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Relationship Between HbA1c Level With Retinal Nerve Fiber Layer Thickness In Diabetic Retinopathy

Febrina Art[1*], AK Ansyori[1], Ramzi Amin[1]

[1]Department of Ophthalmology, Faculty of Medicine, Universitas Sriwijaya, Indonesia

*correspondence author email: febrinaart@gmail.com

Abstract

Background: Diabetes mellitus (DM) have a direct effect to retinal neural tissue. Diabetic retinopathy slowly proggress with reserved visual acuity and no symptoms in early stage. Retinal nerve fiber layer thickness significantly decrease in type 2 diabetes mellitus patients related to glycemic blood level.

Methods: A cross sectional analytical study was conducted in RSUP dr. Mohammad Hoesin Palembang from October 2017 until March 2018. Sixty eight type 2 diabetes mellitus patients consist of various grade of diabetic retinopathy. Measurement of HbA1c level was performed on these samples and retinal nerve fiber layer thickness was measured by *Optical Coherence Tomography* (OCT).

Results: There is a significant relationship between duration of DM with RNFL thickness (p = 0,002). There is a significant relationship between hypertension with RNFL thickness (p = 0,007). There is a significant relationship between HbA1c level with RNFL thickness in all quadrants (superior, nasal, inferior quadrants p= 0,000, temporal quadrant p = 0,011). The most important factor of RNFL thinning in superior, nasal and inferior quadrants is HbA1c level (superior and nasal *adjusted p value* 0,002, inferior *adjusted p value* 0,002) while in temporal quadrant is hypertension (*adjusted p value* 0,042).

Conclusion: Thereis a significant relationship between HbA1c level with RNFL thickness in all quadrants in which the patients with HbA1c > 7% have a higher risk of thinner RNFL compared to patients with HbA1c ≤ 7%.

Keywords: retinal nerve fiber layer thickness, HbA1c, type 2 diabetes mellitus, optical coherence tomography

Introduction

Diabetic retinopathy is a frequent complication of diabetes mellitus. Diabetes and diabetic retinopathy have a negative effect on almost all aspects of visual function both photopic and scotopic vision. Diabetic retinopathy is one of the main causes of blindness in developing countries. Individuals suffering from diabetes have a 10-20 times higher risk for blindness. [1-6]

The World Health Organization (WHO) reports that the prevalence of diabetic retinopathy will increase and the number of sufferers who are at risk of vision loss will double by 2030.

The study by Hellgren et al stated that diabetes has a direct effect on neural retinal tissue. Changes that occur in retinal neural tissue can occur for years without any microvasculature changes that can be detected clinically with a simple examination tool. This study also states that diabetic retinopathy develops slowly and vision sharpness can still be good and the patient has no symptoms.[1-4]

The pathophysiology of RNFL depletion is multifactorial and the exact mechanism is still being debated. Possible theories include ganglion cell dysfunction and apoptosis. Chronic hyperglycemia can also affect neurons. Chronic hyperglycemia activates various metabolic pathways which ultimately cause oxidative stress in the retina and damage to neuronal tissue.[2,4]

Optical coherence tomography (OCT) is a method used to determine the thickness of the RNFL. This method relies on Michelson's interferometry principle, that is, light reflected from a surface will be processed into a shadow. This method is reliable in measuring the thickness of RNFL in various diseases. OCT is a good non- invasive examination tool and is quite easy to do to detect early neurodegenerative changes in the retina. [2, 9, 13]

Based on the need to detect neuronal damage early on the retina that causes depletion of RNFL so that it can ultimately have an impact on visual function, this is what researchers are interested in. do research on this matter.

Methods

This study used a cross-sectional study design to determine the relationship of HbA1c levels to the thickness of the retinal nerve fiber layer (RNFL) in diabetic retinopathy patients. This research was conducted at the eye clinic of RSUP dr. Mohammad Hoesin Palembang from October 2017 to March 2018. All patients with type 2 diabetes mellitus who have diabetic retinopathy or who don't have diabetic retinopathy, Intraocular pressure of 10-21 mmHg, Patients who have never undergone photocoagulation laser therapy, Clear refraction media, Willing to follow the stated research by signing an informed consent letter are inclusion criteria. For exclusion criteria Patients with comorbidities or complications other than diabetic retinopathy such as papillary atrophy, macular edema, retinal detachment or glaucoma, Patients who are not cooperative so it is difficult to do the examination Optical Coherence Tomography (OCT).

