

Differences of Retinal Nerve Fiber Layer and Ganglion Cell Layer-Inner Plexiform Layer Thickness in Patients without Diabetes Mellitus, with Diabetes Mellitus Type 2 without Diabetic Retinopathy and with Diabetic Retinopathy

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Abstract

Introduction: Prevention of Diabetic Retinopathy (DR) require an examination method that can identify earliest damage before clinical symptoms observed. This study aimed to determine the novel and objective way to detect those damage through RNFL and GCL-IPL thickness.

Methods: This analytical cross sectional study research conducted at the eye polyclinic and the Diabetic Center of IGNG Ngoerah Hospital, Denpasar. This study comparing the difference in thickness of RNFL and GCL-IPL in patients without DM, with Type 2 DM without DR and with DR in average and each quadrant thickness through Kruskal Wallis and One Way Anova test.

Results: The sample was 59 people which then divided into three groups, namely 20 samples in the group without DM, 19 samples in the DM group without DR and 20 samples with DR. The samples were then examined for RNFL and GCL-IPL and the results were compared between groups. The mean age of the subjects were 58.80 ± 9.65 years old. In the RNFL measurement, it was found that there were differences in values between groups in all quadrants except the temporal quadrant ($p=0.518$). After covariate analysis by variables of age, HbA1c, blood pressure, visual acuity, IOP and axial length, the results change with the nasal and inferior quadrants as the only found significant. In the GCL-IPL analysis there were significant differences between groups, especially in the superotemporal, temporal and inferotemporal quadrants ($p<0.005$). These results remained after being controlled by covariate analysis.

Conclusion: This study proved a neurodegeneration process that occurred focally in certain areas that can be detected through the RNFL and GCL-IPL measurement modalities. These examinations were expected to be useful in terms of screening both primary and secondary in patients with type 2 DM.

Keywords: Diabetes Mellitus Type 2, Diabetic Retinopathy, Retinal Nerve Fiber Layer, Ganglion Cell Layer-Inner Plexiform Layer
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INTRODUCTION

Diabetic retinopathy (DR) is a complication of type 2 diabetes that may cause severe vision impairment, especially at an advanced stage.[1] Diabetic retinopathy was the 6th leading cause of moderate to severe visual impairment in the global population in 2015. Global meta-analysis in the United States, Australia, Europe, and Asia reported that 1 in 3 patients with DM had diabetic retinopathy, and 1 in 10 (10.2%) patients had vision-threatening DR, namely proliferative type DR or diabetic macular edema. [2] DM sufferers in the world are estimated to increase to 191 million people and around 56.3 million will experience DR in 2030 without adequate prevention. [3]

Prevention of diabetic retinopathy requires an examination method that can identify damage as early as possible before clinical symptoms can be observed. Diabetic retinopathy primarily caused by microvascular damage due to the disintegration of the blood-retinal barrier, resulting in impaired neurovascular interaction. [4] The retinal nerve fiber layer (RNFL) is the main component of the inner retinal layer. Changes in the RNFL are assumed to detect neurodegeneration processes in patients with DM.

RNFL thickness in patients with diabetic retinopathy has shown mixed results in previous studies. Research by Li, et al., showed that RNFL correlated with vascular density in the optic nerve. The study showed a significant relationship between RNFL thickness and optic nerve vascular density in DM patients without and with diabetic retinopathy. [5] The study conducted by El Hifnawi, et al., showed that there was no significant difference between the thickness of each RNFL quadrant in the group of healthy individuals and the group with NPDR.[6] Another study conducted showed that there was no significant difference between RNFL thickness in

diabetic retinopathy patients and in the control group.[7] But those studies is known to only display the RNFL thickness parameter as a single parameter.

