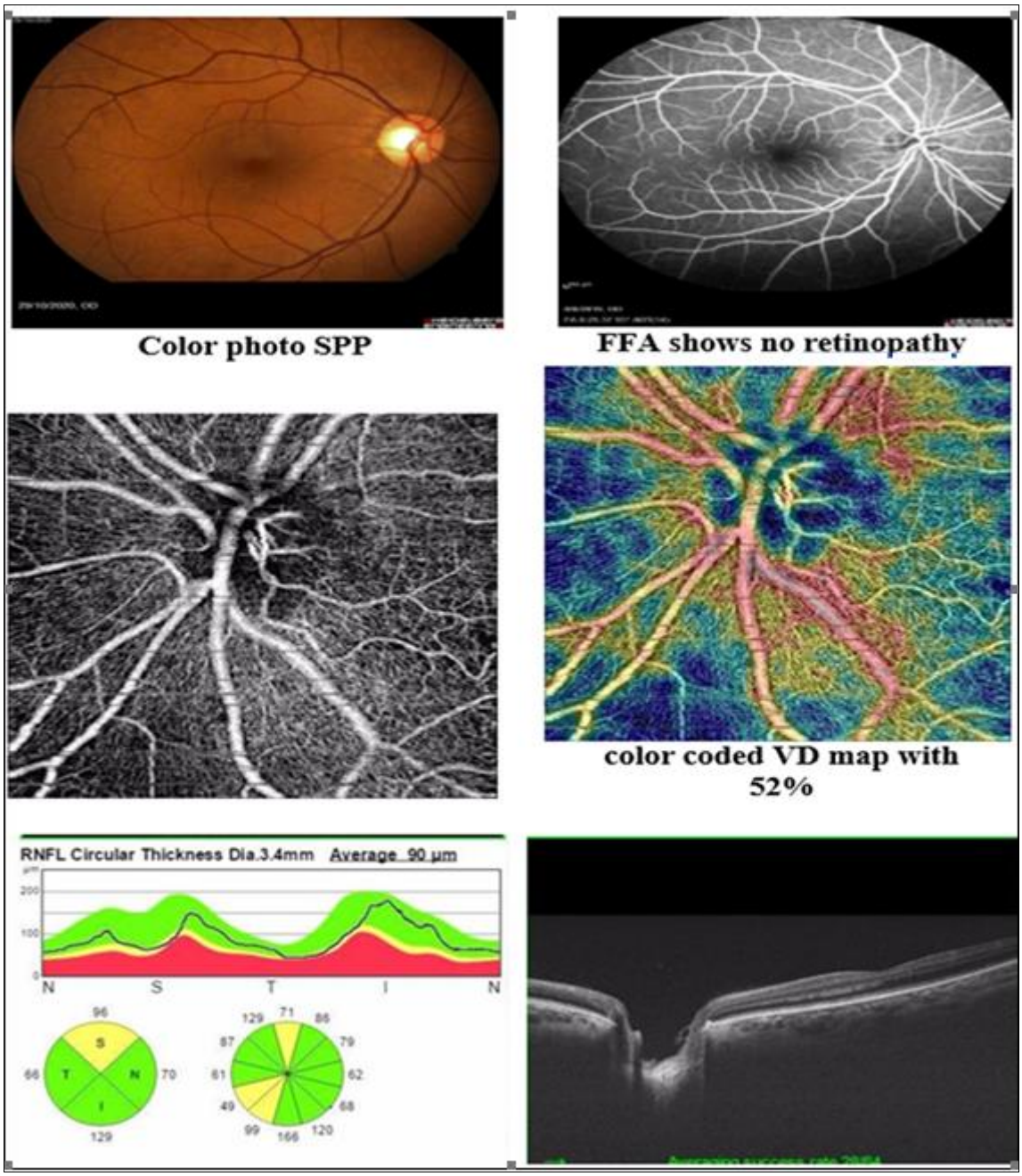

Fig 3: Retinal nerve fiber layer thickness of right eye It shows border – line thinning of upper area

Cases with Non proliferative diabetic retinopathy showed micro aneurysms in FFA and decreased VD% disc and peri papillary area and Thickness of the PRNFL compared to normal subjects. Figure 4

