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Intraocular Pressure and Central Corneal Thickness Associated with Glycemic Control in Indonesian Type 2 Diabetes Mellitus Patients: A Hospital Based Study

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Abstract:
Aim: *To analyze of intraocular pressure and central corneal thickness associated with glycemic control in Indonesian type 2 diabetes mellitus patients.*
Materials and Methods: *A prospective, analytical observational with cross sectional study was conducted in Universitas Sumatera Utara Hospital, Medan, Indonesia from February 2020 to May 2020. The study included 66 participants with type 2 DM. The patients were investigated for HbA1c level and ophthalmology examination including visual acuity (VA), intraocular pressure (IOP) measurement by Goldmann Applanation Tonometer, central corneal thickness with SD Optovue OCT.*
Results: *This study showed a significant correlation between HbA1c variations with IOP (p=0.037) and CCT (p= 0.045). There is also significant correlation between HbA1c with VA (r =0.245; p=0.048), IOP (r=0.270; p=0.028), CCT (r=0.308; p=0.012) and duration of DM (r=0.414; p= 0.001)*
Conclusion: *Higher HbA1c correlated with elevated IOP and thicker CCT as a risk factor for glaucomatous damage in Type 2 Diabetes Mellitus patients.*
Keyword: *IOP, CCT, HbA1c, Type 2 Diabetes Mellitus*

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I. Introduction

Diabetes Mellitus (DM) defined as a disease characterized by hyperglycemia and disorders of carbohydrate, fat, and protein metabolism associated type 1 diabetes or type 2 diabetes from secretion of insulin.[1] Type 2 diabetes also known as insulin-free diabetes mellitus (DMTTI), the incidence is about 90 - 95% of total DM cases and has increased markedly in Asian countries.[2] Due to change in lifestyle specially in Asia region, type 2 diabetes become a major public health problem that induces complications specific in microvascular complication which contribute to ocular complications including elevated intraocular pressure and risk of glaucomatous damage that can be cause of irreversible blindness.[3]

According to the latest International Diabetes Federation (IDF) figures, there are currently 463 million people living with DM and the total expected to rise 700 million by 2045. In Indonesia, according to the IDF, there were 9.1 million people with DM in 2014, expected increase to 14.1 million people in 2035. Based on these data, in 2014 Indonesia was ranked 5th in the world for people with diabetes.[4,5]

IOP is the fluid pressure inside in the eye. Higher IOP is a risk factor for developing glaucoma and the effective treatment of glaucoma is reduction the IOP. This condition can use to evaluate the distribution and risk factors of IOP for glaucoma Thus of this condition to known the risk factors and distribution of IOP for glaucoma prognosis and prevention. Many factors related to IOP, such as blood pressure (BP), age, gender, genetic, diabetes mellitus (DM), central corneal thickness (CCT), but the results were different in some studies.[6,7]

The underlying pathogenesis linking diabetes and elevated IOP have not been explained certainly. One study by Roy have explained that high glucose levels induced excess extracellular matrix (ECM) synthesis by cells of trabecular meshwork that can leads to aqueous outflow obstruction.[8] Pimentel study suggest that small vessel involvement in diabetes may cause the optic nerve become more susceptibility to pressure related damage, but whether variations in glucose levels could lead IOP is not known.[9] Paulsen et al report that hyperglycemia has been shown to lead in conversions at cellular level affecting the corneal endothelial cells, which can cause possibility to change central corneal thickness and responsible to maintaining stromal hydration by actively pull-out water in accordance with the levels of blood glucose.[10] A nother studies suggest that hyperglycemic condition may disrupt cell and repair function in cornea and potential to affecting the central corneal thickness.[11,12,13] Many previous studies report the correlation between DM and IOP but did not consider CCT measurement, which one of possible factor to IOP regulating.[14,15]

Central corneal thickness is important as an indicator pump of corneal endothelium and corneal health and serving as an index for corneal hydration and metabolic.[16] Some study from a population-based study showed that patient with diabetes had thicker cornea.[17] IOP may lead to thinner and thicker of central corneas.[18,19] This further suggest that importance to measure CCT when interpreting the IOP measurement. Glycated haemoglobin (HbA1c) is an important indicator for control glycemic.[20] Some studies have showed that higher IOP was correlated with higher HbA1c, while another study found no correlation.[15]

The strong evidence suggest that systemic condition and ocular biometric parameters are affected by environmental factors and genetic.[21,22] Specifically, Indonesia has multifactorial ethnic that influenced by environmental and hereditary factors, the relationship between type 2 DM with intraocular pressure and central corneal thickness still needs to be investigated. As my knowledge, there is no study has investigated the correlation between type 2 DM, IOP and CCT in Indonesian population specially in North Sumatera, we though to analyze the glycated haemoglobin level correlated with intraocular pressure and central corneal thickness in Type 2 DM in Indonesian population.