There are also other parameters that can indicate the presence of neurodegeneration in the retina, such as the thickness of the GCL-IPL layer and GCC complex. Booroah et al (2018) showed that the mean Ganglion Cell Layer-Inner Plexiform Layer (GCL-IPL) in patients without diabetic retinopathy was found to be thinner than the control group.[8] Ganglion Cell Complex (GCC) is a complex consisting of RNFL, GCL and IPL. This layer previously had clinical value in the early detection of retinal damage associated with glaucoma. Ganglion Cell Complex represents the loss of dendrites characterized by depletion of IPL, while ganglion cell bodies present in the GCL and nerve axons that can be assessed from the thickness of the NFL.[9]

The differences between RNFL, GCL and IPL can be seen through Spectral Domain-Optical Coherence Tomography (SD-OCT). As a complement to previous studies, this study not only displays data on the thickness of the RNFL but also other parameters that also show the degeneration process, such as the thickness of GCL-IPL in various quadrants so that the conclusions obtained will be more accurate. This study aimed to compare differences in RNFL thickness and GCL-IPL thickness in patients without DM, patients with DM without DR and in patients with diabetic retinopathy using the SD-OCT device. It is expected that the results of this study can contribute to education, early detection and clinical consideration of providing neuroprotective therapy before irreversible microvascular damage occurs.

METHODS

This study was a cross-sectional analytic approach. Data collection conducted prospectively. Sampling was carried out consecutively using primary data. The study was conducted at the Eye Polyclinic and the Diabetic Center Polyclinic of the IGNG Ngoerah Hospital Denpasar by recording

patient data for ONH-OCT (RNFL data) and macular OCT (GCL+IPL data) in June 2021-December 2021.

The target population was divided into three groups, namely for the group without diabetes, the target population was patients without diabetes mellitus. For the group with diabetes without diabetic retinopathy, the target population is patients with type 2 diabetes. The group without type 2 diabetes mellitus was obtained from ophthalmology polyclinic patients who underwent medical check-ups or who had only anterior segment abnormalities such as mild refractive errors or mild cataracts (Peng, et al., 2009). The group with diabetes mellitus without diabetic retinopathy was taken from the Diabetic Center Polyclinic of IGNG Ngoerah Hospital. The group with diabetic retinopathy was obtained from diabetic retinopathy patients who came to Vitreoretinal division of Ophthalmology Polyclinic and patients from the Diabetic Center who on examination found diabetic retinopathy. All samples was taken consecutively based on minimum sample requirement.

The inclusion criteria for non DM group was subjects aged 40-70 years and without a history of any type of diabetes, subjects can be from ophthalmology polyclinic patients who are checked for medical check-up, patients with refractive errors not less than Sph -3D and not greater than +3D, or cataract patients with minimal lens opacities with maximum lens opacities NO4NC4 or P4 if there is posterior subcapsular opacification (LOCS criteria) and willing to be the subject and have a complete eye examination including pupil dilation, ONH and macular OCT.

The exclusion criteria was subjects with glaucoma or have a history of glaucoma or have a family with glaucoma, with Type 1 Diabetes Mellitus, subjects

have eye pressure >21 mmHg measured by Goldmann applanation, subjects whose axial length of the eyeball is beyond the normal limit, i.e. eyeball length >25 mm or <23mm measured by non-contact optical biometry, history of congenital optic neuropathy, history of ocular trauma, papillary OCT results with signal strength <6/10, a history of previous eye surgery and history of previous active intraocular infection. The DM group inclusion criteria only including the type 2 DM. The DR subjects were subject that confirmed by fundus photography by 2 senior consultants (AA and AS).

The null hypotheses was there was no differences between the average or each quadrant between the three group.

All the data was calculated using Anova test if normally distributed and Kruskal-wallis if not normally distributed. Covariate analysis calculated with covariates as followed: Age, HbA1c, blood pressure, visual acuity, IOP, axial length because those variable may contribute as a potential confounders. The p value is declared significant if $p < 0.05$. Calculation was done using SPSS 15.0.

RESULTS

The sample of this study consisted of 59 people selected consecutively from the reachable population, namely all patients who came to the Eye Polyclinic and Diabetic Center at Sanglah General Hospital, Denpasar, who met the inclusion and exclusion criteria. The sample was divided into three groups: 20 patients without Diabetes Mellitus, 19 patients with type 2 DM without diabetic retinopathy, and 20 patients in the group with diabetic retinopathy (Table 5.1). No missing data in this report.

