Relationship between Serum Levels of 25-Hydroxy Vitamin D and Ganglion Cell Complex (GCC) Thickness in Primary Open Angle Glaucoma Patients

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Abstract. *Background.* Vitamin D is one of antioxidants regulating the protective function of nerve cells in central and optic nervous systems. Vitamin D actively works by suppressing oxidative damage, reducing the production of ROS, increasing the viability of larger cells, and preventing the secretion of pro-inflammatory cytokines, which in some studies is believed to be an independent risk factor for glaucoma.

Objective. To determine the relationship between serum levels of 25-hydroxy vitamin D and ganglion cell complex (GCC) thickness in primary open-angle glaucoma (POAG) patients.

Methods. Case control study design was conducted in 20 patients with POAG in comparison with 20 controls from the Ophthalmology Clinic in University of Sumatera Utara Hospital and affiliate hospitals from February to August 2021.

Results. The overall values of average, superior, and inferior GCC were lower in POAG than in control groups, although no significant difference ($p > 0.05$) was found. FLV and GLV were higher in POAG group compared to control group, had a significant difference in FLV and GLV values case and control group ($p<0.001$). The median serum 25-hydroxy vitamin D in POAG and control group was 2.70 (1.31 - 27.5) and 4.20 (1.19 - 37.11) ng/mL, respectively, but no significant difference ($p = 0.091$) was found. No significant relationship between serum 25-hydroxy vitamin D and all parameters of GCC thickness was found in both case group and control group ($p>0.05$).

Conclusion. Overall GCC thickness (average GCC, superior GCC, and inferior GCC) was lower in the POAG group compared to control group, although the relationship showed no difference between serum 25-hydroxy vitamin D and all parameters of GCC thickness.

Keywords: vitamin D, ganglion cell complex, POAG

Introduction

Glaucoma is the major cause of irreversible blindness, with primary open-angle glaucoma (POAG) accounted for nearly half of the patients, and patients with glaucoma are estimated to be more than 23 million by 2020 (Tham, 2014). Glaucoma is characterized by changes of the optic nerve head (ONH) and progressive loss of retinal ganglion cells (RGCs) (Kemenkes, 2007; Quigley, 2011).

In recent years, the focus of glaucoma research has been directed at finding more accurate methods for its early detection. The layers that become thinner in glaucoma are the three inner retinal layers: (i) the inner plexiform layer (IPL) including the dendrites; (ii) the ganglion cell layer (GCL) including the cell body, and (iii) the RNFL (retinal nerve fiber layer). These three layers form the ganglion cell complex (GCC) (Kim, 2016; Vidas et al., 2017).

Vitamin D level has been presented in various studies as risk factors of glaucoma. The mechanism of vitamin D role in glaucoma is still unknown, vitamin D has been widely known as an antioxidant and suppressor of inflammation genes. Various studies have correlated oxidative stress and vitamin D contribution in pathogenesis of glaucoma (Huynh, 2020).

Vitamin regulates neuroprotective functions in the central nervous system, including the optic nerve. Treatment with 1,25-dihydroxy vitamin D3 ($1,25(OH)_2D_3$) increased the oxidative

stress effects of hydrogen peroxide-induced toxicity on retinal pigment epithelial cells. Active vitamin D causes inflammation through antioxidant signaling pathways and suppression of oxidative damage and causes less reactive oxygen species (ROS), greater survival and less secretion of vascular endothelial cytokines and growth factors (Lucas et al., 2011; Schreiner, 1985; Tohari et al., 2019). Uro et al. (2015) found that low levels of vitamin D in older patients may be associated with a decrease in mean GCC thickness, which may indicate with optic nerve damage, before the onset of RNFL loss.

This study aims to reveal the relationship between serum 25 (OH) vitamin D levels and the ganglion cell complex (GCC) thickness in patients with POAG.

