International Journal of Retina (*IJRETINA*) 2021, Volume 4, Number 2.
P-ISSN. 2614-8684, E-ISSN.2614-8536

IJRETINA
International Journal of Retina

RELATIONSHIP BETWEEN PERIPAPILLARY RETINAL PERFUSION AND PERIPAPILLARY RETINAL NERVE FIBER LAYER THICKNESS IN DIABETES MELLITUS PATIENTS WITHOUT DIABETIC RETINOPATHY

Sindi Dwijayanti[1], Irawati Irfani[2], Susanti Natalya Sirait[3], Elsa Gustianty[4], Erwin Iskandar[5], R. Angga Kartiwa[6]

[1] *Cicendo National Eye Hospital, Bandung, Indonesia*
[2] *Pediatric Ophthalmology and Strabismus Division, Cicendo National Eye Hospital, Bandung, Indonesia*
[3] *Refraction, low vision, and contact lens Division, Cicendo National Eye Hospital, Bandung, Indonesia*
[4] *Glaucoma Division, Cicendo National Eye Hospital, Bandung, Indonesia*
[5] *Vitreoretina Division, Cicendo National Eye Hospital, Bandung, Indonesia*
[6] *Reconstruction, Oculoplasty, and Oncology Division, Cicendo National Eye Hospital, Bandung, Indonesia*

Abstract

Introduction: *Impaired blood flow is an early sign of retinal dysfunction in diabetes mellitus (DM). Microvascular abnormalities of the radial peripapillary capillaries, which nourished the Retinal Nerve Fiber Layer (RNFL), can affect the RNFL or ganglion cell function.*

Methods: *This analytic cross-sectional study was conducted on 41 people (79 eyes) divided into two groups, group A (healthy subjects) 19 people (37 eyes) and group B (DM type 2 without diabetic retinopathy) 22 people (42 eyes). Peripapillary retinal perfusion was assesed using Optical Coherence Tomography (OCT) Angiography and RNFL thickness was assesed using OCT. Pearson or Spearman correlation statistics test were used to analyze the result. P value ≤0.05 was considered significant.*

Result: *There was a decrease in peripapillary retinal perfusion density in the inferior quadrant (P = 0.003) and flux index throughout the peripapillary retinal quadrant (P = 0.0001), but an increase in RNFL thickness in the peripapillary temporal quadrant (P = 0.012) compared to control grup. Positive correlation was found between peripapillary retinal perfusion density and RNFL thickness globally (r = 0.480, P = 0.001), superior quadrant (r = 0.436, P = 0.004), and inferior quadrant (r = 0.608, P = 0.000). A positive correlation was also found between the peripapillary flux and RNFL thickness globally (r = 0.517, P = 0.000), superior quadrant (r = 0.630, P = 0.000), and inferior quadrant (r = 0.519, P = 0.000).*

Conclusion: *There was a relationship between peripapillary retinal perfusion and RNFL thickness in DM patients without diabetic retinopathy.*

Keywords: Diabetes, Peripapillary perfusion, RNFL thickness.
Cite This Article: DWIJAYANTI, Sindi et al. Relationship of Peripapillary Retinal Perfusion with Peripapillary Retinal Nerve Fiber Layer Thickness in Diabetes Mellitus Patients without Diabetic Retinopathy. International Journal of Retina, [S.l.], v. 4, n. 2, p. 119, sep. 2021. ISSN 2614-8536. Available at: <https://www.ijretina.com/index.php/ijretina/article/view/161>.doi: https://doi.org/10.35479/ijretina.2021.vol004.iss002.161.

Correspondence to:
Sindi Dwijayanti,
Cicendo National Eye Hospital,
Bandung, Indonesia,
sindi.dwijayanti@gmail.com

INTRODUCTION

World Health Organization (WHO) stated that in 2020, there were 8.4 million people suffering from diabetes mellitus (DM) in Indonesia. This number is estimated to increase to 21.3 million by 2030. Global meta-analysis studies from the United States, Australia, Europe, and Asia, reported that-diabetic retinopathy (DR) affects 1 out of 3 patients with DM, and 1 in 10 (10.2%) patients have vision threathening diabetic retinopathy such as, proliferative diabetic retinopathy (PDR) or diabetic macular edema (DME).

