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The Role of High-Density Lipoprotein Cholesterol to Ganglion Cell Complex Thickness in Primary Open-Angle Glaucoma with a History of Type 2 Diabetes Mellitus

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Abstract. *Introduction:* One of glaucoma's risk factors is diabetes, which can be through changes in biochemical pathways, changes in blood flow by disorders of the endothelial auto regulation of blood vessels that cause glaucomatous and increases oxidative stress by lipid metabolism. *Method:* A cross-sectional study was organized at Universitas Sumatera Utara Hospital and partnership hospitals on 33 POAG patients with history of type 2 diabetes and 32 POAG patients without diabetes. All study subjects were examined for venous blood samples to measure HDL-C levels and assessed GCC thickness using SD-OCT. *Results:* The mean HDL-C in the POAG group with a history of type 2 diabetes was 48.24±11.53 mg/dL and in the other group was 44.59±8.30 mg/dL. The results of GCC thickness for each parameter and the relationship between HDL-C and GCC did not show a significant difference between the POAG with a history of type 2 diabetes groups and the POAG without diabetes groups ($p>0.05$). *Conclusion:* There was a decrease in GCC thickness values (average GCC, superior GCC, and inferior GCC) and increase in FLV, GLV values for POAG patients with type 2 diabetes compared to POAG patients without diabetes, but no statistically significant difference was found between two groups.

Keywords: type 2 diabetes, Primary open-angle glaucoma, Ganglion cell complex, HDL-C

Introduction

Nowadays, diabetes has become a global public health issue. In 2019, it was reported that there were approximately 463 million adults were living with diabetes. The number is projected to rise to 700 million by 2045 (the International Diabetes Federation, 2019). More than half of people with diabetes (79%) were living in low and middle-income countries, including Indonesia. Around 10 million people with diabetes mellitus were living in Indonesia (IDF, 2019; INFODATIN, 2018). Risk factors that cause retinal neurodegeneration due to diabetes mellitus (DM) included oxidative stress, increased levels of AGEs (Advanced Glycation Endproducts), activation of the local angiotensin renin system, accumulation of glutamate, apoptosis and decreased neuroprotective factors (Iwona, 2016).

High-Density Lipoprotein (HDL) has a density more than 1.063 g/ml and small diameter about 5-17 nm (Assmann, 2004). The basic form of HDL consists of 2-5 molecules of apo A-1 and 100 molecules of phospholipids. These molecules have pleiotropic, anti-atherogenic, antioxidant, immunity effects, also cell proliferation and migration (Lüscher et al., 2014). Hellgren et al stated that hyperglycemia not only affects blood vessels but also neuroretina which results in disturbances and loss of visual acuity (Hellgren et al., 2014).

Primary Open Angle Glaucoma (POAG) is accompanied by characteristic cupping and optic disc atrophy, loss of field of view, open-angle image, in the absence of any ocular conditions or any underlying systemic conditions. This type of glaucoma is a progressive and chronic optic neuropathy. In most cases of POAG, the intraocular pressure rises above the normal range reflecting a reduced facility of aquatic humor flow (Khurana, 2015). Loss of the retinal nerve fiber layer (RNFL) has previously been observed in patients with type 1 and type 2 DM. Borooah M et al in 2018 stated that there was a statistically significant decrease from the average IPL, GCL, and RNFL in type 2 diabetes with mild-degree diabetic retinopathy

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(DR) and without DR. This suggests that the neuroretinal changes occur before the vascular changes in diabetic retinopathy take place (Borooah et al., 2018; Shi et al., 2018). The IPL, GCL and RNFL form a ganglion cell complex can be measured using the SD-OCT tool. In 2017, Vidas et al. state that the GCC parameters had a better ability to distinguish and predict patients with glaucoma compared to examining the RNFL thickness. To the best of authors` knowledge based on several studies, investigators have not found any studies that explain the relationship of HDL-C levels to the GCC thickness in POAG patients with a history of type 2 diabetes. This prompted investigators to determine the relationship between HDL-C levels and GCC thickness in POAG patients with a history of type 2 diabetes and POAG without diabetes.

Material and Methods

This study was an analytic observational with cross-sectional data collection method and the sampling technique is consecutive sampling. Data were taken from 65 subjects and divided into two groups (33 subjects diagnosed with POAG with a history of type 2 diabetes and 32 subjects diagnosed with POAG without diabetes) at the Universitas Sumatera Utara Hospital and the Partnership Hospitals, Medan, Indonesia. Another requirement is that patients with visual acuity ≥ 1.00 and give consent to participate in this study. The study was organized from October 2020 to January 2021. This study was approved by the Health Research Ethical Clearance Committee of the Medical Faculty of Universitas Sumatera Utara, Medan, Indonesia (No.766/KEP/USU/2020).