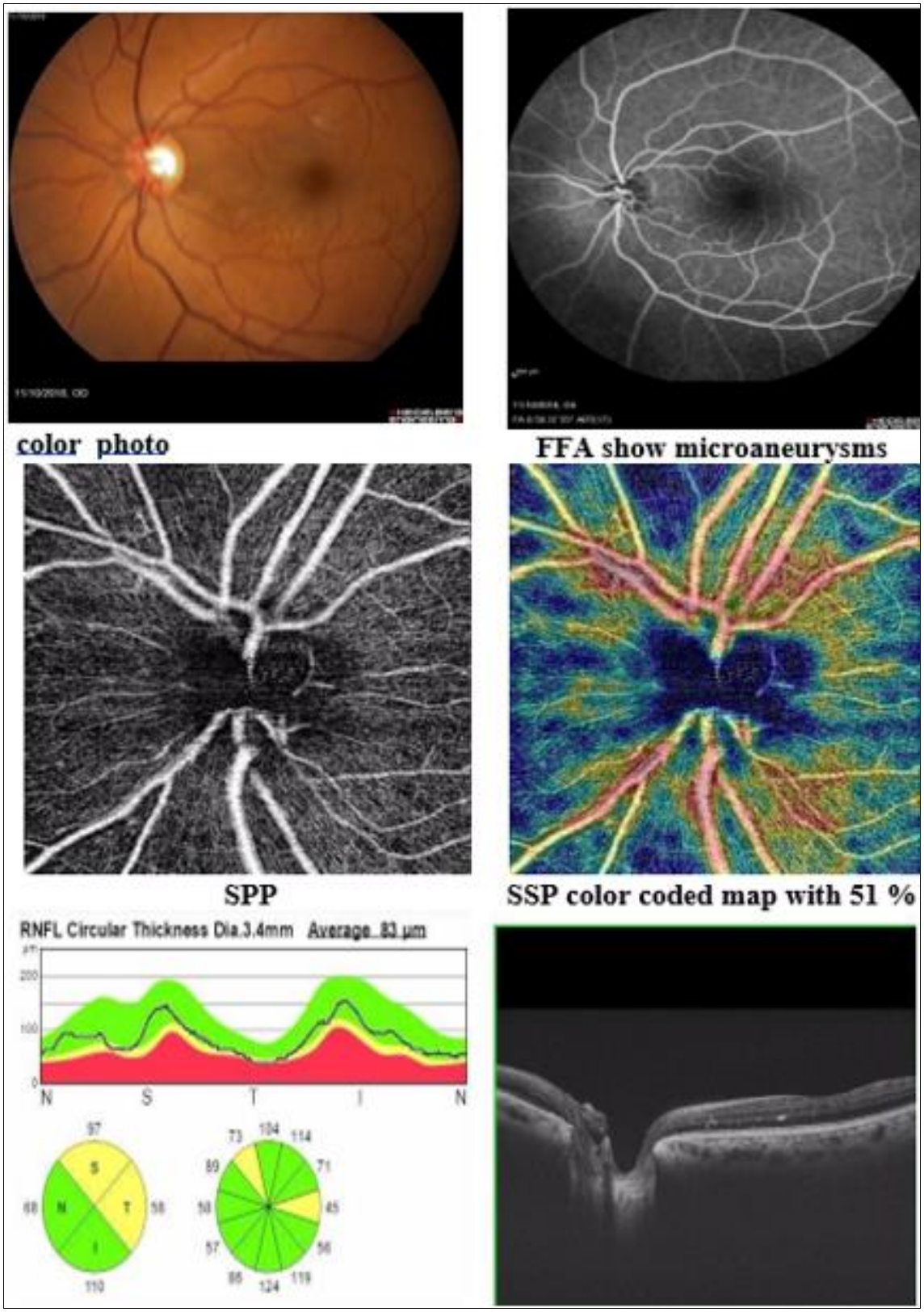

Fig 4: Retinal nerve fiber layer thickness of left eye It shows border – line thinning of upper nasal & temporal areas

Case with proliferative diabetic retinopathy showed tiny leakage dot in FFA and decreased VD% disc and peri papillary area and Thickness of the PRNFL compared to normal subject.