In people aged 40 years and over, DR affects 4.2 million people (28.5%) in the United States, and 93 million people (34.6%) worldwide. In areas with low-moderate resources and lack of health care systems, DR patients will be diagnosed only after symptoms appeared or after complications have occurred.[1-4]

Dysfunction of the retinal blood vessels autoregulation occur early in diabetes, resulting in insufficient nutrients and oxygen delivery to the retina. The Retinal Nerve Fiber Layer (RNFL) acquires some of its nutrients from radial peripapillary capillaries originating from the peripapillary branches of the adjacent retinal arteries. Microvascular dysfunction at this area can affect RNFL or ganglion cell function. Optical Coherence Tomography Angiography (OCTA) is a non-invasive technique that can be used to map ocular capillary blood circulation, while Optical Coherence Tomography (OCT) can detect loss of retinal nerve tissue by quantitatively measuring RNFL thickness. This study was performed to see the relationsip between peripapillary retinal perfusion and peripapillary RNFL thickness in DM without DR patients. [3,5,6–12]

SUBJECTS AND METHOD

This study is an analytic cross-sectional study conducted in February-April 2019 at the Primary Health Centre around Bandung City and the Cicendo Eye Hospital, Bandung. The study protocol was approved by Health Research Ethics Committee of Padjadjaran University, Bandung. Inclusion criteria are type 2 DM without DR patients aged 40 to 75 years and healthy subjects without DM with matched characteristics. Exclusion criteria are history of ocular trauma, ocular surgery, optic nerve abnormalities and ocular abnormalities or diseases that can affect ocular perfusion such as, optic neuropathy, optic nerve atrophy, glaucoma, venous or retinal artery occlusion, ≥-6D refraction, and OCT/OCTA result with signal strength ≤ 5/10. Diabetes Mellitus was diagnosed based on American Diabetes Association criteria, which are classic symptoms diabetes (polyuria, polydipsia, and weight loss) with random glucose ≥ 200 mg/dl, or fasting glucose ≥ 126mg/dl, or two-hour postprandial glucose ≥ 200mg/dl.

Subjects were divided into two groups, group A (healthy subjects without DM with matching characteristics) and group B (type 2 DM without DR patients). Healthy subjects were screened for DM, and DM patients were screened for DR. Subjects that meets the criteria were sent to Cicendo Eye Hospital for further examination. Each patient underwent a complete ophthalmology examination including history taking, visual acuity examination, intraocular pressure, anterior segment examination using slit lamp biomicroscope and posterior segment examination using indirect funduscopy. The RNFL thickness was measured using a High-Definition OCT (carl zeiss CIRRUS HD OCT) 200x200 optical disc cube. Peripapillary retinal perfusion was measured using AngioPlex software (carl zeiss CIRRUS OCT Angiography) ONH Angiography 4.5 x 4.5 mm. The analyzed blood vessels were radial peripapillary capillaries presented by two parameters, capillary perfusion density and flux index. Capillary perfusion density was defined as the percentage of area that have perfused blood vessels, and flux index was defined as capillary perfusion, weighted by the brightness (intensity) of the flow signal.

Data analysis was performed using T test, Mann-Whitney test, and Chi-Square test for significance, and for the correlation test using Pearson and Spearman test. The strength of correlation (r) was defined based on Guillford criteria, 0.0 - <0.2 = very weak; 0.2 - <0.4 = weak; 0.4 - <0.7 = moderate; 0.7 - <0.9 = strong; 0.9 -1.0 = very strong. Positive correlation means that as one variable increases, the other variable also increases. Negative correlation means that as one variable decreases, the other variable also decreases. P value ≤0.05 means statistically

significant. Data was processed using SPSS version 24.0.

RESULTS

Seventy nine eyes of 41 people from 18 Primary Health Centre around Bandung city and Cicendo Eye Hospital, Bandung, were enrolled in this study and divided into two groups, group A (healthy people with matched characteristics) 19 people (37 eyes), and group B (type 2 DM without DR) 22 people (42 eyes). The subject characteristics are presented in table 1. There were no significant differences in the subject characteristics between group A and group B ($p>0.05$).