II. Material And Methods

The study was analytical prospective with cross sectional study comprising sixty-six type 2 DM patients referred from Internal Medicine Department to Ophthalmology Department. Subjects were recruited with consecutively method at Universitas Sumatera Utara Hospital, North Sumatera, Indonesia from February 2020 to May 2020. The study was conducted in accordance with the ethical standards of Helsinki Declaration and approved by Medical Faculty Universitas Sumatera Utara Ethics Committee and was obtained from all patients.

Inclusion criteria: Type 2 DM patients, aged ≥ 18 years, and approved the consent form. Exclusion criteria: Type 2 DM with anterior segment infection, cataracts, diabetic retinopathy, and patients taking concurrent topical and oral steroids.

Procedure:

All the subjects underwent ophthalmology examination included best correction visual acuity, intraocular pressure, and central corneal thickness. The primary data of patients such as age, gender, HbA1c level, intraocular pressure, central corneal thickness, duration of DM were documented.

The IOP measurement using Goldmann Applanation Tonometer Haag-Streit (R900) that was calibrated to the best readings. Central corneal thickness was measurement using SD OCT Optovue. Goldmann Applanation Tonometer.[23] This study was conducted by one ophthalmologist and measure at the same time to avoid diurnal variation by using the same Goldmann Applanation Tonometer and CCT tools. HbA1c measurement using HbA1c kit with High Performance Liquid Chromatography (HPLC) methods.[24] Based on Indonesian Association of Endocrinology (PERKENI) classification of HbA1c level divided 2 groups: HbA1c<6,5% indicate good glycemic control and HbA1c ≥ 6,5% indicate poor glycemic control.[4]

Statistical Analysis:

Data was collected and analyzed by using SPSS version 26 in all participants. We used Kolmogorov-Smirnov for normally distributed variables. Chi-square test was used to analyze correlation HbA1c level with IOP and CCT. Pearson test and Spearman Test was used to analyze correlation HbA1c with Sex, Age, Visual acuity, IOP and CCT and duration of type 2 DM. A value of < 0.05 was considered significant.

III. Result

In this study as many 66 patients with type 2 diabetes mellitus that fulfill inclusion criteria were included to analyzes. The table 1 showed the clinical and demographic baseline characteristics.

Table 1. The clinical and demographic baseline characteristic

Variable	N	%	*Mean ± SD*	*Min*	*Max*
Sex					
Male	19	28.8			
Female	47	71.2			
Age			56.50 ± 7.045	43	79
26-45 y.o	5	7.6	43.60 ± 0.894	43	45
46-65 y.o	56	84.8	56.23 ± 4.234	48	64
>65 y.o	5	7.6	72.40 ± 5.857	66	79
Visual acuity (LogMar)			0.606 ± 0.4627	0.0	1.3
-0.2-0.1	20	30.3	0.050 ± 0.0513	0.0	0.1
0.2-0.5	11	16.7	0.409 ± 0.1300	0.2	0.5
0.6-0.9	15	22.7	0.760 ± 0.1549	0.6	0.9

1.0-1.3	20	30.3	1.155 ± 0.1395	1.0	1.3
IOP			16.94 ± 5.239	10	30
≤21 mmHg	47	71.2	14.09 ± 2.527	10	21
>21 mmHg	49	28.8	24.00 ± 2.981	22	30
CCT			553.11 ± 29.957	498	612
< 540 um (thin)	21	31.8	516.95 ± 9.708	498	535
540-560 um (average)	18	27.3	551.17 ± 7.229	540	560
>560 um (thick)	27	40.9	582.52 ± 13.423	563	612
HbA1c			8.453 ± 2.4824	5.0	13.4
Good glicemic: <6.5%	19	28.8	5.968 ± 0.3713	5.0	6.4
Poor glicemic:≥ 6.5%	47	71.2	9.457 ± 2.2523	6.7	13.4
Duration of DM			7.29 ± 4.187	2	15
DM ≤5 years	23	34.8	2.65 ± 0.775	2	4
DM 6-10 years	27	40.9	7.78 ± 1.281	6	10
DM ≥10 years	16	24.2	13.13 ± 1.586	11	15