Table 5.1. Characteristics of the Research Sample

Variable	Without DM n:20	DMT 2 without DR n:19	With DR n: 20
Avg Age (years) (Mean±SD)	55,57±7,72	62,37±10,99	58,45±9,37
Sex, n (%)			
Male	7 (30,4%)	10 (43,5%)	6 (26,1%)
Female	13 (36,1%)	9 (25,0%)	14 (38,9%)
Domicile, n (%)			
Denpasar	11 (39,3%)	9 (32,1%)	8 (28,6%)
Outside Denpasar	9 (29,0%)	10 (32,3%)	12 (38,7%)
Laterality, n (%)			
Right eye (OD)	9 (32,1%)	11 (39,3%)	8 (28,6%)
Left Eye (OS)	11 (35,5%)	8 (25,8%)	12 (38,7%)
Duration of Diabetes (years) (Median(IQR))	-	6 (6,8)	4 (7,0)
Blood Pressure (MAP) (mmHg) (Median(IQR))	90,50 (9)	91,00 (3)	90,00 (4)
Axial Length (mm) (Median(IQR))	24,5 (1,2)	23,9 (0,9)	24,2 (0,9)
Visual Acuity (logMAR) (Median (IQR))	0,00 (0,00)	0,20 (0,20)	0,55 (0,70)
IOP (Mean±SD)	13,85±2,47	12,37±2,89	12,70±2,99
Central Macular Thickness (Median(IQR))	255,5 (42)	244,0 (61)	257,0 (41)
HbA1c (Median(IQR))	4,35 (0,9)	8,9 (2,4)	8,65 (2,9)

Measurement of the difference in OCT RNFL values in each quadrant is summarized in table 5.2. The distribution of RNFL data on all means was not normally distributed (p value > 0.05 using Shapiro-Wilk analysis). The results of bivariate analysis in more than two groups were not normally distributed with the Kruskal-Wallis Test showing that in all quadrants there were significant differences between groups, both in the inferior, superior, nasal and mean quadrants, except for the RNFL temporal quadrant. In the calculation of the temporal quadrant RNFL, there was no significant difference with a value of $p = 0.518$ (table 5.2).

We also try to assess the influence of potential bias through covariate analysis. After covariate analysis with assumed confounding variables, such as age, HbA1c, blood pressure, visual acuity, IOP, axial length, it was found that the quadrants that had significant differences were the nasal and inferior quadrants. This shows that there are confounding variables that have an influence on the thickness of the RNFL. Variables that significantly proved to be influential included: age ($p=0.024$) and axial length ($p=0.007$). Other variables, namely HbA1c, blood pressure, vision and IOP, did not prove to have an effect on RNFL thickness in the three groups ($p>0.05$).

Table 5.2.

Differences in Retinal Nerve Fiber Layer (RNFL) values between groups

RNFL (μm) (Median(IQR))	Without DM	DMT 2 without DR	With DR	Bivariate p value*	Covariate p value**
Inferior	155,50 (95)	138,00 (12)	128,50 (59)	0,000	0,021
Superior	122,0 (44)	98,00 (30)	89,00 (15)	0,001	0,202
Nasal	121,00 (29)	106,00 (11)	77,50 (17)	0,041	0,045
Temporal	93,00 (33)	83,00 (37)	92,50 (44)	0,518	0,297
Rerata (Average)	122,37 (36)	105,5 (24)	96,37 (13)	0,000	0,121

*P-value was calculated using the Kruskal Wallis Test, p-value was significant if $p < 0.05$ **Covariate analysis results (ANCOVA) with covariates: Age, HbA1c, blood pressure, visual acuity, IOP, axial length. The p value is declared significant if $p < 0.05$. All data in the table is not normally distributed.

The distribution of GCL-IPL data for all means was not normally distributed (p value > 0.05 by Shapiro-Wilk analysis) except for the average GCL-IPL value ($p < 0.05$) (table 5.3). Bivariate analysis with One Way ANOVA was used for normally distributed data, while the Kruskal-Wallis Test was used for non-normally distributed data. In the statistical results, it was found that there was a decrease in each quadrant, but what showed significant results was from the temporal quadrant, namely inferotemporal, superotemporal, temporal and the mean GCL-IPL value. The other quadrants, although showing decreasing values according to the presence or absence of diabetic retinopathy, did not show statistically significant differences (p value > 0.05). These results remained the same even after covariate analysis was performed. This shows that the confounding variables, namely age, HbA1c, blood pressure, visual acuity, IOP, axial length, did not prove to have an effect on the thickness of GCL-IPL ($p > 0.05$).

Table 5.3.