Results

Observational analytic research with cross sectional design to determine the relationship HbA1c levels to the thickness of the retinal nerve fiber layer (RNFL) in patients with diabetic retinopathy has been carried out from October 2017 to March 2018 at RSUP Dr. Mohammad Hoesin Palembang. 68 samples of type 2 diabetes mellitus (DM type 2) patients were obtained that met the inclusion and exclusion criteria.

The results of this study are presented in univariate analysis (frequency distribution of research subjects), bivariate analysis to determine whether there is a statistical relationship between the independent variables and the dependent variable and multivariate analysis to determine the effect of the independent variables on the dependent variable simultaneously.

General characteristics of research subjects are shown in table 4.1. From 68 respondents, 37 people (54.4%) were male and 31 people (45.6%) were female in which the majority of patients had an age range of 50-59 years (48.5%), patients with age ≥ 60 years as many as 23 people (33.7%) and the age range of 40 -49 years as much 12 people (17.6%).

The majority of the work of type 2 diabetes mellitus patients in the study These are 23 housewives (33.8%), 11 civil servants (16.2%), 18 private employees (26.5%) and 16 other jobs (23.5%) %). In addition, it was found that the majority of the last education of diabetes mellitus patients in this study were 42 people (61.8%) high schools, 14 universities (20.6%), 10 people

(14.7%) junior high schools and elementary schools as many as 2 people (2.9%).

Table 1. Baseline Characteristics

Characteristics	Result	Percentage
Gender		
• Male	37	54,4
• Female	31	45,6
Age		
• 40-49 Year	12	17,6
• 50-59 Year	33	48,6
• ≥ 60 Year	23	33,8
Work		
• Civil Servant	11	16,2
• Swasta	18	26,5
• Housewives	23	33,8
• Other	16	22,5
Education		
• Elemntary School	2	2,9
• Junior High School	10	14,7
• Senior High School	42	61,8
• University	14	20,6
Result	**68**	**100**

In this study, patients with type 2 diabetes mellitus with a long history of suffering from DM <5 years as many as 25 people (36.8%), 5-10 years as many as 24 people (35.3%) and> 10 years as many as 19 people (27.95). Of the 68 respondents, 35 (51.5%) had blood pressure normal, patients with stage I hypertension were 26 people (38.2%), stage II hypertension were 5 people (7.4%) and 2 people (2.9%) had low blood pressure.

The majority of patients had a normoweight body mass index (79.4%), patients with an overweight body mass index were 14 people (20.6%) and no patients with an underweight and obesity body mass index were found.

The mean HbA1c level of diabetes mellitus patients in this study was 8.319 ± 1.854% with a range of 5.6% - 13% where patients with HbA1c> 7% were 42 people (61.8%) while HbA1c ≤ 7% there were 26 people (38.2%). With the Fisher Exact test it was concluded that there was a significant relationship between HbA1c levels with superior RNFL thickness where patients with HbA1c levels> 7% had a significantly higher risk of having

thinner superior RNFL compared to patients with HbA1c ≤ 7% (PR = 33.333 (CI95% 4.122 - 12.2 - 269,529); p = 0,000).

With the Fisher Exact test it was concluded that there was a significant relationship between HbA1c and temporal RNFL thickness where patients with HbA1c levels> 7% were significantly more at risk had thin temporal RNFL thickness compared to patients with HbA1c ≤7% (PR = 11,207 (CI95% 1,368 - 91,803); p = 0.011). With the Fisher Exact test, it was concluded that there was a significant relationship between HbA1c with nasal RNFL thickness where patients with HbA1c levels> 7% had a significantly higher risk of having thin nasal RNFL thickness compared to patients with HbA1c ≤ 7% (PR = 33.333 (CI95% 4.122 - 12.2 - 269,529); p = 0,000).

With multivariate analysis using logistic regression test, the most significant risk factor influencing the thickness of RNFL is the HbA1c level (unadjusted OR 33,333, unadjusted p value 0,000 and adjusted OR 33,549, adjusted p value 0.002) where patients with HbA1c levels> 7% have a risk of 33 times and a history of hypertension has a risk of 7 times significantly to the thinness of RNFL in the superior quadrant. With multivariate analysis using logistic regression test, the most significant risk factors influencing the thickness of RNFL were HbA1c levels (unadjusted OR 33,333, unadjusted p value 0,000 and adjusted OR 33,549, adjusted p value 0.002) where patients with HbA1c levels> 7% had a risk of 33 times and the presence of a history of hypertension has a 7 times significant risk of thin RNFL in the nasal quadrant.

