Relationship between Tumor Necrosis Factor (TNF)-α Levels with Intraocular Pressure, Visual Field Defect, and Cup-Disc Ratio in Primary Open Angle Glaucoma (POAG)

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Abstract

Background: Glaucoma is a group of progressive optic neuropathy disease characterized by degeneration of retinal ganglion cells. This causes changes in the optic nerve and loss of visual field. Several studies reveal that there is a role for Tumor Necrosis Factor (TNF)-α in glaucoma cases.

Objective: To determine the relationship between TNF-α levels with intraocular pressure, visual field defects and cup-disc ratio in patients with primary open angle glaucoma.

Method: This study was an analytical observation with cross sectional design. Intraocular pressure was measured using a non-contact tonometer. Visual field was assessed with *Humphrey visual field perimetry*. Examination of cup-disc ratio was assessed with optical coherence tomography and TNF-α was measured with ELISA.

Result: The sample of this study was 30 subjects with 16 male (53.3%) and 14 female (46.7%). Using the Spearman correlation test showed that there was no significant correlation between TNF-α and intraocular pressure (p=0.230). TNF-α was also found not significantly correlated with visual field (p=0.119) and cup-disc ratio (p=0.940).

Conclusion: TNF-α level was not significantly associated with intraocular pressure, cup-disc ratio and visual field defects.

Keywords: POAG, intraocular pressure, cup-disc ratio, visual field, TNF-α

Introduction

Glaucoma is a group of progressive optic neuropathy disease characterized by degeneration of retinal ganglion cells. This nerve degeneration causes changes in the optic nerve and loss of visual field. Loss of ganglion cells is associated with increased intraocular pressure but is also influenced by other factors (Shields et al., 2011; Stamper, Lieberman, & Drake, 2009; Weinreb, Aung, & Medeiros, 2014; Khouri & Fechtner, 2015; Joos & Kuchtey, 2008).

Primary Open Angle Glaucoma (POAG) is the most common form of glaucoma. POAG has a tendency to be inherited and its incidence increases with age, in black races, myopia and certain systemic diseases such as diabetes mellitus and cardiovascular disorders. On ophthalmology examination, the anterior chamber angle of the eye was normal and open and usually did not cause complaints until there was extensive loss of visual field (Shields et al., 2011; Stamper, Lieberman, & Drake, 2009; Khouri & Fechtner, 2015).

POAG is irreversible, but the only controllable factors which is intraocular pressure can be controlled with medical therapy, lasers and surgical procedures. Treatment generally begins with hypotensive eye drops, then laser trabeculoplasty and surgical therapy can be performed to slow the progression of the disease (Joos & Kuchtey, 2008; Bowling, 2016; Cantor, Rapuano, & Cioffi, 2016).

Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine with multiple functions in the immune response. Since the early discovery of serum factors as a causative agent of tumor necrosis, it has become clear that in addition to their remarkable function in

the regulation of the inflammatory process, this potent immune mediator is also a major mediator of apoptosis.

Growing evidence supports that TNF, through binding to the TNF-1 receptor (TNF-R1), a receptor that dies, is involved in mediating retinal ganglion cell (RGC) death during glaucoma neurodegeneration. In vivo study findings support that TNF- α and TNF-R1 also suggest that there is an increase in intraocular pressure (IOP) and TNF- α signaling is involved in the process of RGC death during neurodegeneration in ocular hypertension (Wong et al., 2015; Ghanem, Arafa, & Elewa, 2011).

TNF-α secreted by stressed glial cells during the neurodegenerative process of glaucoma can cause RGC death via receptor-mediated caspase cascade, mitochondrial dysfunction, and oxidative damage. As caspase-8 is associated with an apoptotic pathway triggered by TNF death receptor binding, these findings stimulate interest in the role of TNF-α signaling in glaucoma. Following these preliminary observations, a series of experiments provided evidence that TNF-α signaling is indeed involved in RGC death during glaucoma neurodegeneration.

The correlation of TNF- α with glaucoma has been established in in-vivo human and animal studies that have shown that serum or intraocular TNF-α levels are elevated in patients with glaucoma or normal ocular exposure to TNF-α. Sawada et al. have shown that TNF-α levels in the aqueous humor of glaucoma patients are significantly increased compared to non-glaucoma patients.

The purpose of this study was to determine the relationship between Tumor Necrosis Factor (TNF)- α levels with IOP, visual field defects and Cup-disc Ratio in patients with Primary Open Angle Glaucoma at the University of Sumatera Utara Hospital and affiliate Hospital.