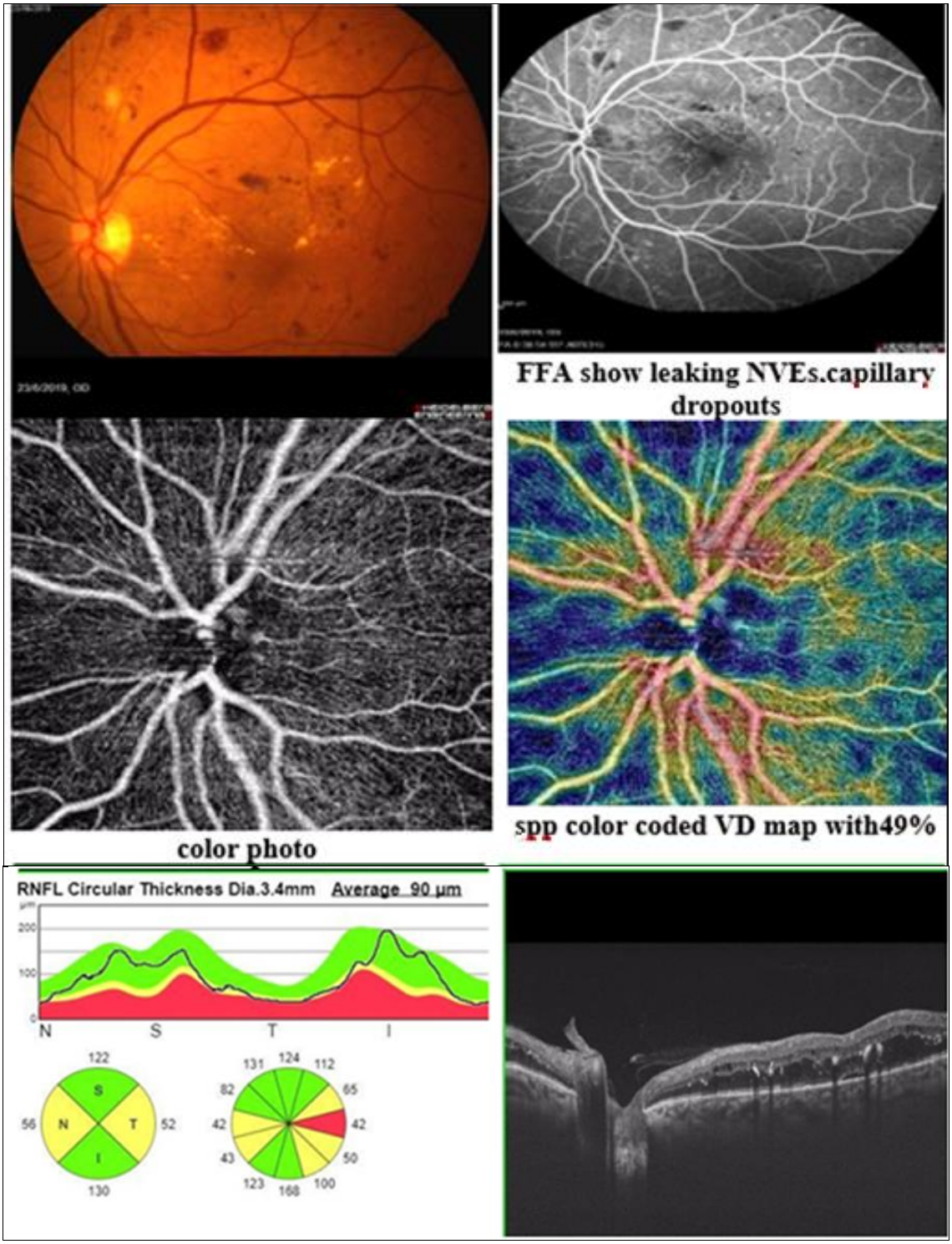

Fig 5: Retinal nerve fiber layer thickness of left eye It shows border – line thinning of nasal & temporal quadrant & significant difference of the temporal quadrant

Discussion

One of the world's most pressing public health issues is diabetic retinopathy (DR) due to its major contribution to blindness [10]. The pathophysiology of DR has been reported to be significantly influenced by retinal neurodegeneration, which includes death of retinal neuronal cells and weakening of PRNFL [11]. The RPCs are a special capillary plexus located deep within the pRNFL. The pRNFL is particularly susceptible to ischemia injury due to the enormous energy demands of the unmyelinated axons situated there [5].

A recent noninvasive imaging technique, OCTA, shows repeatability and reproducibility in vascular density (VD) measurements of RPCs and thickness measurements of the PRNFL [11].

Our results were supported by a research of Liu *et al*. [10] as they reported, there was no significant difference observed between groups in terms of age, sex, side and also was observed between groups regarding disease duration and in the VD was observed between the controls and the no DR. Also showed a representative sample of VD in the peripapillary area with increasing DR severity. A significant decrease in VD was observed in the peripapillary area among the four groups ($p< 0.001$) also observed in the DRs versus the controls and with the no DR also observed in the severe DR versus the mild DR and in the thickness of the

PRNFL were observed in the no DR versus the controls ($p< 0.05$). Significant associations ($p< 0.001$) were observed between DR severity and VD in the peripapillary area. In addition, when post hoc multiple comparisons were made, they demonstrated a significant increase in thickness of the PRNFL along the periphery as DR severity increased. The thickness of the PRNFL in the peripapillary area did not vary significantly ($p>0.05$) across the four groups. No significant relationship between DR severity and Thickness of the PRNFL in the peripapillary area was discovered ($p> 0.05$). There was no significant difference ($p> 0.05$) in peripapillary Thickness of the PRNFL among the no-DR, mild-DR, or severe-DRs using the student's t-test.