Differences in Ganglion Cell Layer-Inner Plexiform Layer (GCL-IPL) values between groups

GCL-IPL-(μm) (Median(IQR))	Without DM	DMT 2 without DR	with DR	Bivariate p value*	Covariate p value***
Inferior	109,00 (12)	108,00 (14)	108,00 (34)	0,677*	0,158
Inferonasal	119,00 (19)	114,00 (16)	109,50 (50)	0,796*	0,200
Inferotemporal	109,50 (9)	87,00 (9)	72.50 (10)	0,000*	0,000
Superior	113,00 (11)	110,00 (32)	108,50 (27)	0,380*	0,500
Superonasal	123,50 (16)	111,00 (36)	108,0 (27)	0,169*	0,253
Superotemporal	115,00 (12)	96,00 (13)	77.00 (22)	0,000*	0,009
Nasal	122,25 (15)	112,00 (27)	110,25 (34)	0,114*	0,289
Temporal	171,00 (36)	113,50 (43)	103,25 (13)	0,000*	0,000
Rerata (Average)	146,96 \pm 17,8	125,40 \pm 18,6	109,28 \pm 21	0,000**	0,000

*Kruskal Wallis Test results. The p value is considered significant if $p < 0.05$ ** One Way Anova Test results. The p value was declared significant if $p < 0.05$ *** Results of covariate analysis (ANCOVA) with covariates: Age, HbA1c, blood pressure, vision, IOP, axial length. The p value is declared significant if $p < 0.05$. All data in the table is not normally distributed except the average GCL-IPL.

DISCUSSION

This study showed that there was a statistically significant decrease in the average (average) RNFL between groups. Several studies conducted in the type 2 DM group without and with mild NPDR showed similar results. The results of those studies emphasized the presence of neurogenic changes in

the eyes of patients with type 2 DM without DR which were seen clinically, especially in the area close to the optic disc. [10-11] Other studies that compared control patients with patients with diabetic retinopathy also showed a significant reduction in the mean RNFL. [8,12,13]

In this study, in addition to the difference in mean between groups, the temporal quadrant is the only quadrant that is not showing significant changes. This study is in line with previous meta-analysis studies which showed that the temporal quadrant of the RNFL did not experience the same thinning as other quadrants. [14,15] This is related to capillary perfusion and the highest flux index in the temporal quadrant including superotemporal and inferotemporal as evidenced by previous OCT Angiography examinations study performed in the DM population with and without diabetic retinopathy. [16]

This study also shows that the condition of type 2 DM can affect neurons, especially in the Optic Nerve Head (ONH) and this condition can be observed by OCT examination of the ONH. After controlling for confounding variables using covariate analysis, such as age, HbA1c, blood pressure, vision, IOP, axial length, there was a thinning that was still found to be significant in the nasal and inferior quadrants. This proved that there is a confounding variable effect on the thickness of the RNFL. Through the covariate analysis, we found that confounding variables that may influence the result was age and axial length. Previously it was known that an increase in age is associated with a decrease in the thickness of RNFL and GCL-IPL, which is around 0.26% or around -0.54 μm per year [17-19] and reaches 0.56% per year at the age of over 75 years. [20] This is due to a decrease in vascular density and structure related to aging which increases the process of apoptosis in ganglion cells. [21,22] Long axial length in previous studies was associated with a decrease in ganglion cell density. [23] So that the RNFL thickness measurement will show thinner results if it is done on subjects with a long axial length (more than 25 mm). This could be related to the higher scan distance in patients with high axial length and the presence of stretching of the Bruch's Membrane Opening (BMO). Likewise, if the measurement is

performed on subjects who have a low axial length (<23mm), the ganglion cell density will be increases and results in thicker RNFL measurements.

The results of the covariate analysis also showed that HbA1c had no effect on differences in the results of RNFL thickness. These results indicate that the neurodegeneration that occurs is more conducive to vascular causes than the effect of metabolic control. The study conducted by Nor-Sharina, et al. (2013) suggested using Hemoglobin Advanced Glycation End-products (Hb-AGE) as a more stable metabolic parameter compared to HbA1c. Other parameters can also be used such as GDP or GDS with similar results. Chihara, et al. (2013) also showed that HbA1c was not related to the degree of diabetic retinopathy. The study also assumes that there are other pathogenesis such as ischemia which can underlie the decrease in the thickness of the RNFL.[24,25]

In line with the this study, a meta-analysis conducted by Chen, et al. (2015) also found thinning in the superior, inferior and nasal areas associated with increased of retinal medial layer thickness in the choroidal vessels.[14,15,26] Shahidi, et al. (2012) and Shi, et al. (2017) showed that the inferior quadrant showed significant depletion compared to normal subjects.[4,27] These results are expected to be the basis for the development of screening of patients with preclinical diabetic retinopathy which is convincingly towards vascular factors rather than metabolic factors.