Materials and Methods

This study was an observational analytic with cross sectional data design. This study was conducted on patients with primary open-angle glaucoma (POAG) at the Glaucoma Division of the Ophthalmology Department at University of Sumatera Utara Hospital and its affiliated hospital from October 2021 to March 2022. The inclusion criteria in this study were subjects over 40 years old POAG patients, willing to be the study sample, was not in a state of fever or inflammation, and did not have any autoimmune disease. Exclusion criteria for this study were patients with ocular disorders including corneal abnormalities and vitreous disease and patients with a history of secondary glaucoma or with a clinical history of other optic neuropathy. The study begins with an explanation to the patient and family regarding the method of examination and the purpose of the examination to be carried out, then, vital signs were examined, visual acuity was examined using a snellen chart, tonometry examination with non-contact tonometer, examination of the anterior segment with a slit lamp, gonioscopy examination with three-mirror gonioscopy lens, examination of the posterior segment with fundoscopy, perimetry examination with Humphrey Injection PS-T100 to assess damage to visual field defects. After the examination, 3 cc of the patient's venous blood sample was taken and stored in the EDTA tube. The data obtained were then processed and analyzed using SPSS.

Results

This study included 30 subjects with diagnosis of POAG who visited the Glaucoma Division of Ophthalmology Department at the University of Sumatera Utara Hospital and affiliate hospitals. The characteristics of the subjects were shown in Table 1.

Table 1. Characteristics of study subjects

Subject Characteristics	**n = 30%**
Gender, n (%)	
Man	16 53.3
Woman	14 45.7
Age, years	
Average (SD)	55.73 (13.09)
Median (Min – Max)	52.5 (37 – 85)
40-45 years old	8 (26.7)
46 – 65 years old	14 (46.7)
> 65 years old	8 (26.7)
Eyes examined, n (%)	
OD	15 (50)
OS	15 (50)

Male subjects were 16 subjects (53.3%) and female subjects were 14 subjects (46.7%). The mean age of the subjects was 55.73 years with the youngest was 37 years old and the oldest was 85 years old. The highest age group subjects was in 46-65 years old group, which were 14 subjects in total (46.7%).

The results of the IOP, MD, CDR and TNF- α levels were shown in Table 2.

Table 2. Examination results of IOP, MD, CDR, and TNF-α

Variable	**n = 30**
IOP, mmHg	
Average (SD)	26.17 (6.95)
Median (Min – Max)	24.5 (15 – 41)
21 mmHg	24 (80)
< 21 mmHg	6 (20)
MD, dB	
Average (SD)	-12.99 (8.28)
Median (Min – Max)	-13.86 (-29.48 - -1.85)
Early	8 (26.7)
Moderate	6 (20)
Advanced	16 (53.3)
CDR, mm	
Average (SD)	0.78 (0.13)
Median (Min – Max)	0.76 (0.55 – 0.99)
TNF Alpha, pg/mL	
Average (SD)	1.01 (0.53)
Median (Min – Max)	0.91 (0.37 – 2.46)

The mean IOP value was 26.17 mmHg with the lowest value being 15 mmHg and the highest being 41 mmHg. A total of 24 subjects (80%) showed an increase in IOP. From the results of the MD visual field examination, the average value was -12.99 dB with the lowest value -29.48 and the highest value -1.85. Most of the subjects which amounted to 16 people (53.3%) showed a decrease in field of view. The CDR value shows an average of 0.78 with the lowest CDR value being 0.55 and the highest CDR value being 0.99. The mean TNF-α was 1.01 pg/mL with the lowest value 0.37 pg/mL and the highest value 2.46 pg/mL.

Analysis of the relationship between TNF- α with IOP, MD and CDR was shown in Table 3.

Table 3. Relationship between TNF- α with IOP, MD, and CDR

	TNF-α	
	P	**R**
IOP	0.230*	-0.226
MD	0.119*	-0.290
CDR	0.940*	0.014

Note: *Spearman

Using the Spearman correlation test showed that there was no significant correlation between TNF-α and IOP (p=0.230). TNF- α was also found not to be significantly correlated with MD visual field (p=0.119) and CDR (p=0.940).