All subjects had gone through screening inclusion and exclusion criteria. Exclusion criteria included POAG patients with refractive errors, optic neuritis, retinal disorders, comorbid diseases other than DM, and on certain medications (taking steroids, statins, fibrates, ethambutol, and antioxidants). All measurement were done by glaucoma specialist, ophthalmology resident and laboratory doctor. Furthermore, snellen chart examination to evaluate visual acuity, slit lamp microscope (@Righton) to evaluate the anterior segment, gonioscopic testing (Ocular Three Mirror Universal Laser Lens) to evaluate the angle structure, indirect ophthalmoscope (@HEINE Opthotechnik OMEGA500 to evaluate the posterior segment examination), intraocular pressure measurements with transpalpebral tonometer (Easyton EZTN-01), visual field examination with humprey perimetry (Kanghua APS-T00 Touchscreen Projection), and examination by SD-OCT (RTVue Model-RT100) to assess the thickness of the GCC (average GCC, superior GCC, inferior GCC, global loss volume (GLV), and focal loss volume (FLV)) with measurement results based on significance, namely normal P> 5%, borderline P <5% and outside normal P <1%. POAG was diagnosed based on elevated IOP, optic nerve head changes detected by indirect ophthalmoscope and defects of visual field. In this study, the POAG group with a history of type 2 diabetes was a referral from a specialist in internal medicine and was proven by the results of measuring HbA1c (> 6.5%).

Laboratory testing was performed at the Prodia Clinical Laboratory, Medan, Indonesia. HDL-C levels were checked using the homogeneous essay method (@Architec c8000) by sampling 3 cc of venous blood. The measurement of HDL-C were divided into high (> 60 mg/dL), normal (40-59 mg/dL) and low levels (<40 mg/dL).

This study was analyzed by using the T-independent test, Mann-Whitney and Kruskal Wallis, Pearson correlation test if the data were normally distributed and the Spearman correlation test if otherwise. All data were processed by using SPSS software version 23.0. The P-value which shows results less than 0,05 means that research is statically significant.

Results

A total of 65 subjects were obtained from Universitas Sumatera Utara Hospital and Partnership Hospitals from October 2020 to January 2021. The study subjects were predominantly female, 19 in the POAG group with type 2 diabetes and 21 women in the POAG

group without diabetes. However, there was found to be no statistically significant sex difference. The 46-65 years age group was found to be most diagnosed with POAG, both with type 2 diabetes and without diabetes (27 vs 17 people, p = 0.049). Other characteristics can be seen in Table 1.

Table 1. Baseline Characteristics

Subject Characteristics	POAG with T2DM (n = 33)	POAG without DM (n = 32)	P
Sex, n (%)			
Male	14 (42,4)	11 (34,4)	0,505
Female	19 (57,6)	21 (65,6)	
Age, n (%)			
20 – 45 years old	4 (12,1)	10 (31,2)	0,047
46 – 65 years old	27 (81,8)	17 (53,2)	
> 65 years old	2 (6,1)	5 (15,6)	
Onset of DM, n (%)			
< 5 years	13 (39,4)	-	
6 – 10 years	13 (39,4)	-	
> 10 years	7 (21,2)	-	
HbA1c, n (%)			
< 6,5 %	9 (27,3)	-	
> 6,5%	24 (72,7)	-	
HDL, n (%)			
< 40 mg/dL	9 (27,3)	10 (31,2)	0,251
40 – 60 mg/dL	19 (57,6)	21 (65,6)	
> 60 mg/dL	5 (15,2)	1 (3,1)	
IOP, n (%)			
Normal (< 21 mmHg)	16 (48,5)	12 (37,5)	0,371
Increased (> 21 mmHg)	17 (51,5)	20 (62,5)	
SAP MD, n (%)			
Mild	14 (42,4)	16 (50)	0,005
Borderline	5 (15,2)	13 (40,6)	
Severe	14 (42,4)	3 (9,4)	
SAP PSD, n (%)			
Normal	8 (24,2)	16 (50)	0,031
Abnormal	25 (75,8)	16 (50)	
Average GCC, n (%)			
Normal	28 (84,8)	26 (81,2)	0,344
Borderline	0	2 (6,2)	
Outside Normal	5 (15,2)	4 (12,6)	
Superior GCC, n (%)			
Normal	26 (78,8)	21 (65,6)	0,237
Borderline	3 (9,1)	2 (6,2)	
Outside Normal	4 (12,1)	9 (28,1)	
Inferior GCC, n (%)			
Normal	28 (84,8)	27 (84,4)	0,999
Borderline	1 (3)	1 (3,1)	
Outside Normal	4 (12,1)	4 (12,5)	
FLV, n (%)			
Normal	9 (27,3)	11 (34,4)	0,538
Borderline	1 (3)	3 (9,4)	
Outside Normal	23 (69,7)	18 (56,2)	
GLV, n (%)			
Normal	20 (60,6)	23 (71,9)	0,341
Borderline	0	2 (6,2)	
Outside Normal	13 (39,4)	7 (21,9)	

