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PERIPAPILLARY RETINAL NERVE FIBER LAYER THICKNESS IN DIABETIC RETINOPATHY PATIENTS MEASURED BY OPTICAL COHERENCE TOMOGRAPHY

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ABSTRACT

Introduction: Diabetic retinopathy (DR) is a microvascular complication of diabetes and one of the leading causes of blindness. Retinal function loss in diabetic patients is not only caused by microvascular abnormality but also retinal neurodegeneration. Optical coherence tomography (OCT) can detect retinal neural tissue loss caused by diabetes by measuring the retinal nerve fiber layer (RNFL) thickness on the cross-sectional imaging of the retina. This study is to evaluate the changes of peripapillary retinal nerve fiber layer (RNFL) thickness in diabetic retinopathy patients using OCT and compare it to age matched healthy controls.

Methods: A cross-sectional study of 16 eyes from 11 diabetic retinopathy patients and 10 eyes from 7 aged matched healthy subjects for control. Patients underwent optic nerve OCT imaging, RNFL thickness was recorded globally (average thickness) and segmented for superior, inferior, nasal, and temporal quadrants
Result: There were no significant difference of the average RNFL thickness in diabetic retinopathy group compared to healthy subjects. However, at the nasal quadrant, there were a significant increased thickness of RNFL compared to healthy subject (p value=0.009).

Conclusion: Optical coherence tomography can be used to detect neurodegeneration progression in diabetic retinopathy patients by quantitatively measuring the peripapillary RNFL thickness. This can be used as a diagnostic and prognostic factor in cases of DR.

Keywords: Diabetic retinopathy, peripapillary retinal nerve fiber layer thickness, optical coherence tomography
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INTRODUCTION

Diabetic retinopathy (DR) is a microvascular complication of diabetes and one of the leading causes of blindness. Global meta-analysis study reported that 1 in 3 (34.6%) had any form of DR in the US, Australia, Europe and Asia. Diabetic retinopathy is classified into two groups, non proliverative (mild, moderate, severe) and proliferative. Diabetic macular edema (DME) can be found in eyes at any DR severity level and run independently. Classification of DME include no DME, noncentral-involved DME, or central-involved DME. [1–3]

Histological studies of neural components of the retina revealed that diabetes-induced biochemical mechanisms can potentially cause neural cell degeneration. Retinal neurodegeneration is one of the early pathogenesis of diabetic retinopathy that could participate in microvascular abnormality. Diabetes causes neuronal apoptosis and thinning of retinal nerve fiber layer (RNFL). Studies supports that RNFL thinning occur independently to microangiopathy. Axons of the ganglion cells (nerve fiber layer) from all over the retina converge at the optic nerve head. The changes happening in the axons of the retinal nerves may be more easily detected around the optic nerve head. Nerve fiber layer is the most superficial layer of the retina and can be easily seen with imaging.[2,4–6]

Optical coherence tomography (OCT) makes evaluation of the optic nerve head, the peripapillary area, the macula and the RNFL revolutionary. Optical coherence tomography (OCT) is a non-invasive imaging technology that allows for a quantitative measurement of alterations in retinal thickness with a high resolution. Optical coherence tomography (OCT) can detect retinal neural tissue loss caused by diabetes by measuring the RNFL thickness on the cross-sectional imaging of the retina. Changes in NFL are an early estimate of neurovisual damage. Recognizing retinal neurodegeneration at an early stage can improve the prognosis of diabetic retinopathy. This study is to evaluate the RNFL thickness in diabetic retinopathy patients using OCT.[2–4,6,7]

METHODS

This study is a cross-sectional study with consecutive sampling of all patients with any stage of diabetic retinopathy at Vitreoretina Clinic, Cicendo Nasional Eye Hospital, Bandung from 16 to 30 January 2018. All patients more than 18 years old with a history of Diabetes Mellitus (DM) type 2 and diabetic retinopathy stage non proliferative and proliferative, from 16 to 30 January 2018 are included. Patients with optic nerve diseases such as optic neuropathy, glaucoma and papil atrophy, myopia gravior, epiretinal membrane or tractional retinal detachment near the optic nerve head, history of panretinal photocoagulation (PRP) and poor OCT image quality were excluded. Central-involved diabetic macular edema were also excluded in this study.

Control group included were age matched patients > 18 years old with normal eyes, no history of DM, hipertension and other systemic diseases. Stages of diabetic retinopathy was detemined using internasional counsil of ophthalmology (ICO) guideline, classified into mild non proliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, and proliferative diabetic retinopathy (PDR).

