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The Relationship between Retinal and Ganglion Layer Thickness and Perfusion in Patients with Type 2 Diabetes: A Cross-Sectional Study in Indonesia

ABSTRACT

Objective: To assess the differences and the relationship between retinal nerve fiber layer (RNFL) thickness, ganglion cell-internal plexiform layer (GCIPL) thickness, capillary perfusion density, and flux index in patients with type 2 diabetes (T2D) with and without diabetic retinopathy (DR).

Materials and methods: This cross-sectional analytic study with consecutive sampling, which divided individuals into healthy, people with T2D without DR (no DR), and people with T2D with DR (DR) groups. The subjects were patients with T2D aged 40–75 years with or without DR. The collected data included age, gender, glycated hemoglobin test result (HbA1c), duration of diabetes, intraocular pressure (IOP), RNFL thickness, GCIPL thickness, peripapillary perfusion density, and peripapillary flux index.

Results: This study included 137 eyes from 83 people with T2D. There were significant differences in minimum GCIPL thickness (p = 0.0001), peripapillary perfusion (p = 0.003), and peripapillary flux (p = 0.001) between the 3 groups, but no significant difference in RNFL thickness between the 3 groups (p = 0.222). There were significant positive correlations between RNFL thickness and peripapillary perfusion (p = 0.002, r = 0.264), RNFL thickness and peripapillary flux (p = 0.0001, r = 0.320), GCIPL thickness and peripapillary perfusion (p = 0.003, r = 0.256), as well as GCIPL thickness and peripapillary flux (p = 0.002, r = 0.268).

Conclusions: There were relationships between RNFL thickness and peripapillary retinal perfusion, RNFL thickness and peripapillary flux, GCIPL thickness and peripapillary perfusion, and GCIPL thickness and peripapillary flux, in patients with T2D with and without DR. (Clin Diabetol 2024; 13, 6: 366–372)

Keywords: diabetes mellitus, diabetic retinopathy, RNFL, GCIPL, papillary perfusion density

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Introduction

Diabetic retinopathy (DR) is the most common ocular complication of diabetes mellitus (DM). The global

prevalence is 34.6% or about 93 million people, and it is estimated to double by 2025. It is als estimated that around 10.2% of cases are visual-threatening diabetic retinopathy (VTDR), which can cause blindness. Diabetic retinopathy is the leading cause of blindness in productive age. According to data from the International Diabetes Federation (IDF), the prevalence of diabetes in Indonesia in 2021 was about 10.8%. A population-based cross-sectional study reported that the prevalence of DR among Indonesian adults with type 2 diabetes (T2D) was 43.1% while VTDR affected 26.3% of the population. About one in four adults with T2D had VTDR, and about one in twelve with VTDR was bilaterally blind [1–4].

Indonesia ranked fifth in the world for the number of adults with diabetes, reporting 19.5 million cases in 2021 from a total adult population of 179 million. This number is expected to increase to 28.6 million by 2045. A study by Jang et al. in South Korea found that around one-third of patients with T2D were unaware of their condition, and 10% had already developed DR [1, 5].

Microvascular disorders of the eye form the basis of the pathogenesis of DR, but there is also evidence to suggest that retinal neurodegeneration has occurred before clinically detectable microvascular damage is present. Retinal neuron cell apoptosis and peripapillary nerve layer thinning also play a role in the pathogenesis of DR. The microcirculation, radial peripapillary capillaries, and optic disc regions play a role in providing some nutrition to the retinal nerve fiber layer (RNFL) originating from the adjacent peripapillary retinal arteries. Microvascular dysfunction in this area may affect RNFL or ganglion cell-internal plexiform layer (GCIPL) function [3, 6].

Microvascular changes in the optic disc area could serve as early markers for DR, and they can be identified using non-invasive diagnostic tests such as optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA). There is still limited research investigating this issue, particularly in Indonesia [7]. This study aims to compare and find correlation between RNFL, GCIPL, and peripapillary retinal perfusion in healthy people, people with T2D without DR, and people with T2D with DR. Given the high prevalence of diabetes and DR in Indonesia, this could lead to improved early diagnostic strategies for patients at risk of DR, offering valuable data for public health strategies.

Materials and methods

Study design

This is a cross-sectional study in healthy people, people with T2D without DR, and people with T2D with DR.

Subjects

The inclusion criteria in this study were patients with T2D, with and without DR, with an age range from 40 to 75 years, and healthy people without diabetes with matched characteristics. Exclusion criteria were history of ocular trauma, history of ocular surgery, optic nerve abnormalities, optic nerve atrophy, glaucoma, and retinal vein or artery occlusion, as well as patients with refractive errors more than or equal to S-6.00 diopters (high myopia).