Abbreviations: SD, standard deviation; Min, minimal; Max, maximal; IOP, intraocular pressure; CCT, central corneal thickness; y.o , years old

Table 2. Correlation HbA1c level with IOP

	HbA1c			
IOP	**< 6.5%**	**≥ 6.5%**	**N**	**p.**
≤ 21 mmHg	17(25.8)	30(45.4)	47(71.2)	0.037*
> 21 mmHg	2(3)	17(25.8)	19(28.8)	
Total	19(28.8)	47(71.2)	66(100)	

Notes : * Chi-square test

Table 3. Correlation HbA1c level with CCT

	HbA1c			
CCT	**< 6.5%**	**≥ 6.5%**	**N**	**p.**
< 540 µm	10(15.2)	11(16.7)	21(31.8)	0.045*
540-560 µm	5(7.6)	13(19.7)	18(27.3)	
>560 µm	4(6.1)	23(34.8)	27(40.9)	
Total	19(28.8)	47(71.2)	66(100)	

Notes : * Chi-square test

Table 4. Correlation HbA1c with Sex, Age, Visual acuity, IOP, CCT and duration of type 2 DM

	HbA1c	
Variable	*R*	*p*.value
Sex		0.049*
Age	0.054	0.669
Visual acuity	0.245	0.048**
IOP	0.270	0.028**
CCT	0.308	0.012**
Duration of DM	0.414	0.001**