The structural changes in the retina at the optic papilla, such as intracellular and extracellular edema, hemorrhage, exudation, or glial fibrillary degeneration, may account for the lack of a significant difference in Thickness of the PRNFL between the no DR, mild DR, and severe DRs observed here. In addition, OCTA has been widely employed in the past to examine Thickness of the PRNFL variations in the first stages of DR. In individuals with severe DR, measuring Thickness of the PRNFL may be a significant clinical problem. Consistent with prior research, we observed that the Thickness of the PRNFL was significantly lower in the no DR compared to the controls [12].

Also, in the research Samara *et al*. [13] data on Diabetic cases, there was no significant difference in age, and eye condition between DR cases with progression and DR cases without progression. a significant correlation between BCVA (Decimal) and degree of Diabetic retinopathy. Similar to our results, Vujosevic *et al*. [14] observed a significant decrease in VD of RPC in the peripapillary area in cases with DR,

Also, Lim *et al*. [15] cases with DM but no DR showed a decrease in RPC VD in the peripapillary area. Totaling 164 eyes, the research included 63 controls, 101 cases with type 2 diabetes (49 cases without DR [non-DR], and 52 cases with mild to moderate non proliferative DR [NPDR]), and 63 eyes from cases with T2DM who had lost pRNFL. The mean and sector Thickness of the pRNFL of the periphery were measured annually for three years as the participants were followed. Using a linear mixed model, we compared the three groups with regards to their expressed mean rate of pRNFL loss.

Furthermore, Li and Wang [16] revealed alterations in the microcirculation of the optic disc in preclinical DR, with a decrease in VD in the peripapillary area and inside the optic disc. In addition, the Thickness of the PRNFL surrounding the temporal disc was reported to be lower in the preclinical group compared to the controls ($t = - 2.20$). The preclinical group had a substantially reduced VD compared to the controls in the superior and temporal sectors of the peripapillary area ($t = - 2.27$ and $t = - 2.15$). The average Thickness of the PRNFL in the preclinical DR was favorably linked with the density of the vessels in the periphery ($r = 0.344$). Upper disc Thickness of the PRNFL was positively correlated with blood flow density ($r = 0.612$) and temporal disc Thickness of the PRNFL was positively correlated with blood flow density ($r = 0.468$).

Vascular abnormalities and micro-vasculopathy are known risk factors for the severe manifestations of DR. However, because of its link to vascular dysfunction, retinal degeneration may be a decisive determinant for DR severity. OCTA is a noninvasive imaging method that can assess the thickness of each layer of the retina. Therefore, OCTA can be a helpful diagnostic tool for determining neurodegeneration role in the pathophysiology of DR. [17].

There is mounting proof that retinal neurodegeneration is central to the development of DR. Diabetic cases, with or without mild DR, have thinner PRNFLs compared to controls in cross-sectional OCTA studies [13]. Also, Chen *et al*. [18] observed that Preclinical DR cases had a much thinner pRNFL than controls. There has to be more focus on neurodegenerative alterations in preclinical DR. There were 668 diabetes cases and 556 controls chosen from 13 case-control studies. Studies using OCTA showed that pThickness of the PRNFL was considerably lower in individuals with preclinical DR compared to controls. Reduction of Thickness of the PRNFL was significant in the superior quadrant, the inferior quadrant, the nasal quadrant, but was not significant in the temporal quadrant in diabetic cases [19].

Neurodegeneration caused by hyperglycemia, seen as the degeneration of retinal ganglion cells, may occur before vascular abnormalities become visible to the observer during clinical testing. Optical coherence tomography (OCT) is a painless method of measuring the depth of structures like the retina and choroid. Swept-source OCT has made it possible to automatically and accurately measure the thickness of the pRNFL [20].

Limitations: a cross-sectional research that makes it hard to determine the causative relation between Peripapillary microcirculation changes and neurodegenerative alterations. The low number of cases used in each group of the research makes the results possible to change when conducted on larger number of cases

Conclusions

RPC VD in the peripapillary area decreased with increasing DR severity, whereas PRNFL VD increased. Diabetics, people with or without DR all had thinner peripapillary areas than controls. Changes in Thickness of the PRNFL were observed to correlate with DR severity, suggesting that close observation of RPC VD in the peripapillary area could indicate PRNFL changes in the early phases of clinical DR.

Financial support and sponsorship: Nil

Conflict of Interest: Nil

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How to Cite This Article
Elgamal AA, Toukhy ELHM, Komy ELHAE, Atef ELDMS. Evaluation of peripapillary area and retinal nerve fiber layer thickness using OCT angiography in diabetic retinopathy. International Journal of Medical Ophthalmology. 2023;5(1):30-37.