Ethical approval

This study received ethical clearance from the Ethics Committee of the Faculty of Medicine Universitas Padjadjaran, and it was carried out based on the ethical principles of the Declaration of Helsinki. The study was conducted at the National Eye Center, Cicendo Eye Hospital, Bandung from February to April 2020.

Data collection

Subjects were divided into 3 groups, namely, a control group consisting of healthy individuals, people with T2D without DR (No DR), and people with T2D with DR (DR). All subjects were examined using OCT (Carl Zeiss CIRRUS HD OCT) and OCTA (Carls Zeiss CIRRUS OCT Angiography) to measure the RNFL thickness, GCIPL thickness, capillary perfusion density, and flux index. The RNFL thickness measurement was carried out using an OCT optical disc cube 200 × 200 scan program with a signal strength of at least 6/10. Measurement of GCIPL thickness was carried out using the OCT program ganglion cell analysis macular cube 200 × 200. Capillary perfusion density and flux index were measured using OCTA by measuring the percentage of areas that have perfused blood vessels and capillary perfusion as seen from the brightness (intensity) of the flow signal with the optic nerve head program angiography at 4.5 × 4.5 mm.

Statistical analysis

Statistical analysis for numerical variables using one-way ANOVA test with the Kruskal-Wallis alternative test. Categorical data were obtained out by using the chi-square test. Furthermore, correlation tests were carried out to determine the correlation between each variable if the data has normal distribution followed by Pearson's correlation statistical test, while for abnormal data Spearman's test was used. The strength of the correlation was based on the criteria of Guillford (1956), as follows: 0.00 to < 0.2 very weak; 0.2 to < 0.4 weak; 0.4–0.7 moderate; 0.7 to < 0.9 strong; and 0.9–1.0 very strong, with a significance criterion of

Table 1. Comparison of the Characteristics of Patients in the Three Groups

Variable	Group			P-value
	Control N = 22	No DR N = 22	DR N = 39	
Age [years]				0.181
Mean ± SD	50.64 ± 6.477	53.09 ± 5.309	53.38 ± 5.764	
Gender				0.185
Male	8(36.4%)	4(18.2%)	16(41.0%)	
Female	14(63.6%)	18(81.8%)	23(59.0%)	
HbA1c [%]				0.0001*
Mean ± SD	5.50 ± 0.463	9.05 ± 1.909	9.374 ± 2.082	
DM duration [years]				
Mean ± SD	—	4.51 ± 3.225	8.32 ± 5.898	0.030*
IOP (N = 137 eyes) [mmHg]	N = 39	N = 42	N = 56	0.481
Mean ± SD	15.92 ± 2.507	16.21 ± 2.754	15.46 ± 3.751	

For numerical data, the p value is tested by one-way ANOVA test if the data are normally distributed or the Kruskal-Wallis test if the data are not normally distributed. For categorical data, the p value was tested with the chi-square test. The significance is based on the value of $p < 0.05$. * indicates the p-value < 0.05

DM — diabetes mellitus; HbA1c — glycated hemoglobin; IOP — intra-ocular pressure; SD — standard deviation

$p < 0.05$. The data were processed using SPSS version 24.0 for Windows.

Results

The subjects in this study comprised 83 people (137 eyes), who were divided into 3 groups: a control group consisting of 22 healthy people (39 eyes), people with T2D without DR comprising 22 people (42 eyes), and people of T2D with DR comproising 39 people (56 eyes). The mean age in this study was 51.32 ± 5.764 (41–64) years with 28 males (33.7%) and 55 females (66.3%). Table 1 shows the characteristics of the subjects in the 3 groups.

Table 2 shows papillary perfusion and papillary flux in the 3 groups. There was a significant difference of papillary perfusion between the 3 groups both overall and assessed per quadrant except for the temporal quadrant. Moreover, there was a significant difference of papillary flux between the 3 groups in all quadrants.

Table 3 shows the comparison of RNFL thickness and GCIPL thickness in the 3 groups. In this study, the thickness of the RNFL did not show a significant difference in general, but there was a tendency for GCIPL thickness thinning, and a significant difference can be seen in the ratio of the minimum GCIPL thickness.

Table 4 shows the correlation between papillary flux with RNFL thickness and GCIPL thickness. There was a significant positive correlation between RNFL thickness and average papillary perfusion density and flux ($p = 0.002$ and $p = 0.0001$, respectively), although the correlation strength was weak ($r = 0.264$ and $r = 0.320$, respectively). There was also a significant positive correlation between papillary perfusion density and papillary flux with GCIPL thickness ($p = 0.003$ and $p = 0.002$, respectively), even though the correlation strength was weak ($r = 0.256$ and $r = 0.268$, respectively).