Methods

Case control study design from 20 POAG subjects and 20 subjects with normal eyes as control from the Ophthalmology Clinic of the University of Sumatera Utara Hospital and affiliate hospitals, since February 2021 until the number of samples achieved. The inclusion criteria was all POAG patients who came to the Ophthalmology Clinic, University of Sumatera Utara Hospital and affiliate hospitals. Exclusion criteria was patients with ocular disorders including corneal abnormalities and vitreous disease, history of secondary glaucoma or with other clinical history of optic neuropathy, history of systemic disease (hypertension, diabetes, and stroke). Control inclusion criteria was subjects with normal eyes and accepted to participate in this study.

The study started by providing explanations to patients and their families who fulfilled the inclusion criteria that fitted to the method and purpose of this study. Examination consisted of vital signs, visual acuity with Snellen chart, anterior segment with slit lamp and gonioscopy, intra ocular pressure (IOP) with trans palpebral tonometry, posterior segment with direct fundoscopy, visual field with Humprey perimetry. Spectral-domain optical coherence tomography (SD-OCT) assessed Ganglion Cell Complex thickness. The patient's venous blood sample was obtained for serum vitamin D levels by ELISA method. The results were recorded and analyzed using statistical analysis. Categorical data was presented in frequency distribution and numerical data that normally distributed as mean (standard deviation) or abnormally distributed data as median (minimum-maximum). Spearman's correlation test was tested to determine the relationship between serum vitamin D levels and GCC thickness.

Results

Characteristics of Research Subjects

Subjects in POAG group were mostly female for 14 (70%) patients while in the control group, most of them were male for 11 (55%) subjects. No differences were found in the characteristics of subjects based on gender in the two groups ($p = 0.110$). The largest age group in POAG group was 45-65 years for 14 (70%) patients, while control group was mostly <45 years old for 19 subjects (95%), and a significant statistically difference was found ($p < 0.001$).

Table 1. Characteristics of research subjects

Variable	POAG Group n = 20	Control Group n = 20	p
Gender, n (%)			
Male	6 (30)	11 (55)	0.110[a]
Female	14 (70)	9 (45)	
Age, years old, n (%)			
< 45	4 (20)	19 (95)	<0.001[b]
45 – 65	14 (70)	1 (5)	
> 65	2 (10)	0	

Intra ocular pressure, n (%)			
Normal (< 21 mmHg)	8 (40)	20 (100)	<0.001[c]
High (> 21 mmHg)	12 (60)	0	
Perimetry mean deviation (MD), n (%)			
Mild	10 (50)	19 (95)	0.007[b]
Borderline	8 (40)	1 (5)	
Severe	2 (10)	0	
Perimetry pattern standard deviation (PSD), n (%)			
Normal	12 (60)	12 (60)	1.000[a]
Abnormal	8 (40)	8 (40)	
Average GCC, n (%)			
Normal	13 (65)	20 (100)	0.016[b]
Borderline	1 (5)	0	
Outline Normal	6 (30)	0	
Superior GCC, n (%)			
Normal	7 (35)	20 (100)	<0.001[a]
Borderline	3 (15)	0	
Outline Normal	10 (50)	0	
Inferior GCC, n (%)			
Normal	12 (60)	20 (100)	0.008[a]
Borderline	2 (10)	0	
Outline Normal	6 (30)	0	
Focal Loss Volume (FLV), n (%)			
Normal	5 (25)	19 (95)	<0.001[b]
Borderline	0	1 (5.6)	
Outline Normal	15 (75)	0	
Global Loss Volume (GLV), n (%)			
Normal	8 (40)	20 (100)	<0.001[b]
Borderline	1 (5)	0	
Outline Normal	11 (55)	0	

Note: [a]*Chi Square*, [b]*Kruskal Wallis*, [c]*Fischer's Exact*

Twelve patients (60%) suffered from increased IOP in POAG group while there was none in control group. Significant difference in IOP value between the two study groups ($p<0.001$) was found. From the results of the MD perimetry examination, in POAG group, most of the cases were classified as mild for 10 patients (50%), while in the control group for 9 subjects (95%). There was a difference in MD perimetry between the case and control groups ($p=0.007$). From the results of the PSD perimetry examination, the case and control groups showed normal results in 12 subjects (60%) and no difference in PSD perimetry between the case and control groups ($p=1$).