Notes : * Pearson test ** Spearman's test

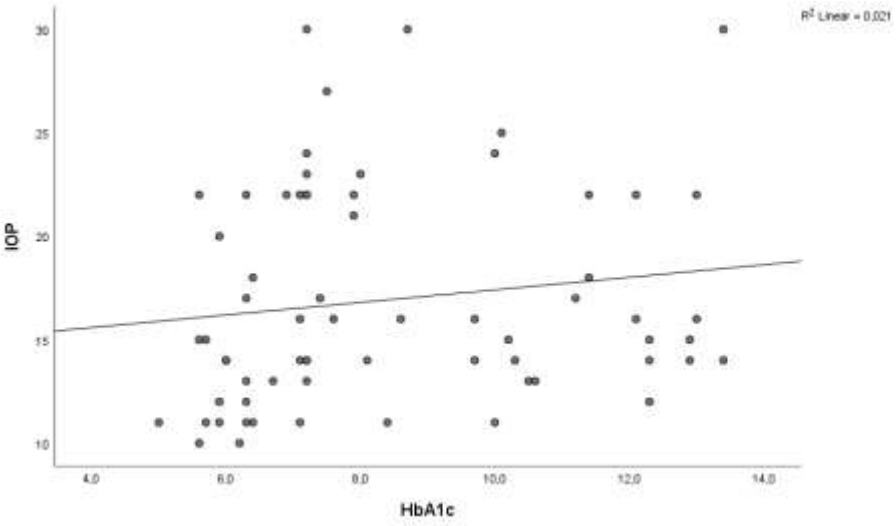

Figure 1. *Scatter Plot* between HbA1c and IOP

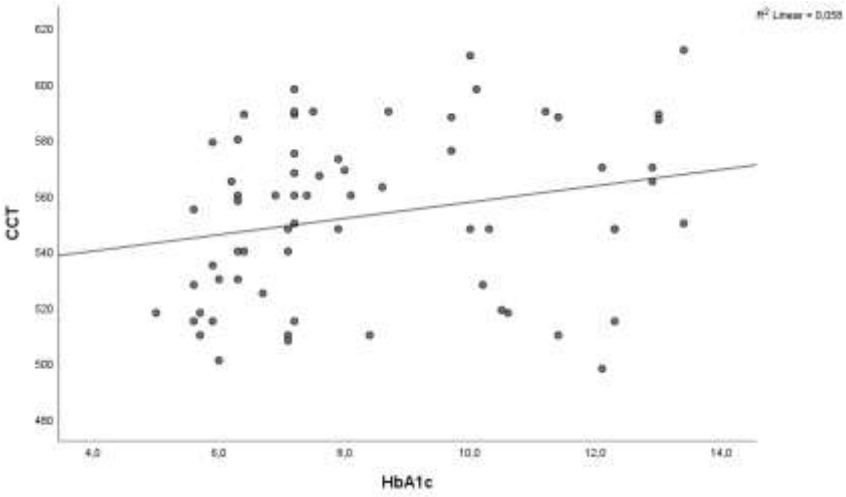

Figure 2. *Scatter Plot* between HbA1c level with CCT

IV. Discussion

Although on ophthalmology examination have history of type 2 DM, until now it was not known whether glycemic control could influence the IOP and CCT. In this study report that provides the glycemic control (HbA1c) with IOP and CCT based on poor glycemic control (HbA1c $\geq$ 6.5%) and good glicemic control (HbA1c <6.5%). Our findings that the majority of this patients are female (71,2 %), age range 43-79 years old with the youngest age 43 years old and the oldest age 79 years old. Prabhavati study reported that female more suffering DM cause of female more to lose protection of blood vessels due to hormonal dysfunction in which correlated with estrogen deficiency, especially after menopause and the average of DM is 41-60 years old.[25] The duration of suffering type 2 DM is 2-15 years. The study reported found the risk of metabolic syndrome in younger age with suffering of type 2 DM in longer duration.[26,27] In this study we found a significant correlation between levels of HbA1c on VA, IOP, CCT and duration of type 2 DM. HbA1c levels correlated with higher IOP in poor glycemic control ($p<0.05$) which explained that magnitude of higher glycemic control in IOP. Dysfunction of trabecular meshwork may increase IOP, this was related with the accumulation of advanced glycation end (AGE) products which induce apoptosis of human trabecular meshwork cells and promote cellular senescence.[28] The current study suggest similar with various studies in the past. Baltimore Eye Study found an association between diabetes mellitus with elevated IOP.[29] Zhao et al report that duration of diabetes as a significant risk for developing glaucoma.[30] Rotterdam and Framigham study report that hyperglicemia as a risk factor for elevated IOP. However the lower IOP shown in controlled diabetic patients.[30] Larsen et al reported patient with severe hypoglicemia have a lower IOP.[31] Barbados Eye Study reported positively correlated between higher IOP with age and systolic blood pressure.[6] The exact mechanism between higher IOP and DM still investigated. The possible factor that high glucose levels can leads the aqueous outflow obstruction by induces excess ECM synthesis by cells of trabecular meshwor.[8] Pimentel study suggest that small vessel

involvement in diabetes may cause the optic nerve become more susceptibility to pressure related damage.[9] The Blue Mountain Study report that osmotic gradient cause of increased fluid in intraocular space created raised blood level.[32] Some study reported that genetic factor asociated with family history also influence.

Central corneal thickness is important as an indicator pump of corneal endothelium and corneal health and serving as an index for corneal hydration and metabolic.[16] In this study our findings the significance increase of CCT with poor glicemic control ($p<0.05$), which explained that the influence of CCT with glicemic control. The current study similar with Singapore Malay Study that diabetes and hyperglicemia correlated with thicker CCT in Singapore's Malay population.[33] Another population-based study also documented correlation diabetes mellitus with thicker central cornea[34], but another population-based study not found significant correlation between CCT and diabetes mellitus.[35,36] Corneal endothelium in diabetic patients is considered as a tissue under continuous metabolic stress and it has increased coefficient of variation of endothelial cell area, increased corneal auto fluorescence and decreased percentage of hexagonality.[37] It is postulated that hyperglycemia may lead to accumulation of sorbitol in cornea and sorbitol may result in the influx of water from aqueous into cornea. CCT is related of IOP measurement. Measuring IOP with applanation tonometry is examined in flat area of the cornea. Therefore a thinner cornea may to underestimation and a thicker cornea may lead to overestimation of IOP.[38]

The current study found the positively correlation between higher HbA1c as an indicator of glycemic control with VA (r= 0.245), IOP (r= 0.270), CCT (r=0.308), duration of DM (r=0.414) as a risk factor of glaucoma, it means that higher HbA1c level, the IOP getting raised and the CCT is getting thicker. Based on our findings, glycemic control level have influence magnitude of IOP and CCT as revelant for diagnostic, treatment management and prognosis. Clinicians should consider the patient's glicemic control level variations concurrently with IOP and CCT assessment in diabetes mellitus.

The limitation of our study, it wasn't a population based but rather health centre based, may cause a selection bias but further studies are needed to prospective longitudinal clinical trials on larger populations and more longer times to conclude another risk factor which correlated with diabetes mellitus.

V. Conclusion

In conclusion, the light of our findings that HbA1c as an indicator of glycemic control in DM correlated with IOP and CCT. Measuring IOP and CCT in diabetics patients should be mandatory in order to identify patients at higher risk of developing severe eye complications and enabling the ophthalmologist to treat more accurately.

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