Discussion

Diabetes mellitus is a complex metabolic disease that affects the microvascular system, including the eyes. Diabetic retinopathy is the leading cause of blindness in patients with diabetes mellitus (DM) and is the leading cause of visual impairment in working-age adults. Indonesia has a specific range for productive age, which is 18 to 55 years. The prevalence of DM increases with age; this is related to a decrease in pancreatic function with increasing age. Type 2 (adult-onset) or noninsulin-dependent diabetes mellitus is characterized by insulin resistance accompanied by insulin deficiency or impaired insulin secretion [8–10].

In Indonesia, individuals with T2D are in the age range of 55–64 years (6.3%), 65–74 years (6.03%), then 45–54 years (3.9%) with a higher rate in women (1.8%) than men (1.2%). More people with T2D live in urban areas (1.9%) than in rural areas (1.0%). Mihardja et al. [9] stated that in 2007 4.6% of the population had DM, 10.4% were 45–55 years old, and 5% were 35–44 years old. The prevalence of T2D increases with age and is higher in high socioeconomic groups. Diabetes mellitus affects women 1.6 times (95% CI 1.4–1.7) more than men.

Table 2. Overview and Comparison of Peripapillary Perfusion Density and Peripapillary Retinal Flux Index

Variable	Group			P-value
	Control N = 39	No DR N = 42	DR N = 56	
Superior perfusion				**0.002***
Mean ± SD	43.09 ± 2.298	42.29 ± 3.523	41.25 ± 2.922	
Inferior perfusion				**0.001***
Mean ± SD	44.00 ± 1.761	42.29 ± 2.802	42.05 ± 3.554	
Temporal perfusion				**0.715**
Mean ± SD	46.03 ± 2.115	46.68 ± 2.582	44.95 ± 8.055	
Nasal perfusion				**0.032***
Mean ± SD	42.10 ± 1.934	42.96 ± 3.494	42.20 ± 2.941	
Total perfusion				**0.003***
Mean ± SD	44.01 ± 1.201	43.55 ± 2.355	43.03 ± 2.123	
Superior flux				**0.003***
Mean ± SD	0.403 ± 0.033	0.383 ± 0.035	0.385 ± 0.041	
Inferior flux				**0.040***
Mean ± SD	0.409 ± 0.024	0.392 ± 0.035	0.394 ± 0.037	
Temporal flux				**0.001***
Mean ± SD	0.437 ± 0.038	0.401 ± 0.053	0.403 ± 0.053	
Nasal flux				**0.013***
Mean ± SD	0.393 ± 0.036	0.370 ± 0.040	0.371 ± 0.045	
Total flux				**0.001***
Mean ± SD	0.423 ± 0.029	0.390 ± 0.036	0.389 ± 0.041	

For numerical data, the p value is tested by one-way ANOVA if the data are normally distributed, or with the Kruskal-Wallis test if the data are not normally distributed; for categorical data, the p value was tested with the chi-square test. The significance is based on the value of $p < 0.05$. *indicates the p-value < 0.05

DR — diabetic retinopathy; SD — standard deviation

There was no significant difference in IOP between the 3 groups, this is so that the results are not influenced by vascular resistance that can occur due to IOP. Autoregulation of arteriolar and capillary vascular resistance serves to compensate for changes in IOP. Arterioles are also responsible for regulating blood flow in response to neural activity – retinal arterioles dilate to increase neuronal activity locally so that working neurons get adequate blood supply. The average glycated hemoglobin (HbA1c) test result in the no DR group was 9.05 ± 1.909 and in the DR group it was 9.374 ± 2.082, which indicates that glycemia is still not well controlled. HbA1c can only describe glycemic values in the last 3 months and cannot show fluctuations in glycemia, so HbA1c is not a perfect parameter to determine good metabolic control [11, 12].

Peripapillary neurovascular coupling (connection between vascular and neuronal) may reflect early changes in the progression of vascular disease. Axons from all ganglion cells pass through the RNFL and converge to the optic disc. Microvascular dysfunction in these areas may affect RNFL or ganglion cell function. Decreased vascular density may reflect microvascular disorders. The results of this study showed a decrease in total flux index ($p = 0.001$) and a decrease in total perfusion density ($p = 0.003$).