Discussion

Based on the results of the analysis conducted, the sex of the subjects in this study was dominated by men as many as 37 people (54.4%), while women numbered 31 people (45.6%). In several studies show that more men experience diabetic retinopathy, as reported by He et al (2012) and Al-Amer (2008) but in research conducted by Wang et al (2013) found that women (64.5%) more suffer from diabetic retinopathy compared to men (35.5%) [29,30] Basically sex does not have a significant relationship with the prevalence of diabetic retinopathy. This difference is caused by differences in sample size where in the two studies the number of samples was far more than 1000 samples compared to this study which was only 68 samples.

The age range of the most research subjects was the age group of 50-59 years (48.5%), the age group ≥ 60 years were 23 people (33.7%) and the age range of 40-49 years were 12 people (17.6%) . This is close to the same results reported by Park et al (2012) who found the average age of patients with diabetic retinopathy was 55.3 years. Whereas Yau et al (2012) found that the average age of patients with diabetic retinopathy was 58.1 years. Al- Amer (2008) obtained an average age of 57.8 years (SD ± 9.9) with 40 percent sufferers in the age group 56-65 years.[29,32,34] This difference is caused by differences in sample size where in the study by Park et al, Yau et al and Al Amer et al the number of samples is much more reaching thousands of samples compared to this study which only 68 the sample. This difference in results might also be caused by the age range under study ie in the study starting at the age of 20 years while in this study starting at 40 years.

With the Fisher Exact test it was concluded that there was a significant relationship between HbA1c with superior quadrant RNFL thickness and nasal quadrant where patients with HbA1c levels> 7% had a higher risk of superior RNFL thickness in patients with diabetic retinopathy compared to patients with HbA1c ≤ 7%.

Changes in RNFL thickness are preliminary estimates of neurovisual damage. Clinical changes in retinopathy are usually in the form of advanced, irreversible damage. Changes that can be seen in diabetic retinopathy are usually caused by microvascular damage whereas neurodegenerative changes are difficult to detect clinically. Some studies show that neurodegenerative changes in the retina occur earlier than microvascular changes. Measurement of the thickness of the retinal nerve fiber layer can detect the presence of neurodegeneration at an early stage. A meta-analysis of diabetes mellitus patients showed evidence of significant depletion of RNFL depletion.[2]

Paul et al in their study stated that the higher the level of glucose in their blood, the lower the thickness of RNFL. Biallosterski et al (2007) in their study stated that early retinal depletion is an important comorbidity in diabetes mellitus that occurs due to neuroglial damage. Some researchers have concluded that diabetes mellitus causes apoptosis of neural tissue and depletion of RNFL as a manifestation of this neurodegeneration.[9] Chihara et al reported that depletion of RNFL in patients with diabetes mellitus was caused by microvascular nonperfusion in the absence of visible signs on the retina. Microvascular

changes in diabetic retinopathy including endothelial dysfunction, thickening of the vascular basal membrane, peripheral apoptosis and capillary occlusion which can also involve capillary blood vessels in the optic nerve. [7] RNFL depletion is associated with dysfunction and apoptosis of retinal ganglion cells. In diabetic models with animals, retinal neuronal cell damage and depletion of the inner retina occur in the initial degree of diabetic retinopathy. Barber et al. Also reported the presence of retinal neuronal apoptosis in diabetic retinopathy patients. An experiment with diabetic animal models shows that anterograde and retrograde axonal transport is thought to be caused by damage to polyol metabolism and damage to mitochondrial function of retinal ganglion cells. Additionally, it is reported that there is an accumulation of advanced glycation end products (AGEs) in the lamina cribriform, connective tissue and blood vessels around the optic nerve in diabetes. AGEs play a role in the dysfunction of intracellular antioxidant enzymes, transcription factors and mitochondrial proteins. In addition to changes in early neuronal degeneration, microangiopathies in the optic papil caused by diabetes also play a role in RNFL defects.[7]