T2DM = type 2 diabetes mellitus; HbA1c = hemoglobin A1c; IOP = intraocular pressure; MD = mean deviation; PSD = pattern standard deviation; SAP = standard automated perimetry; GCC = ganglion cell complex; FLV = focal loss volume; GLV = global loss volume

The Relationship between GCC Thickness in POAG Patients with a History of Type 2 diabetes and POAG without Diabetes

Table 2 presents the thickness of the GCC, where the average GCC, superior GCC and inferior GCC were lower in POAG patients with history of type 2 diabetes, compared with POAG patients without diabetes. This is inversely proportional to the greater FLV and GLV in POAG group with history of type 2 diabetes compared with the POAG group without diabetes. The mean GCC, superior and inferior GCC in the POAG group with a history of type 2 diabetes appeared lower than that in the POAG group without diabetes (p> 0.05) (Table 2). The relationship between HDL-C and GCC in both groups was no statistically significant (p value> 0.05; Table 3).

Table 2. GCC thickness in POAG sufferers with a history of type 2 diabetes and POAG without diabetes

GCC Thickness	POAG with T2DM (+) n = 33	POAG without DM n = 32	P
Average GCC, µm			
Mean (SD)	92,74 (11,84)	96,42 (16,80)	0,310
Median (min – max)	94,46 (63,83 – 111,91)	96,59 (47,95 – 144,46)	
Superior GCC, µm			
Mean (SD)	91,62 (12,57)	97,70 (19,21)	0,288
Median (min – max)	91,35 (63,07 – 111,58)	96,11 (64,15 – 170,11)	
Inferior GCC, µm			
Mean (SD)	94,30 (14,39)	95,36 (18,49)	0,508
Median (min – max)	95,88 (58,90 – 130,16)	97,37 (28,99 – 126,02)	
FLV, %			
Mean (SD)	6,22 (5,50)	5,40 (6,40)	0,369
Median (min – max)	5,12 (0,01 – 20,96)	3,49 (0,02 – 32,02)	
GLV, %			
Mean (SD)	10,11 (7,57)	9,07 (9,08)	0,379
Median (min – max)	8,37 (0,17 – 24,06)	5,66 (0,28 – 43,99)	

T2DM = type 2 diabetes mellitus; GCC = ganglion cell complex; FLV = focal loss volume; GLV = global loss volume

Table 3. Relationship of HDL-C to GCC in POAG patients with type 2 diabetes and without diabetes

HDL-C	Average GCC p>5%		p<5%		p<1%		*P value* (r)	
	DM (+)	DM (-)	DM (+)	DM (-)	DM (+)	DM (-)	DM (+)	DM (-)
Low	8 (88,9)	7 (70)	0	0	1 (11,1)	3 (30)	0,669 (-0,77)	0,929 (0,016)
Normal	15 (78,9)	18 (85,7)	0	2 (9,5)	4 (21,1)	1 (4,8)		
High	5 (100)	1 (100)	0	0	0	0		
GCC Superior								
Low	7 (77,8)	7 (70)	2 (22,2)	1 (10)	0	2 (20)	0,217 (-0,221)	0,091 (-0,304)
Normal	15 (78,9)	13 (61,9)	1 (5,3)	1 (4,8)	3 (15,8)	7 (33,3)		
High	4 (80)	1 (100)	0	0	1 (20)	0		
GCC Inferior								
Low	8 (88,9)	7 (70)	0	0	1 (11,1)	3 (30)	0,932 (0,015)	0,686 (-0,074)
Normal	15 (78,9)	19 (90,5)	1 (5,3)	1 (4,8)	3 (15,8)	1 (4,8)		
High	5 (100)	1 (100)	0	0	0	0		
FLV								
Low	3 (33,3)	4 (40)	0	0	6 (66,7)	6 (60)	0,531 (0,113)	0,999 (0,001)
Normal	5 (26,3)	6 (28,6)	1 (5,3)	3 (14,3)	13 (68,4)	12 (57,1)		
High	1 (20)	1 (100)	0	0	4 (80)	0		
GLV								
Low	5 (55,6)	7 (70)	0	0	4 (44,4)	3 (30)	0,997 (0,001)	0,572 (0,104)
Normal	13 (68,4)	15 (71,4)	0	2 (9,5)	6 (31,6)	4 (19)		
High	2 (40)	1 (100)	0	0	3 (60)	0		