The study of Vujosevic et al. [13] stated that there was no difference in perfusion density (total area filled with blood vessels) between the control group, T2D without DR, and mild DR, but there was a difference in vascular density (capillary blood vessels only, not including large vessels). The study of Rodrigues et al. [14] stated there was a decrease in peripapillary perfusion density in all groups with diabetic eyes in multivariate analysis when compared to the control group (no DR = 2.95, $p < 0.001$; mild non-proliferative DR [NPDR] = 1.76, $p = 0.017$; and moderate NPDR = 2.82, $p < 0.001$). According to the study of Cao et al. [15], there was a decrease in vascular density in the peripapillary and within the disc, which was significantly lower in diabetic patients without DR compared to controls, and a decrease in vascular density was evident in 8 peripapillary sectors in diabetic eyes (all $p < 0.05$). Cao et al. [15] also mention higher axon density in the superior

Table 3. Overview and Comparison of Peripapillary RNFL and GCIPL Thickness

Variable	Groups			P-value
	Control N = 39	No. DR N = 42	DR N = 56	
RNFL total				0.222
Mean ± SD	97.87 ± 8.189	98.40 ± 12.031	103.46 ± 18.191	
GCIPL average thickness				0.076
Mean ± SD	83.74 ± 3.878	83.10 ± 9.929	77.21 ± 18.019	
GCIPL minimum thickness				0.0001*
Mean ± SD	81.38 ± 4.482	77.98 ± 12.765	61.00 ± 24.336	

For numerical data, the p value is tested by one-way ANOVA if the data are normally distributed or the Kruskal-Wallis test if the data are not normally distributed. For categorical data, the p value was tested with the Chi Square test. The significance is based on the value of $p < 0.05$. * indicates the p-value < 0.05

GCIPL — ganglion cell-inner plexiform layer; RNFL — retinal nerve fiber layer; SD — standard deviation

Table 4. Correlation between Papillary Perfusion Density and Papillary Flux with RNFL Thickness and GCIPL Thickness

Variable	Correlation	R	P-value
Correlation between AVG RNFL thickness and AVG papillary perfusion density	*Spearman*	0.264	0.002*
Correlation between AVG RNFL thickness and AVG papillary flux	*Spearman*	0.320	0.0001*
Correlation between AVG GCIPL thickness and AVG papillary perfusion density	*Spearman*	0.256	0.003*
Correlation between MIN GCIPL thickness and AVG papillary perfusion density	*Spearman*	0.323	0.0001*
Correlation between AVG GCIPL thickness and AVG papillary flux	*Spearman*	0.268	0.002*
Correlation between MIN GCIPL thickness and AVG papillary flux	*Spearman*	0.330	0.0001*

*indicates the p-value < 0.05

AVG — average; GCIPL — ganglion cell-inner plexiform layer; MIN — minimum; r — correlation coefficient; RNFL — retinal nerve fiber layer

and inferior regions making the superior and inferior quadrants more susceptible to ischemia. The significant decrease in density in the superior ($p = 0.002$) and inferior ($p = 0.001$) quadrant perfusion in this study may be due to the higher axon density in both making them more susceptible to ischemia [16].

Decreased blood flow in patients with T2D occurs due to changes in capillary structure including basement membrane thickening, pericyte apoptosis, and endothelium dysfunction, which can reduce blood flow and block capillaries. Retinal vascular endothelial cells are damaged by releasing endothelial nitric oxide synthase, which affects retinal vascular autoregulation. There is also an increase in plasma viscosity, platelet aggregation, and decreased red blood cell deformability, leading to impaired retinal and optic nerve head perfusion [10, 11, 15, 17].

Lott et al. [18] stated that patients with type 2 diabetes had impaired vasodilation and vasoconstriction responses, which may be due to impaired nitric oxide (vasoregulatory factor) in diabetes. Flicker-induced vasodilation is impaired, and hyperoxia-induced vasoconstriction occurs. To maintain a constant oxygen level, the velocity of blood flow is decreased by increasing the partial pressure of arterial oxygen (hyperoxia). Pechauer et al. [19] said that there was a greater percentage decrease in flux index compared to vascular density after hyperoxia. The population variation is smaller in the flux index compared to vascular density, so the flux index is more sensitive in detecting the hyperoxia response. In this study, the flux index decreased in all quadrants, and perfusion density also decreased in all quadrants except the temporal quadrant [11, 18–21].

In this study, there was no significant difference in the total thickness of the RNFL in the 3 groups. The results of this study are in accordance with Li et al. [22], in whose study there was no difference in peripapillary RNFL thickness between the T2D group without DR and the control group, in contrast to the study of Rodrigues et al. [14], where there was a depletion of RNFL in the diabetic eye group (T2D without DR, mild NPDR, moderate NPDR) compared to controls. The absence of significant RNFL depletion and temporal quadrant RNFL thickening in this study may be due to glial cell

swelling, which is part of the neuroinflammatory process that occurs early in diabetes, so RNFL depletion does not occur due to neural cell swelling. Muller cells, which are highly susceptible to hyperglycemia, can also undergo hypertrophy because of inflammation (gliosis), which can affect the thickness of the retinal nerve layer. Thickening of the RNFL can also be caused by damage to the inner blood retinal barrier leading to edema [12–14, 22].