Patients attended the clinic for a single visit, with no further follow up. Retinal nerve fiber layer thickness was measured by High-Definition (HD) OCT (carl zeiss CIRRUS HD OCT), optic disc cube 200x200, and analyzed using CIRRUS review software. Thickness was recorded globally (average thickness) and segmented for superior, inferior, nasal, and temporal quadrants. Minimum signal strength used was 5/10. Diagnosis of macular edema was based on macular OCT, measured by High-Definition (HD) OCT (carl zeiss CIRRUS HD OCT), macular cube 512x128. Center-involving macular edema is when the fovea appears thickened on optical coherence tomography

We compare the average, superior quadrant, nasal quadrant, inferior quadrant, temporat quadrant RNFL thickness between the control grup and diabetic retinopathy group and also control grup with each diabetic retinopathy stage group (mild NPDR, moderate NPDR, severe NPDR, PDR)

Statistical Analysis

Statistic analysis were performed using SPSS software. Data was calculated for normal distribution using saphiro wilk tests. Comparative analysis for non normaly distributed data was calculated using mann-whitney test, normaly distributed data using independent T-test. P value <0.05 were considered statistically significant.

RESULTS

A total of 26 eyes from 18 patients were included in this study. This include 10 eyes from 7 aged matched healthy subjects for control, 16 eyes from 11 diabetic retinopathy patients (2 eyes with mild NPDR, 7 eyes with moderate NPDR, 5 eyes with severe NPDR, 2 eyes with PDR). Patients demography are reported in table 1. Each patients characteristics based on OCT retinal nerve fiber layer thickness are shown in table 2 for each eye.

Table 3 shows mean RNFL thickness in 10 eyes of healthy subject (control group) and 16 eyes of diabetic retinopathy group. The average Retinal nerve fiber layer is thicker in diabetic retinopathy group compared to healthy subjects. Superior, nasal, and temporal quadrant were also thicker, but the only data that was statistically significant was the nasal quarant with a p-value 0.009.

Table 1. **Patients Demography in Diabetic Retinopathy Group and Healthy Group**

	Diabetic Retinopathy (N=11)	**Healthy (N=7)**
Age (year)	54±7	57±6.7
Sex :		
Male	3 (27.3%)	4 (57.1%)
Female	8 (72.7%)	3 (42.9%)

Each stage of diabetic retinopathy were described and presented in table 4. the average RNFL thickness was thinnest in the moderate NPDR group with (96.6±10.52 µm) and thickest in PDR group with (115±18.38 µm). Superior qudrant was thinnest in moderate NPDR (121.0±11.55 µm) and thickest in severe NPDR (141.6±24.83 µm). Nasal quadrant was thicker in all stages of diabetic retinopathy. Inferior quadrant was thinnest in moderate NPDR (114.9±18.99µm) and thickest in PDR group (160.5±92.3µm). Temporal quadrant was thinnest in mild NPDR (68.5±7.78µm) and thickest in severe NPDR group (85.4±10.45µm).

Table 2. **Patients Characteristics based on OCT Retinal Nerve Fiber Layer Thickness**

Sex/Age	Diagnosis	OCT Nerve Fiber Layer Thickness				
Case		**average**	**superior**	**nasal**	**inferior**	**temporal**
1. F/58	Severe NPDR	88	109	58	102	84
2. F/51	Severe NPDR	113	153	73	153	73
3. M/53	Mild NPDR	110	142	97	138	63
4. M/53	Mild NPDR	104	138	83	123	74
5. F/33	Moderate NPDR	100	118	80	109	92
6. F/52	Severe NPDR	125	176	88	135	102
7. F/53	PDR	128	109	100	226	76
8. F/53	Moderate NPDR	95	132	77	109	62
9. F/53	Moderate NPDR	92	117	69	118	62
10. F/59	Severe NPDR	100	134	76	106	85
11. F/59	Severe NPDR	101	136	80	107	83
12. F/49	Moderate NPDR	108	126	80	142	83
13. F/49	PDR	102	134	102	95	76
14. M/59	Moderate NPDR	104	129	96	122	68
15. M/59	Moderate NPDR	101	127	97	124	54
16. M/63	Moderate NPDR	76	98	62	80	66
Control						
1. M/51	N/A	104	137	71	122	87
2. M/51	N/A	110	151	68	141	78
3. F/56	N/A	96	121	61	124	76
4. M/54	N/A	100	115	68	130	88
5. M/54	N/A	105	131	75	127	86
6. M/54	N/A	104	128	64	159	63
7. M/54	N/A	106	147	76	143	57
8. F/59	N/A	97	128	66	128	64
9. M/65	N/A	105	121	85	133	79
10. F/72	N/A	77	95	52	100	60