GCC = ganglion cell complex; FLV = focal loss volume; GLV = global loss volume

Discussion

The characteristics of the subjects in the study are parallel to the study by Pasquela in the Nurses Health Study (NHS) in Boston in 2006 which explained that the incidence of type 2 diabetes was related with the risk of POAG in women (Louis, 2006). This might be because of women are more susceptible to lose the blood vessel protection that occurs because of estrogen deficiency related to hormonal dysfunction, especially after menopause which will cause metabolic dysregulation (Prabhavathi et al., 2014). According to Khan et al, in 2007 women are more prone to changes in vascular coagulation function, blood vessel function, and lipid profiles (especially cholesterol and HDL) than men (Khan et al., 2012). In addition to gender, age is also a risk factor for POAG in DM patients as found in this study, namely the range 46-65 years. In line with that, Pavlijasevic et al in 2009 stated that the risk of POAG is genetically likely to appear in older life (around 50 years or more) and metabolic disorders can occur together with glaucoma with other accompanying risk factors, such as age, gender and family history (Pavljašević & Aščerić, 2009).

Some studies reveal that increased IOP is highly correlated. DM can also be associated not only with glaucoma, but also with secondary effects on systemic or local factors. However, our study did not show a statistically significant causal relationship between IOP and POAG in either group. This study found the effect of DM on the severity of POAG (seen from the perimetric values of MD and PSD in Table 1). The level of oxidative DNA damage are significantly correlated to the increase IOP and visual field defects in type 2 diabetes patients (Saccà, 2005).

A study by Masitha et al in 2020 in North Sumatra found that subjects with higher LDL-C and HbA1c levels were associated with higher IOP, defects in visual field, thinner RNFL, and correlates with the length of suffering from type 2 diabetes (Masitha et al., 2020). The onset of DM has also been considered as a predisposing factor for the development of POAG resulting in depletion of the RNFL at an early stage. In DM, it is known that the autoregulation of the retina and the nerves of the eye are affected by the vascular complications, resulting in damage to the vascularization of the eye, which induce ischemic damage to ganglion cells and optic nerve fibers, further causing a glaucomatous state (Song et al., 2016).

Diabetes is associated with quantitative changes in the number of circulating lipids, particularly an increase in triglycerides and LDL, also decrease in HDL. The state of inflammation that continues to increase in DM cases results in large changes in HDL proteomes due to oxidation and glycation; this change not only removes HDL from its normal function but also converts it into proatherogenic particles (Farbstein & Levy, 2012). Hyperglycemia and glycation can also cause HDL dysfunction by decreasing its antioxidant activity. Several studies have suggested that low HDL-C levels are statistically significant with POAG. The study in India by Rema et al., in 2016 also confirmed a significant difference between HDL-C levels in people with type 2 diabetes and diabetic retinopathy (Rema et al., 2016). Study by Sasso et al. in 2019 explained that there was a very significant relationship between diabetic retinopathy and increased HDL-C (> 60 mg / dL), as well as the research of Yokomichi et al. 2016 in evaluating the relationship between changes in IOP and metabolic syndrome parameters, it was found that increased triglyceride levels and changes in levels HDL-C accompany an increase in IOP (Sasso et al., 2019; Yokomichi et al., 2016).