Table 1. **Characteristic of subject**

Variable	Group		p value
	A (control) N=19	B (DM) N=22	
Age			0.39˟
Mean±Std	51.32±5.52	52.77±5.14	
Sex			0.32^
Men	7 (36.8%)	5 (22.7%)	
Women	12 (63.2%)	17 (77.3%)	
Systolic blood pressure (mmHg)			0.09*
Mean±Std	121.58±10.14	125.68±9.55	
Diastolic blood pressure (mmHg)			0.60*
Mean±Std	79.47±6.21	80.45±5.75	
Duration of DM (year)			-
Mean±Std	-	4.56±3.26	
HbA1C (%)			-
Mean±Std	-	8.83±1.75	
IOP (mmHg)	**N=37**	**N=42**	0.31˟
Mean±Std	15.54±2.78	16.26±2.66	

˟unpaired T test,*Mann Whitney test, ^Chi Square test. P<0.05 is statistically significant.

Table 2 presents the comparison of peripapillary retinal capillary perfusion density. There were no significant differences in superior, nasal, temporal quadrant, and global perfusion density ($p>0.05$), but there was a significant difference in the inferior quadrant ($p<0.05$).

Table 2. **Comparison of peripapillary retinal perfusion density**

Perfusion density (%)	Group		P value
	A (control) N=37	B (DM) N=42	
Superior quadrant			0.20*
Median	43.10	42.80	
Range (min-max)	39.10-47.70	29.80-51.10	
Nasal quadrant			0.65˟
Mean±Std	42.44±1.91	42.18±3.00	
Inferior quadrant			**0.00***
Median	44.30	43.05	
Range (min-max)	41.30-48.50	31.00-52.60	
Temporal quadrant			0.51˟
Mean±Std	46.65±1.81	46.34±2.30	
Global perfusion			0.23*
Median	44.30	44.10	
Range (min-max)	42.00-46.70	36.30-48.20	

˟unpaired T test,*Mann Whitney test. P<0.05 is statistically significant.

Table 3 presents the comparison of the peripapillary retinal flux index. There were significant differences in all quadrants and global flux between the two study groups ($p<0.05$).

Table 3. **Comparison of peripapillary retinal flux index**

Flux (0-1)	Group		P value
	A (control) N=37	B (DM) N=42	
Superior quadrant			**0.00**˟
Mean±Std	0.41±0.02	0.38±0.03	
Nasal quadrant			**0.00**˟
Mean±Std	0.40±0.03	0.37±0.04	
Inferior quadrant			**0.00**˟
Mean±Std	0.42±0.02	0.39±0.03	
Temporal quadrant			**0.00***
Median	0.45	0.39	
Range (min-max)	0.37-0.48	0.31-0.49	
Global Flux			**0.00***
Median	0.43	0.38	
Range (min-max)	0.37-0.45	0.32-0.46	

˟unpaired T test,*Mann Whitney test. P<0.05 is statistically significant.

Table 4 presents the comparison of peripapillary RNFL thickness. There were no significant differences in superior, nasal, inferior quadrant, and global RNFL thickness ($p>0.05$), but there was a significant difference in the temporal quadrant ($p<0.05$).

Table 4. **Comparison of peripapillary RNFL thickness**

RNFL thickness (µm)	Group		P value
	A (control) N=37	B (DM) N=42	
Superior quadrant			0.61*
Median	123.00	127.00	
Range (min-max)	91.00-153.00	53.00-165.00	
Nasal quadrant			0.92˟
Mean±Std	72.08±10.78	71.86±9.45	
Inferior quadrant			0.24*
Median	130.00	127.00	
Range (min-max)	103.00-161.00	59.00-165.00	
Temporal quadrant			**0.01**˟
Mean±Std	67.41±5.83	72.26±10.41	
Global RNFL			0.48*
Median	98.00	100.00	
Range (min-max)	81.00-118.00	58.00-128.00	

˟unpaired T test,*Mann Whitney test. P<0.05 is statistically significant.

Table 5 presents the correlations of peripapillary retinal capillary perfusion density and peripapillary RNFL thickness in DM without DR. There was a significant positive moderate correlation (≥0.40 - <0.70) in the superior, inferior quadrant, and global ($p<0.05$). Figure 1 illustrates the correlation of capillary perfusion density with RNFL thickness.