Table 3**. Comparation Of Retinal Nerve Fiber Layer Thickness in Healthy Subjects (Control Group) and Diabetic Retinopathy Group**

RNFL thickness	Diabetic retinopathy (N=16)	Healthy (control) (N=10)	P-value (95% CI)
Average	102.9±12.78	100.4±9.25	0.979**
Superior	129.8±18.56	127.4±6.10	0.792**
Nasal	**82.4±13.42**	**68.6±9.02**	**0.009****
Inferior	124.3±32.91	130.7±15.45	0.572*
Temporal	75.2±12.61	73.8±11.83	0.979**

*Independent-sample T test
**Mann-Whitney test

Picture 1**. Difference of Nasal Rnfl Thickness Between Diabetic Retinopathy and Healthy Group in Box Plot**

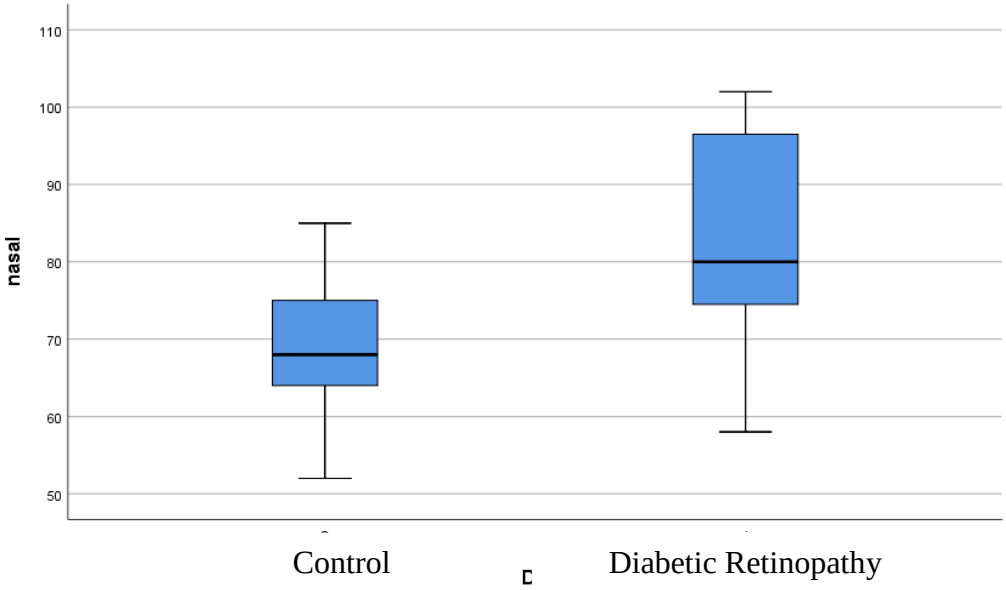

Table 4. **Retinal Nerve Fiber Layer Thickness Based on Each Stage of Diabetic Retinopathy**

RNFL Thickness	Diabetic Retinopathy (N=16)	
average	mild NPDR	107±4.24
	moderate NPDR	96.6±10.52
	severe NPDR	105.4±14.08
	PDR	115±18.38
superior	mild NPDR	140±2.83
	moderate NPDR	121.0±11.55
	severe NPDR	141.6±24.83
	PDR	121.5±17.68
nasal	mild NPDR	90±9.90
	moderate NPDR	80.1±12.90
	severe NPDR	75±11.05
	PDR	101±1.41
inferior	mild NPDR	130.5±10.61
	moderate NPDR	114.9±18.99
	severe NPDR	120.6±22.37
	PDR	160.5±92.3
temporal	mild NPDR	68.5±7.78
	moderate NPDR	69.6±13.26
	severe NPDR	85.4±10.45
	PDR	76±0

DISCUSSION

Retinal function loss in diabetic patients is not only caused by microvascular abnormality but also retinal neurodegeneration. Neuronal apoptosis and reactive gliosis has been detected in patient with diabetes without microvascular changes. Retinal neurodegeneration include neuronal apoptosis, loss of ganglion cell bodies, glial reactivity defect, and inner retina thickness reduction. Retinal neurodegeneration can also contribute to capillary degeneration including breakdown of the blood–retinal

barrier and impairments in neurovascular interaction. Glutamate accumulation in the extracellular space, oxidative stress, an imbalance in the retinal production of neuroprotective factors, and inflammation are the main factors involved in the development of neurodegeneration in the setting of DR.[7–10]