Conclusions

From 68 respondents, there were 42 patients with HbA1c level> 7% (61.8%) while HbA1c ≤ 7% were 26 patients (38.2%). Obtained average superior quadrant RNFL thickness of 106.12 µm ± 36.11 µm, mean nasal quadrant RNFL thickness of 78.72 µm ± 37.79 µm, mean inferior quadrant is 102.43 µm ± 36.29 µm and mean temporal quadrant RNFL thickness is 76.97 µm ± 30.45 µm. There is a significant relationship between HbA1c levels and RNFL thickness in all quadrants where patients with HbA1c levels> 7% are significantly more at risk of having thinner RNFL thicknesses than patients with HbA1c ≤7%. HbA1c levels are the most important risk factor in reducing RNFL thickness in patients with type 2 diabetes mellitus.From studies that show RNFL depletion in patients with HbA1c levels> 7%, it can be recommended to conduct routine peripapillary RNFL OCT examination for all patients with type 2 diabetes mellitus. For research results that better describe the general population, further research can be done with a community based population.

References

1. Jackson GR, Gardner TW. Visual fields refine understanding of diabetic retinopathy progression. *Diabetes* 2014;63:2909–2910
2. Chakrabarty D et al. Relation of retinal nerve fiber layer thickness with blood glycemic parameters in diabetic subjects: a study from Eastern India. *Int J Sci* 2016;5(9):1745-1749
3. Tah V et al. Diabetic retinopathy - an update on pathophysiology, classification, investigation and treatment. Ophthalmology - current clinical and research update. INTECH. 2014
4. Yu et al. Neuroinflammatory response in diabetic retinopathy. Journal of Neuroinflammation 2015;12:141
5. Olsen TW et al. Diabetic retinopathy. Retina/Vitreous Preferred Practice Pattern. American Academy of Ophthalmology. 2014
6. Wong T et al. ICO Guidelines for Diabetic Eye Care. International Council of Ophthalmology. 2017
7. Chen X et al. Peripapillary retinal nerve fiber layer changes on preclinical diabetic retinopathy: a meta-analysis. PLoS ONE 2015;10(5):1-12
8. Tarr JM, Kaul K, Chopra M et al. Pathophysiology of diabetic retinopathy. ISRN Ophthalmology. 2013
9. Paul et al. Study of retinal nerve fiber layer thickness in type 2 diabetes mellitus by 3- dimensional optical coherence tomography from Eastern India. Journal of applied pharmaceutical science 2014;4(05):034-038
10. Florkowski C. HbA1c as a diagnostic test for diabetes mellitus - reviewing evidence. Clin Biochem Rev 2013;34:75-83 79
11. Saudek C, Brick J. The clinical use of Hemoglobin A1c. Journal of Diabetes Science Technology 2009;3(4):629-634
12. HV Nema, Nitin Nema. Diagnostic procedures in ophthalmology. Jaypee Brothers Medical Publisher. New Delhi. 2009
13. Park H, Shin J, Lee J et al. Retinal nerve fiber layer loss in patients with type 2 diabetes and diabetic neuropathy. Diabetes care 2016;39:e69-70
14. Dhasmana R, Sah S, Gupta N. Study of retinal nerve fiber layer thickness in patients

with diabetes mellitus using fourier domain optical coherence tomography. Journal of Clinical and Diagnostic Research 2016;10(7):05-09.