GCC Thickness

Overall values of average, superior, and inferior GCC were lower in POAG than in control groups, although no significant mean difference ($p > 0.05$) was found. FLV and GLV were higher in POAG group than in control group, and There was a difference in FLV and GLV values between the case and control groups ($p<0.001$).

Table 2. GCC thickness in POAG patients and controls group

	POAG group n = 20	Control group n = 20	p
Avg GCC, µm			
Median (min-max)	89.47 (68-128.68)	99.79 (63.83-111.91)	0.072[a]

Superior GCC, µm			
Mean (SD)	87.93 (17.37)	97.24 (7.34)	0.037[b]
Inferior GCC, µm			
Median (min-max)	91.24 (58.9-182.73)	98.88 (89.69-114.1)	0.336[a]
FLV, %			
Median (min-max)	8.17 (0.05-26.02)	0.47 (0.01-2.10)	<0.001[a]
GLV, %			
Mean (SD)	14.69 (9.61)	2.82 (1.88)	<0.001[b]

Note: [a]Mann-Whitney, [b]Independent T-test

Serum Value of 25-Hydroxy Vitamin D

The median serum 25-hydroxy vitamin D in POAG and control group was 2.70 (1.31-27.5) and 4.20 (1.19-37.11) ng/mL, respectively. There was no significant difference in serum 25-hydroxy vitamin D values between the case and control groups (p = 0.091).

Table 3. Serum 25-hydroxy vitamin D value in POAG patients and controls

25-hidroxy vitamin D serum, ng/mL	POAG group n = 20	Control group n = 20	p
Median (min – max)	2.70 (1.31-27.5.)	4.2. (1.19-37.11)	0.091[a]

Note: [a]Mann-Whitney

Relationship between Serum 25-Hydroxy Vitamin D and GCC

There was no significant relationship between serum 25-hydroxy vitamin D and all parameters of GCC thickness in both the case group and the control group (p>0.05). Table 5 showed no significant relationship between serum 25-hydroxy vitamin D and GCC thickness parameters (p>0.05).

Table 4. Relationship of serum 25-hydroxy vitamin D to GCC in POAG patients and controls

		25-hidroxy vitamin D serum, mean (SD)					
		N	POAG group	p	n	Control group	p
Average GCC	Normal	13	6.17 (8.72)	0.429[a]	20	9.41 (10.95)	-
	Borderline	1	16.66		0	-	
	Outline Normal	6	3.18 (1.56)		0	-	
Superior GCC	Normal	7	5.95 (7.93)	0.612[a]	20	9.41 (10.95)	-
	Borderline	3	7.94 (7.75)		0	-	
	Outline Normal	10	5.04 (7.96)		0	-	
Inferior GCC	Normal	12	6.53 (9.01)	0.982[a]	20	9.41 (10.95)	-
	Borderline	2	9.23 (10.51)		0	-	
	Outline Normal	6	3.18 (1.56)		0	-	
FLV	Normal	5	14.53 (11.72)	0.05[b]	19	9.71 (11.16)	0.931[b]
	Borderline	0	-		1	3.79	
	Outline Normal	15	2.88 (1.41)			-	
GLV	Normal	8	8.43 (10.67)	0.271[a]	20	9.41 (10.95)	-
	Borderline	1	1.41		0	-	
	Outline Normal	11	4.28 (4.36)		0	-	

Note: [a]Kruskal Wallis, [b]Mann Whitney

Discussion

Subjects in POAG group were mostly female, amounting to 14 subjects (60.9%) while in the control group, most of them were male for 11 subjects (64.7). These results were in line

with Varanant et al., who reported that 11% female subjects had POAG more than male subjects (Vajaranant, 2012). The Canadian Glaucoma Study stated that female is a risk factor for POAG, due to hormonal changes that often occur in female and age (Chauhan, 2008).