Table 5. **Corelation of peripapillary retinal perfusion density with peripapillary RNFL thickness in DM without DR**

Variable	Corelation	R	P value
Superior quadrant	*Spearman*	**0.44**	**0.00**
Nasal quadrant	*Pearson*	0.24	0.12
Inferior quadrant	*Spearman*	**0.61**	**0.00**
Temporal quadrant	*Pearson*	0.17	0.28
Global	*Spearman*	**0.48**	**0.00**

*P<0.05 is statistically significant.

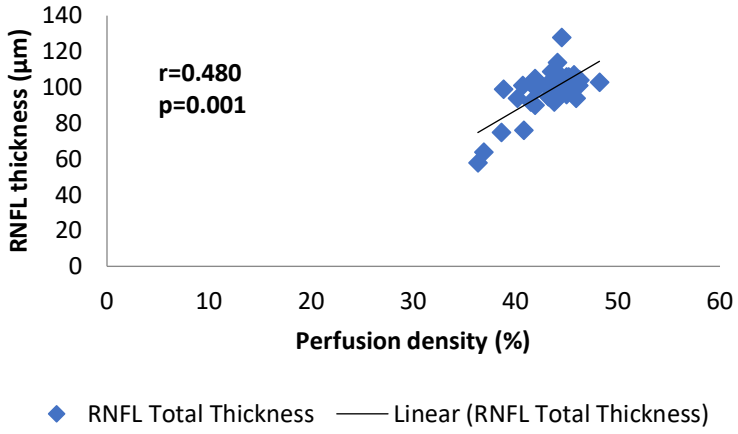

Figure 1. **Linier graph of corelation perfusion density with RNFL thickness**

Table 6 presents the correlation of peripapillary retinal flux index with peripapillary RNFL thickness in DM without DR. There was a significant positive moderate correlation (≥0.40 - <0.70) in the superior, inferior quadrant, and global (p<0.05). A negative weak correlation (0.2 - <0.4) was found in the temporal quadrant, although not statistically significant (p>0.05). Figure 2 illustrates the correlation of flux index with the RNFL thickness

Table 6. **Corelation of peripapillary retinal flux index with peripapillary RNFL thickness in DM without DR**

Variable	Corelation	R	P value
Superior quadrant	*Spearman*	**0.63**	**0.00**
Nasal quadrant	*Pearson*	0.25	0.10
Inferior quadrant	*Spearman*	**0.52**	**0.00**
Temporal quadrant	*Pearson*	-0.29	0.06
Global	*Spearman*	**0.52**	**0.00**

*P<0,05 is statisticaly significant.

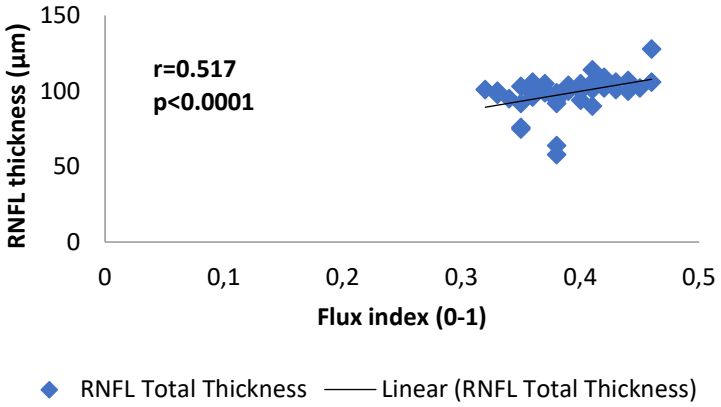

Figure 2. **Linier graph of corelation flux index with RNFL thickness**

DISCUSSION

The number of DM without DR patients in this study had an average age of 52.77 ± 5,14 years (41-64 years) with more women than men, 17 people (77.3%). These results are similar to the Riskesdas data in 2018, where most of the DM patients were on the age range 55-64 years (6.3%), 65-74 years (6.03%), then 45-54 years (3.9%) with more women (1.8%) than men (1.2%).[3,13]