In contrast to the studies previously described, other studies showed no significant thinning in the inferior quadrant.[28] Study by Sugimoto, et al. (2005) showed that the superior quadrant has thinner attenuation than the other quadrants.[9,15,29] Other studies also showed that RNFL values in patients with type 2 DM were not significantly different compared to controls, but this study did not include samples with diabetic

retinopathy and did not perform a standard fundus photo examination. [3,30]

The average value of the GCL in this study showed a significant difference between the three groups. These results are similar to a study conducted by Van Dijk, et al., (2010), which found a thinner GCL layer in the pericentral area of the macula in patients with mild NPDR compared to patients without diabetes. [31,32] Meyer-Rüsenberg, et al. (2006) showed a decrease in the number of midget cells and parasol cells in the GCL-IPL layer that occurred in patients with Type 2 DM.[33] Another study also showed that the average GCL-IPL thickness was lower in patients with diabetes compared to control patients, although there was no significant difference in mean RNFL.[34] The result from this study and as supported by previous studies, shows that there is damage to neurons on the macula that can be objectively measured through the thickness of the GCL-IPL. According to several studies, these results are caused by the presence of hyperglycemia which causes an increase in the release of VEGF, NO, glutamate, inflammatory cytokines and ROS (Reactive Oxygen Species). This process can cause retinal ganglion cell apoptosis through various mechanisms such as BRB disruption, neuronal excitotoxicity, and increased intracellular calcium accumulation.[35,36]

Although little is known about optic nerve dysfunction in patients with diabetes mellitus, some postulate that the diabetic condition affects the anterograde and retrograde transport of large and medium sized ganglion cell axons even though there is no quantitative or morphological abnormality of these cells. [37-39]

This study not only showed that there is a difference in the average GCL-IPL between groups, but also shows that there is depletion that occurs in certain quadrants, namely the temporal quadrant including superotemporal, temporal and

inferotemporal. These results remained the same after controlling for confounding variables such as age, HbA1c, visual acuity, CMT and axial length. These results may indicate that the confounding variable has no effect on the GCL-IPL thickness results including the glycemic control variable or HbA1c. Similar to the results of RNFL analysis, the factor that has a greater role in the difference in GCL-IPL thickness is the vascular factor. This is supported by research by Byeon, et al. (2009) who showed an expansion of the FAZ (Foveal Avascular Zone) area seen on OCT Angiography associated with damage to the GCL-IPL layer in the fovea. The expansion of the FAZ area indicates a macular ischemic condition in patients with diabetic retinopathy due to loss of vascular blood supply. [40]

There are three vascular networks that supply the macula, namely the Superficial Capillary Plexus (SCP), Deep Capillary Plexus (DCP) and the choriocapillary vascular layer (CC layer). The superficial capillary plexus (SCP) supplies the superficial retinal layer area from the inner plexiform layer down to 15.6 μm below the inner plexiform layer (IPL), and the DCP supplies the underlying layer. The Choriocapillaris (CC) layer supplies the bruch membrane area to 10.4 μm below it. [41-42] Vascular density and capillary flux in SCP were found to be lower in patients with microvascular disorders including diabetes. Macular vascular density was found to be lower in patients with diabetes, but the association was found to be significant only in the temporal area. The low density of blood vessels in the temporal area in diabetic patients is assumed to occur due to early capillary dropout which occurs before there are clinically identifiable signs of diabetic retinopathy. [43] Another study also found similar capillary dropout using other imaging modalities. [43] Apart from the dropout, this decrease in density is also caused by an increase in the fovea avascular zone in patients with diabetes. [44,45] In a study conducted by Attalah, et al. (2019),

the presence of the Avascular Fovea Zone (FAZ), both superficial and deep retinal plexus, is associated with a decrease in fovea thickness. In patients with diabetic retinopathy without macular edema, enlarged FAZ areas are mainly found in the superficial plexus, so it is assumed that the process of decreasing foveal thickness is influenced by the superficial plexus layer. [46] However, several other studies have shown different results. The study conducted by Araszkiwicz, et al. (2012) showed different results, namely in patients with diabetes mellitus without diabetic retinopathy, the GCL was thicker than the control group without diabetes mellitus, especially in the superior and inferior quadrants. [8,47,48] These results are assumed to be associated with more female gender with mechanisms that cannot be explained. [48]