In this study, there was a significant depletion of GCIPL minimum ($p = 0.0001$) in the control group (81.38 ± 4.482), the no DR group (77.98 ± 12.765), and the DR group (61.00 ± 24.336). These results are in line with the study of van Dijk et al. [23] who showed that there was depletion of the ganglion cell layer (GCL) in the pericentral area in diabetic patients with minimal DR compared to the control group [23].

The results of this study showed a weak positive correlation of average papillary perfusion density and flux with average RNFL thickness. This indicates that in patients with T2D without DR, perfusion density and radial peripapillary capillary flux index decrease with RNFL thickness, and vice versa. The results of this study are consistent with that of Shin et al. [10], who reported that there is a correlation between perfusion density and vascular density with the average thickness of GCL and RNFL in the DM group without retinopathy and NPDR. In contrast to the study of Liu et al. [17], there was a significant positive correlation between vascular density and RNFL thickness in the mild NPDR group, but no significant relationship in the group without diabetic retinopathy. This may be due to the shorter duration of DM without retinopathy in Liu et al.'s study, which took place over 3 years. The study by Mase et al. [24] conducted on healthy people showed that there was a correlation between RNFL thickness and vascular density. These results indicate that the radial peripapillary capillaries are responsible for providing nutrition to the peripapillary RNFL. In healthy individuals, the radial peripapillary capillaries are the most important structures in maintaining the integrity of the nerve fiber layer. The combination of high metabolic demand and low vascular supply resulting from diabetes may decrease the neural ability of the retinal layer to adapt to metabolic stress [10, 12, 15, 17, 24].

In this study, there was a significant positive correlation between papillary perfusion and GCIPL thickness ($p = 0.003$), although the correlation strength was weak ($r = 0.256$). The study by Kim et al. [25] described strong positive correlations between loss of macular GCIPL and vessel density from baseline to 24 months ($r = 0.817$, $p < 0.001$). Multivariable regression analysis showed that thinner baseline macular GCIPL and greater loss of macular GCIPL thickness ($B = 0.658$, $p < 0.001$) were significantly associated with change of vessel density. The study of Serrato-Martin et al. [26] found a weak positive correlation of complete and deep papillary perfusion with inferior and inferotemporal retinal ganglion thickness.

We also found a significant positive correlation between papillary flux and GCIPL thickness ($p = 0.002$), although the correlation level was weak ($r = 0.268$). There has been no previous research that examines this finding.

Currently there is limited research on the significance of peripapillary flux in pre-diabetic retinopathy, although early retinal changes may occur before DR becomes clinically apparent. Additionally, there are limited studies looking at the association of peripapillary density and peripapillary flux with GCIPL; most of them are associated with RNFL. This study focuses on peripapillary flux and its correlation with GCIPL thickness in patients with T2D in Indonesia, utilizing non-invasive techniques like OCT and OCTA, which provide valuable and accessible diagnostics for retinal assessments. However, the cross-sectional design of this study limits the ability to draw causal conclusions, and it restricts insights into longitudinal changes in retinal thickness and perfusion. The absence of a control group for pre-diabetic retinopathy also limits the understanding of these markers at the earliest stages of disease progression. Further longitudinal studies with a broader participant base, including those at pre-diabetic stages, are recommended to explore how early changes in retinal thickness and perfusion metrics could improve early detection and intervention strategies for DR.

The findings of this study indicate significant relationships between RNFL thickness, GCIPL thickness, and peripapillary perfusion and flux. Peripapillary vascular and neuronal (neurovascular coupling) relationships may represent early markers of microvascular dysfunction in DR, suggesting that monitoring of RNFL and GCIPL thickness and perfusion density with non-invasive diagnostic tools such as OCT and OCTA could support early identification of patients at risk for DR progression.

Article information

Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Ethical approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and with the approval of the

protocol by the local Ethics Committee of Universitas Padjadjaran, Bandung, Indonesia. (https://kep.unpad.ac.id). Approval number: 0320010094. Informed consent to participate the study was obtained from the patient.

Author contributions

RMR, SD: conceptualization and original draft writing; AP, BA, ASK: review and editing.

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Conflict of interest

The authors declare no conflict of interest.

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