The results of this study showed a decrease in the global flux index and all quadrants (superior, inferior, nasal, temporal) (p=0.00), but only the inferior quadrant (p=0.00) had a decreased perfusion density. The results of this study were similar with Liu et al in which there was no significant difference in peripapillary perfusion density in the DM without DR group compared to the control group. The study of Li et al stated that there were only two quadrants (inferonasal and superotemporal) with decreased perfusion density in DM without DR patients compared to normal. In contrast to the studies of Shin et al, Rodrigues et al and Cao et al where there were significant decreased in vascular density of DM without retinopathy group compared to controls. The results difference may be due to the differences in duration of DM, which were 6.2 ± 6.4 years in shin et al, 16.37 ± 8.41 years in Rodrigues et al, and 8.7 ± 5.2 years in Cao et al. [9,14-17]

In this study there was no significant difference in global RNFL thickness in DM without DR patients compared to controls, but there was a significant thickening in the temporal quadrant (p=0.01). There was RNFL thinning in the inferior quadrant, although not statistically significant (p=0.24). This result was similar with Li et al in which there was no difference in peripapillary RNFL or GCL thickness between the DM without DR and control group. In contrast to the studies of Liu et al and Mehboob et al where there was thinning of RNFL in the DM without DR group compared to control. The lack of significant RNFL thinning and RNFL thickening in the temporal quadrant in this study may be due to the glial cell swelling which is part of the neuroinflamation process that occurs at the early stage of diabetes, therefore thinning of RNFL or GCL has not yet occurred due to the swelling of neural cells. Muller cells, which are very susceptible to hyperglycemia, can also become hypertrophied due to inflammation (gliosis) which can affect the thickness of the retinal layer. Thickening of RNFL can also be caused by damage to the inner blood-retinal-barrier causing edema. [9,14,18-20]

This study found a positive moderate correlation (0.4 - <0.7) between peripapillary perfusion density and peripapillary RNFL thickness globally, and in the superior and inferior quadrants. A positively moderate correlation (0.4 - <0.7) was also found between the peripapillary flux index and peripapillary RNFL thickness globally, and in the superior and inferior quadrants. This indicates that in DM without DR patients, the radial peripapillary capillary perfusion density and flux index decrease with RNFL thickness, and vice versa. The results of this study were similar with Shin et al, where there

was a correlation between perfusion and vascular density with an average thickness of GCL and RNFL in the DM without retinopathy and NPDR group. In contrast to Liu et al, there was a significant positive correlation between vascular density and RNFL thickness in the mild NPDR group, but there was no significant relationship in the group without DR. This might be due to the shorter duration of DM without retinopathy in Liu et al study, which were 3 years (1-8). These results indicate that radial peripapillary capillaries are responsible for providing important nutrition to peripapillary RNFL. The combination of high metabolic needs and low vascular supply due to diabetes can reduce the neural ability of the retinal layer to adapt to metabolic stress. [9,15,17,19,21]

In this study, a negative weak correlation (0.2 - <0.4) was found between the peripapillary retinal flux index and peripapillary RNFL thickness in the temporal quadrant, although not statistically significant (p=0.06). This might be affected by the capillary perfusion density and flux index of temporal quadrant which was the highest compared to other quadrants in the OCTA of the DM without DR and control groups. Therefore, the damage of the inner blood-retinal-barrier in this quadrant can cause greater edema compared to other quadrants. Hafner et al also found the highest peripapillary flux was in the superotemporal followed by inferotemporal quadrant. In the study of Mase et al, the peripapillary perfusion density was significantly higher in the superotemporal and inferotemporal quadrants compared to other quadrants. [9,18,21,22]

There were several limitations of this study. The method we used was cross-sectional, therefore it is difficult to determine the causal relationship between microvascular changes and neurodegenerative changes. Long-term study with periodic OCT and OCTA examination may be able to describe the microvascular and neuronal relationship better, to find the predictive markers of DR. Another limitation is the sample of this study was relatively small. Further research is needed to determine the normal value results of OCTA examination.

In this study, we found that the flux index on OCTA was the most affected parameter by diabetes in DM without DR patients. Flux index examination by OCTA can be recommended as a screening tool in DR to see early microvascular dysfunction in DM.

CONCLUSION

There is a positive~~ly~~ moderate correlation between peripapillary retinal perfusion and peripapillary RNFL thickness in patients with diabetes mellitus without diabetic retinopathy.

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