The value of differences in TNF- α levels based on IOP values and MD visual field was shown in Table 4. TNF-α levels in subjects with IOP 21 mmHg was 0.98±0.58 pg/mL. Meanwhile, in subjects with IOP values < 21 mmHg, it showed a higher mean of 1.13±0.33 pg/mL. Using the Mann Whitney test showed that there was no significant difference in TNF-α levels based on IOP values (p = 0.378).

Table 4. Relationship of TNF-α with IOP

Variable	**N**	**TNF Alpha**		**P**
		Average (SD)	**Median (Min – Max)**	
IOP				
≥21 mmHg	24	0.98 (0.58)	0.77 (0.37 – 2.46)	0.378a
< 21 mmHg	6	1.13 (0.33)	1.08 (0.8 – 1.67)	
Visual Field Defect, dB				
Early	8	0.68 (0.33)	0.57 (0.37 – 1.39)	0.119b
Moderate	6	1.14 (0.71)	0.96 (0.4 – 2.46)	
Advanced	16	1.13 (0.5)	1.3 (0.37 – 1.89)	

Note: [a]Mann Whitney, [b]ANOVA

TNF- α levels in subjects with early visual field defects were 0.68±0.33 pg/mL. In subjects with moderate visual field defects, the mean TNF- α was 1.14±0.71 pg/mL. Meanwhile, subjects with advanced visual field defects showed a higher mean of 1.13±0.5 pg/mL. Using Oneway Anova test, it was shown that there was no significant difference in TNF-α levels based on the visual field defect category.

Discussion

In this study, there were more male subjects (16 people; 53.3%) than female (14 people; 46.7%). This was in line with the studies conducted by Kondhkar et al. (2018), Wong et al. (2015), and Ghanem, Arafa, and Elewa (2011) that the sample of male was more than female. As for the cause of male being more than female, was still uncertain, but Zhang et al's study in 2021 revealed that male had longer axial length and deeper anterior chamber depth (Kondkar et al., 2018; Wong et al., 2015; Ghanem, Arafa, & Elewa, 2011; Zhang et al., 2021).

Increased intraocular pressure was found in 24 subjects (80%). This was in line with the study conducted by Wong et al. (2015) and Ghanem, Arafa, and Elewa (2011) that most samples was found with increased intraocular pressure. This study also showed decrease in the field of view into the advanced category. This was also in line with the research conducted by

Ghanem, Wong and Kondhkar which found a decrease in the visual field. The mean for CDR in the subjects of this study was 0.78, indicated that cupping enlargement had occurred in the study subjects. This was also in line with study conducted by Wong in 2015 which found an enlargement of the cup-disc ratio with an average of 0.76 (Kondkar et al., 2018; Wong et al., 2015; Ghanem, Arafa, & Elewa, 2011).

In this study, it was found that the correlation between TNF- α and intraocular pressure was not significant. This was also in line with study conducted by Kondhkar et al. (2018) and Wong et al. (2015). However, there was a difference conducted by Ghanem in 2011 where there was a significant correlation of TNF-α to intraocular pressure. In this case, it could be because TNF- α induces the GluA2 subunit of AMPA receptor endocytosis and activates $CA2^{+}$-permeable which lacks AMPA GluA2 receptors in retinal ganglion cells, resulting in retinal ganglion cell death.

In a study conducted by Kondhar and Wong, it was found that the intraocular pressure in patients had been well managed. TNF- α correlation with cup-disc ratio in this study was also not significant. This was in line with study conducted by Kondhkar in 2018 but there were different results obtained in the research conducted by Ghanem in 2011 where significant results were obtained. An insignificant correlation was also found in the TNF- α correlation with visual field defects in Table 3. This was because the Kondhkar study sample in 2018 found POAG patients who had been well-managed medically (Kondkar et al., 2018; Wong et al., 2015; Ghanem, Arafa, & Elewa, 2011).

In this study, it was found that the mean TNF- α level was 0.98 in the group whose intraocular pressure was more than 21 mmHg. This could happen because one of the first-line therapies was using prostaglandin analogues. According to research by Scher and Pillinger (2009), it was found that prostaglandins have an anti-inflammatory effect.

In this study, it had several limitations including the sensitivity of the media used. In this study, the sample media used was serum, that according to several studies by using aqueous humor as sample media, obtained better results than serum sample media. This was due to the limited number of samples for sampling aqueous humor media.

Conclusion

The conclusion of this study is no significant relationship between Tumor Necrosis Factor (TNF)-α levels with intraocular pressure, visual field defects, and cup-disc ratio in primary open angle glaucoma patients.

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