The largest age group in the case group was 45-65 years, totaling 14 subjects (70%), while the control group was mostly <45 years old, totaling 19 subjects (95%), and significant difference was found between the two groups. Similarly, Actis et al. reported the mean age of female POAG patients was 62.11±10.1 years, while in male was 60.1 ± 8.7 years (Actis, 2016). Along with female gender, age was one of the risk factors for POAG, with increasing age, the development of damage will increase too (Chauhan, 2008; Actis, 2016). Chauhan et al. stated age as the main independent predictive factor and found that subjects older than 60 years had seven times higher incidence of glaucoma with perimetric defects than in patients under 40 years (Chauhan, 2008).

From the results of IOP examination, most of the patients in POAG group had an increase of IOP more than 21 mmHg with 12 subjects (60%), while the entire control group had a normal IOP. These results were in accordance with Mahabadi's study which stated that 80% of glaucoma sufferers were POAG (Mahabadi, 2021). Study by Dielemans also stated that IOP from 61.1% of the patients were more than 21 mmHg (Dielemans, 2013).

The majority of cases were classified as mild from the results of MD perimetry examination, amounting to 10 subjects (50%). Meanwhile, MD perimetry control group, which was classified as mild, amounting to 19 subjects (95%). This finding was in line with the research of Ohnell et al. who reported that mild MD perimetry was found in the majority of POAG patients (67%) (Ohnell, 2017). In PSD perimetry examination, majority subjects from case group and the control group had normal PSD perimetry results, accounted for 12 subjects (60%). This finding was similar with study conducted by Heo who reported that the perimetric examination usually had a linear relationship with the MD perimetry examination that the majority of POAG patients had mild MD perimetry (Heo, 2017).

The median serum 25-hydroxy vitamin D in POAG was lower than control group [2.70 (1.31 - 27.5) and 4.20 (1.19 - 37.11) ng/mL, respectively, while Mann Whitney test revealed no significant difference in hydroxy vitamin D serum values in both group (p=0.091). A case-control study in 73 POAG subjects and 71 controls in the Han population in China by Lv Y. et al. reported serum levels of $1\alpha.25(OH)_2D_3$ in POAG patients ($p < 0.001$) was 15% lower than in healthy controls (26.37 ng/ml ± 5.83 versus 30.43 ng/ml ± 3.91). In addition, this study also found higher frequency of vitamin D receptor BsmI 'B' (rs1544410) and TaqI 't' polymorphism (rs731236) in the POAG group compared to the control group, indicating the presence of this allele and low levels of vitamin D was a risk factor for POAG (Lv, 2016). Results of this study was contradicted to Kim et al.'s study who reported that serum hydroxy vitamin D values were found to be lower in POAG patients (Kim et al., 2016). In a meta-analysis study conducted by Ulhaq, patients with glaucoma had lower vitamin D levels than controls, and this could be associated with the development of glaucoma (Ulhaq, 2020).

Ayyagari et al.'s study in patients with advanced glaucoma had lower vitamin D levels when compared to patients with early-stage glaucoma and normal patients (Ayyagari et al., 2019). This was also reinforced by research conducted by Beletskaya who found a role for vitamin D in the regulation of apoptosis and tissue remodeling by primary open-angle glaucoma, where low levels of vitamin D could be considered as a risk factor for glaucoma progression (Beletskaya, 2017). Goncalves et al.'s study also found a decreased serum concentration of 25-HD was associated with the development of POAG, although no significant difference was found between moderate and severe glaucoma (Goncalves et al., 2015). According to Arar et al.'s study, the mean serum vitamin D levels were significantly different in glaucoma patients compared to the control group, concluded that vitamin D levels

could be considered as an initial parameter of glaucoma diagnosis and glaucoma prevention (Arar, 2016).