Retinal hypoxia caused by reduction in retinal blood flow is one of the earliest sign of diabetic retinopathy. Hyperglycemia increased intracellular glucose, accumulation of sorbitol, increased lactate/pyruvate ratio and disturbance of redox balance that causes cell damage. High extracellular glucose increases oxidative metabolism of glucose in the mitochondria, which releases free radicals resulting in direct damage to the nerve axons. Diabetes compromises the ability of the retina to manage glutamate, which could lead to chronic excitotoxicity by allowing a gradual increase in the levels of extracellular glutamate. Over excitation of neurons can lead to an increase in apoptosis.[11,12]

Ganglion cell in diabetic retina are most vulnerable for apoptosis because they express several proapoptosis molecule like caspase-3, Fas, and Bax. Reduces survival of retinal neurons induces retinal glial reactive changes and causes the appearance of abnormal swellings on centrifugal axons. Kern and Engerman et al believed that some parts of the retina lack the normal vasoconstrictor response to adverse stimuli like hypoxia. Therefore they are more prone to develop oxidative damage and nerve cell loss [11,12]

The studies of Barber and colleagues reported a 10% reduction in cells of the ganglion cell layer in streptozotocin-induced diabetic rats. They also reported marked reductions in the thickness of the inner plexiform layers (IPLs) and inner nuclear layers (INLs) and a 10-fold increase in the numbers of apoptotic nonvascular cells. The loss of retinal ganglion cell bodies is also reflected by a reduction in the number of axons in the optic nerve. Dijk et al. and Oshitari et al. also showed that RNFL and RGC layer thickness is reduced over time in DR patients and the degree of thinning was related to the severity of DR.[5,11,12]

In this study we found that there were no significant difference of the average RNFL thickness in diabetic retinopathy group compared to healthy subjects. However, at the nasal quadrant, there were a significant increased thickness of RNFL compared to healthy subject (p value=0.009). Increased thickness probably caused by increased number of axonal swellings in the ganglion cell.

Diabetes reduces axonal transport in both the peripheral and optic nerves, and this may be related to abnormal accumulation of axonal neurofilament. Neurofilaments are intermediate filaments found in the cytoskeleton of neurons with large axons, such as the retinal ganglion cells. Breakdown of the inner blood retinal barrier (BRB) results in accumulation of fluid within the extracellular space. Damage to the outer BRB at the level of the retinal pigment epithelium has been suggested to cause diffuse edema. therefore, increasing retinal thickness. More advanced DR was associated with increased peripapillary retinal thickness.[2,6,12]

El-Hifnawy et al also found that there was no statistically significant difference in RNFL thickness of any quadrant in eyes with early NPDR when compared with healthy age-matched control group. Cho et al reported macular and peripapillary retinal thicknesses in diabetic subjects were significantly greater than that in normal controls ($p<0.05$). All retinal thickness parameters, and particularly peripapillary circular scans, tended to increase with increasing DR severity ($p<0.05$). In contrast with other studies, Dhasmana et al found RNFL thinning was observed in superotemporal (p-value = 0.001) and upper nasal sectors (p-value = 0.031) around the optic disc in eyes with diabetic retinopathy. Takis et al said lower RNFL was found thinner in diabetics, but the 2-year follow-up showed no significant reduction of RNFL thickness in diabetic and normal groups, indicating that RNFL damage may occur early in diabetic patients. Onset of diabetes is a predisposing factor for glaucoma, causing RNFL thinning in early stages, but good compliance to the treatment and glycemic control can minimize further RNFL damage.[6,9,13]

Hsu et al reported that superior/inferior and temporal/nasal ratios were more reliable in evaluating peripapillary RNFL in patients with diabetic retinopathy to eliminate the effect of macular edema. However, their method cannot

be used to analyze each individual peripapillary quadrant and the same amount of RNFL edematous change cannot be guaranteed between quadrants. Hyun Seung Yang et al reported reasons in fluctuation of the RNFL thickness measurement is the peripapillary retinal edema, which is affected by diabetic macula edema. the peripapillary RNFL thickness is strongly affected by retina edema, especially in the peripapillary area, so that peripapillary RNFL thickness itself does not indicate the actual RNFL gain or loss in DR patients [5,14]

Limitation in this study include small sample size and uneven amount of patient on each stages of diabetic retinopathy. Confounding factors such as duration of DM and other systemic factors such as neurodegenerative diseases cannot be evaluated. It is difficult to measure a reliable data because age and sex could influence the results and this study is not large enough to account that.

CONCLUSION

Optical Coherence Tomography can be used to detect neurodegeneration progression in diabetic retinopathy patients by quantitatively measuring the peripapillary RNFL thickness. This can be used as a diagnostic tool and monitor DR progression that can determined prognosis of DR.

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