15. Nor-Sharina et al. Correlation of retinal nerve fiber layer thickness with HbA1c and oxidised LDL innon-proliferative diabetic retinopathy. J Diabetes Metab 2013:298
16. American Academy of Ophtalmology 2014- 2015 : Retina, San Fransisco, American Academy of Ophtalmology 2014.
17. Jack J Kanski : Clinical Ophtalmology, seventh edition, Philadelphia, Elsevier 2011.
18. Sugimoto M et al. Retinal nerve fiber layer decrease during glycemic control in type 2 diabetes. Journal of Ophthalmology 2010:Article ID 569215, 6 pages
19. De Clerk EEB, Schouten JSAG, Berendschot TTJM, et al. Loss of temporal peripapillary retinal nerve fibers in prediabetes or type 2 diabetes without diabetic retinopathy: The Maastricht Study. Invest Ophthalmol Vis Sci, 2017;58:1017-1027
20. Rodrigues et al. Diabetes induces changes in neuroretina before retinal vessels: a spectral-domain optical coherence tomography study. International Journal of Retina and Vitreus 2015; El- hifnawy M, Sabry K, Gomaa A et al. Effect of diabetic retinopathy on retinal nerve fiber layer thickness. Delta Journal of Ophthalmology 2016;17:162-166
21. Pekel E, Tufaner G, Kaya H et al. Assessment of optic disc and ganglion cell layer in diabetes mellitus type 2. Medicine 2014;96:29
22. Hwang DJ, Lee EJ, Lee SY et al. Effect of diabetic macular edema on peripapillary retinal nerve fiber layer thickness profiles. Invest Ophthalmol Vis Sci. 2014;55:4213- 4219
23. Dijk H, Verbraak F, Kok P et al. Early neurodegeneration in the retina of type 2 diabetic patients. Invest Ophthalmol Vis Sci. 2012;53:2715-2719
24. Demir M, Oba E, Sensoz H et al. Retinal nerve fiber layer and ganglion cell complex thickness in patients with type 2 diabetes mellitus. Indian J Ophthalmol 2014;62:719-20
25. Singh VP, Bali A, Singh N et al. Advanced glycation end products and diabetic complications. Korean J Physiol Pharmacol 2014;18:1-14
26. Srinivasan S, Pritchard N, Sampson GP et al. Retinal thickness profile of individuals with diabetes. Ophthalmic Physiol Opt 2016;36:158-166

27. Solish S. Optic nerve and retinal nerve fiber imaging. American Academy of Ophthalmology. 2015
28. Al-Amer, et al. Prevalence and risk factors of diabetic retinopathy among Jordanian patients with type 2 diabetes. Digital Journal of Ophthalmology. Vol 14.2008.
29. He, et al. Factors associated with diabetic retinopathy in Chinese patient with Type 2 Diabetes Mellitus. International Journal of Endocrinology. 2012;53:1156-63
30. Wang J, Zhang R, Chen RP, et al. Prevalence and risk factors for diabetic retinopathy in a high-risk Chinese population. BMC Public Health. 2013;13:633.
31. Yau WY, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care. Vol 35. 2012: 556-564.
32. Xu, et al. Prevalence and risk factors for diabetic retinopathy : the Beijing communities Diabetes Study 6. Retina. 2012;32(2):322-9.
33. Park, et al. Prevalence and risk factors for diabetic retinopathy in Koreans with type II Diabetes: Baseline characteristics of Seoul Metropolitan City- Diabetes Prevention Program (SMC-DPP). BJO. 2012;96:151- 155.
34. Stahl et al. Incidence of type 2 diabetes among occupational classes in Sweden: a 35-year follow up cohort study in middle-aged men. Diabetic Medicine. 2014;31(6):674-680
35. Ghamdi, et al. Rapid assessment of avoidable blindness and diabetic retinopathy in Taif, Saudi Arabia. Br J Ophthalmol. 2012;96(9):1168-72.
36. Jee D, Lee WK, Kang S. Prevalence and risk factors for diabetic retinopathy: The Korean National Health and Nutrition Examination survey 2008-2011. IOVS vol 54. 2013:6827- 33.
37. Van Dijk HW, Verbraak FD et al. Decreased retinal ganglion cell layer thickness in patients with type 1 diabetes. Invest Ophthalmol Vis Sci. 2010;51:3660-5
38. Niazi M et al. Duration of diabetes as a significant factor for retinopathy. Pak J Ophthalmol. 2010;26(4):182-186
39. Lastra et al. Type 2 diabetes mellitus and hypertension: An update Endocrinol Metab Clin North Am. 2014 March ; 43(1): 103–122.
40. Ganz M et al. The association of body mass index with the risk of type 2 diabetes:

a case– control study nested in an electronic health records system in the United States. Diabetology & Metabolic Syndrome. 2014;6:50

41. Gray N et al. The Relationship between BMI and Onset of Diabetes Mellitus and its Complications. South Med J. 2015 January ; 108(1): 29–36
42. Budenz D et al. Determinants of normal retinal nerve fiber layer thickness measured by Stratus OCT. American Academy of Ophthalmology. 2007
43. Harrison WW, Chang A, Cardenaas M et al. Blood pressure, vessel caliber, and retinal thickness in diabetes. Optom Vis Sci 2012;89:1715-20
44. Gangwani R et al. The correlation of retinal nerve fiber layer thickness with blodd pressure in a chinese hypertensive population. Medicine (Baltimore). 2015;94(23):e947