In this study, the overall GCC thickness (average GCC, superior GCC, inferior GCC) was lower in the case group, and FLV, GLV was higher in case group. The relationship between serum 25-hydroxy vitamin D and overall GCC thickness parameters (average GCC, superior GCC, inferior GCC, FLV, GLV) in these groups showed no significant relationship. This result was different from Uro et al.'s study in Germany that reported lower vitamin D level was associated with decrease in mean GCC thickness (Uro, 2015). In a study conducted by Daldal in 2021, low levels of 25-hydroxy vitamin D showed a thinning effect on macula (Daldal, 2021). Furthermore, lower serum 25-hydroxy vitamin D levels were significantly correlated to increased glaucoma risk in female compared to higher serum levels of hydroxy vitamin D patients (Lv, 2016). Yang et al.'s study reported that vitamin D regulated the renin-angiotensin system and promotes vasodilatation of endothelial cell, affecting peripheral circulation and microvasculature (Yang, 2012). From an animal-based study, renin-angiotensin system suppression decreased the risk of glaucoma by increasing ocular blood flow (Shah, 2000).

Vitamin D had been found to be associated with the modulation of inflammation through a variety of factors. Inflammatory factors were known to predispose neurodegeneration. Vitamin D was suggested an inflammatory factor and degeneration of neural tissue. More over from various studies, low vitamin D level had been related with major neurodegenerative diseases, such as multiple sclerosis, Alzheimer's disease, and isolated clinical syndromes. Vitamin D supplementation in multiple sclerosis and Alzheimer's disease was reported beneficial, although more extensive studies were required to support this conclusion (Nebbioso, 2017; Abouzeid, 2020). Vitamin D role in antioxidant, immune and inflammatory was expected to have a major role in neuroprotection. Modulation of the immune system by vitamin D was expected to have a protective role against several eye diseases. Low level vitamin D can be a factor in the pathogenesis of glaucoma (Nebbioso, 2017).

The study conducted by Huynh found that vitamin D had an essential role, mainly related to the role of vitamin D as an anti-inflammatory agent that played a role in the pathophysiology of primary open-angle glaucoma associated with oxidative stress (Huynh, 2020). Patients with vitamin D deficiency had shown evidence of GCC depletion, thus supporting this hypothesis (Uro, 2015). Contrary to our study, no significant association was found between serum 25-hydroxy vitamin D and GCC thickness, However, GCC thickness was reduced in the POAG group compared to the control group. The result might be due to the smaller number of research subjects. Until recent times, data and study on 25-hydroxy vitamin D and its correlation with GCC thickness was still very limited.

This study had several limitations such as relatively small number of samples and the need for matching techniques that could provide the best results in the study. This study only used the analytical observational method to determine and describe the role of serum 25-hydroxy vitamin D on GCC thickness in POAG patients, without looking at the relationship between other subject characteristics variables on GCC. This study also did not measure levels of other vitamins that were associated with the mechanism of glaucoma.

Conclusion

This study found that overall values of average, superior, and inferior GCC were lower in POAG than in control groups, although no significant mean difference ($p > 0.05$) was found. FLV and GLV were higher in POAG group and showed a significance difference ($p<0.001$). The median serum 25-hydroxy vitamin D in POAG and control group was 2.70 (1.31 - 27.5) and 4.20 (1.19 - 37.11) ng/mL, respectively, but no significant difference ($p = 0.091$) was found. No statistically significant relationship between serum 25-hydroxy vitamin D and all

parameters of GCC thickness was found in both the case group and the control group (p>0.05). Further study was needed with a more subjects and more variety of subjects characteristics.

Conflict of Interest

The authors declare that there is no conflict of interest.

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