In another study by Hegazy, et al., (2017), the volume of GCL-IPL differed significantly in mean, superior and inferior values. This suggests that GCL-IPL depletion in patients with diabetes shows a more focal thinning pattern compared to a diffuse thinning pattern. [49]

Sahin, et al. (2014) showed that there was a negative correlation between HbA1c and RNFL mean and assumed that RNFL depletion could be due to increased atherosclerosis in patients with type 2 DM associated with poor glycemic control. [15]

Although data recorded were not assessing ganglion cell function, the results of this study were supported by several previous studies which indicated functional defects, such as visual field abnormalities, contrast sensitivity and color as evidenced by a decrease in the value of the Ishihara panel, Lanthony 15-hue desaturated panel, and Farnsworth–Munsell 100-hue test in patients with type 2 DM. [50] Another study using Frequency Doubling Technology (FDT) showed that patients with T2DM without diabetic retinopathy were more likely to have ≥ 10 subfield defects at all sensitivity

levels, namely 5%, 2% and 1%, compared with patients without DM. This defect was found to be more likely to occur symmetrically and tend to have a diffuse pattern. [51]

Not all studies show similar results with this study, the study by Te, et al. (2016) showed that there was no significant difference between patients with type 2 DM without diabetic retinopathy and those with mild NPDR using the Short Wavelength Automated Perimetry (SWAP) device [52] This study shows that DMT 2 is different from DMT 1 which is a disorder caused by a single disorder, namely insulin deficiency while DMT2 is a multifactorial process with various pathogenesis and manifestations. Pathogenesis pathways that are most often studied include metabolic factors and vascular factors. In this study, we emphasize the dominant link between neurodegeneration and vascular factors compared to metabolic factors.

There are some of the weaknesses of this study. The method used is cross-sectional, making it difficult to determine the causal relationship between microvascular changes and neurodegenerative changes. The research does not reflect differences based on time, so it is necessary to carry out a longer prospective study so that it can be determined whether there is a decrease in the thickness density of RNFL and GCL-IPL. The study did not distinguish between non-proliferative and proliferative diabetic retinopathy, so this study should be continued to obtain results that include subgroup analysis.

We are further suggest further research is needed regarding the analysis of subgroups of patients with diabetic retinopathy with various degrees, namely the nonproliferative type and the proliferative type or involving diabetic retinopathy patients after laser procedures or intravitreal injections. Further research development can be carried out by examining the presence of visual field

defects, contrast and color vision in patients with preclinical diabetic retinopathy. The existence of this paper opens the opportunities for conducting various similar studies in various scientific disciplines other than the field of the eye as a target organ, such as the fields of nephrology, cardiology, and the central and peripheral nervous system.

CONCLUSION

There are differences in RNFL thickness in all quadrants between groups except the temporal quadrant. The quadrants that were most significantly thinned were the nasal and inferior quadrants. There were significant differences in GCL-IPL thickness between groups in the superotemporal, temporal and inferotemporal quadrants. RNFL and GCL-IPL examinations then can be used in preventive, screening, diagnostic and prognostic efforts in diabetic patients even though clinical signs of diabetic retinopathy have not been found. Preventive efforts can be made in the form of providing education about Diabetes Mellitus and the possibility of thinning of the papillae and macula which can be detected using the RNFL and GCL-IPL parameters. Screening and diagnostics on RNFL examination can be done by paying attention to all quadrants except the temporal quadrant. GCL-IPL examination screening is recommended to emphasize especially the temporal area including superotemporal and inferotemporal. Prognostic measures can be made by detecting thinning in certain areas of the RNFL and GCL-IPL that are proportional to the degree of diabetic retinopathy complications.

DECLARATION

Ethics approval and consent to participate

This study was approved by ethical and research committee of Faculty of Medicine

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Consent for Publication

The Publisher has *the Author's permission to publish* the relevant Contribution

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