The Study by Lima found that the group of type 2 diabetes patients have a thinner GCC compared to the control group without DM using SD-OCT. This result supports the concept that diabetes has an early neurodegenerative effect on the retina (Lima, 2016). Table 2 also shows the same results, namely GCC was thinner in the POAG group with DM than in the control group (sequentially; average GCC 92.74 ± 11.84, superior GCC 91.62 ± 12.57 and inferior GCC 94, respectively. 30 ± 14.39 vs average GCC 96.42 ± 16.8, superior GCC 97.70 ± 19.22 and inferior GCC 95.36 ± 18.49), but no significant difference was found. This

insignificant result was also found in the study of Demir M et al. 2014 which explained that the depletion of GCC and RNFL did not have a significant difference in DM patients compared to controls (Demir et al., 2014).

Several mechanisms of GCC loss in hyperglycemia are (1) hyperglycemia-induced nerve damage or ischemic changes that lead to GCC depletion in diabetes; (2) high extracellular glucose elevates the glucose oxidative metabolism in the mitochondria and becomes free radicals that directly damage the neural retinal; (3) glucose can become sorbitol which has poor permeability through the cell membrane resulting in changes in cell structure; and (4) in increasing glutamate levels, increased synaptic activity and changes in glutamate absorption are associated with excitotoxicity which results in the loss of ganglion cells. FLV represents the mean GCC loss in focus over the map area to detect focal GCC damage. Meanwhile, GLV gives the meaning of the number of negative fractional deviations on the entire map. FLV and GLV have a better diagnostic value than the other GCC depletion averages (Srinivasan et al., 2016). Our study demonstrated clinically FLV value (median (min-max) 5.12 (0.01-20.96)) and a GLV value (median (min-max) 8.37 (0.17-24.06)) which was greater in the POAG group with type 2 diabetes compared with the POAG group without diabetes but statistically, there was no significant difference between the two groups. In contrast to 2016, Salvi et al. (2016) got a significant difference in FLV and GLV values in patients with type 2 diabetes compared to patients without diabetes (Salvi et al., 2016).

Oxidative stress is the result of high production of reactive oxygen species (ROS) and low antioxidants defense. Apoptosis induced by oxidative stress in retinal ganglion cells has been implicated in the pathogenesis of glaucoma. Circulating HDL particles, especially HDL-3 protect low-density lipoproteins (LDL) from free radicals associated oxidative degradation and inhibit pro-inflammatory oxidized lipid production (Betzler et al., 2020). The study of Gonome T., et al. in 2020 in Japan in examining the protective effect of astaxanthin (AST) as an antioxidant against the thickness of GCC in animal models (mice), proved the role of lipid profiles and anti-oxidant effects on HDL-C in the progression of retinal nerve tissue damage. Reduction in the GCC depletion due to the protective effect of AST against glutamate neurotoxicity and oxidative stress in the retina has been indicated to the type 2 diabetes (Tanaka-Gonome et al., 2020).

However, it is different from what we found that there was no significant correlation between low HDL-C levels and the risk of POAG. This is in line with studies by Dube Mike 2019, Kurtul BE 2017, Manohar 2013, and Xu M et al 2020 in China who reported genetic causal effects of HDL-C on POAG (Dube, 2019; Kurtul et al., 2017; Manohar et al., 2013). Genetic linkages in this lipid profile used four methods (IVW, weighted median, weighted mode, MR-Egger regression) and showed no relationship between plasma levels (LDL-C, triglycerides, and HDL-C) with the occurrence of POAG (Xu et al., 2020). Yilmaz et al in 2016 also explained that there was no statistically significant relationship between the role of the PON-1 allele (HDL dysfunction) on the occurrence of glaucoma (Yilmaz et al., 2015). Srinivasan et al 2016 research in Australia also explained that HbA1c was not significantly correlated with the FLV value (Spearmen rho = -0.003, p = 0.969) and the GLV value (Spearmen rho = -0.036, p = 0.665) (Srinivasan et al., 2016).

Limitations of this study used an analytical observational method to determine and describe the role of HDL-C to the thickness of GCC in POAG patients, regardless of the relationship between other subject characteristic variables to GCC. Apart from the limited and relatively small number of samples, the investigators did not include other lipid profile measurements that are related to the mechanism of glaucoma in hyperlipidemia.

Conclusions

There was a clinically significant difference in the measurement of GCC thickness in the POAG group with history of type 2 diabetes and POAG without diabetes but there was no significant difference statistically. There was no statistically significant relation between HDL-C and average GCC, superior GCC, inferior GCC, FLV, and GLV. Thus, HDL-C levels have a relationship with GCC thickness which will affect glaucomatous damage in patients with type 2 diabetes, so it is recommended for internists to refer type 2 diabetes patients to an ophthalmologist for GCC thickness examination.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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