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Association of Aqueous Humor Tumor Necrosis Factor Alpha with Retinal Ganglion Cell Thickness in Juvenile versus Adult-Onset Primary Open-Angle Glaucoma

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SUMMARY

Aims: To evaluate the association between aqueous humor tumor necrosis factor alpha (TNF-α) and retinal ganglion cell (RGC) layer in patients with juvenile open-angle glaucoma (JOAG) and their comparison with adult-onset primary open-angle glaucoma patients (POAG).
Material and Methods: This analytical cross-sectional study included 15 JOAG patients (aged 7–40 years) and 15 POAG patients (> 40 years). Aqueous Humor (AH) samples were collected during trabeculectomy, TNF-α concentrations were measured using ELISA, and RGC thickness was assessed by Optical Coherence Tomography (Cirrus HD-OCT, Carl Zeiss). Group differences were analyzed using the independent t-test, and correlations were evaluated with Pearson's test.
Results: The mean AH TNF-α level in the JOAG group (179.02 ±27.04 pg/mL) was significantly higher than in the POAG group (130.17 ±18.62 pg/mL; $p < 0.001$). Mean RGC thickness in JOAG (42.87 ±8.29 µm) was significantly lower than in POAG (58.13 ±14.86 µm; $p = 0.004$). There was a strong negative correlation between TNF-α levels and RGC thickness in both JOAG ($r = -0.726$; $p = 0.02$) and POAG ($r = -0.807$; $p < 0.001$).
Conclusion: Higher intraocular TNF-α levels and reduced RGC thickness in JOAG suggest a prominent neuroinflammatory contribution to early-onset glaucoma. Targeting TNF-α-mediated pathways may offer potential neuroprotective benefits in younger glaucoma patients.
Key words: primary open-angle glaucoma, juvenile open-angle glaucoma; TNF-α, retinal ganglion cell, RGC thickness

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INTRODUCTION

Glaucoma is a progressive optic neuropathy, characterized by optic nerve head cupping accompanied by the irreversible loss of retinal ganglion cells (RGCs), specifically the ganglion cell layer (GCL) and their axons, as well as visual field constriction. The etiology of glaucoma is multifactorial, involving both genetic and environmental factors. However, intraocular pressure (IOP) remains the principal risk factor contributing to disease progression [1]. In most patients, lowering IOP can halt or slow down RGC loss and visual field deterioration [1,2]. Glaucoma is one of the leading causes of permanent blindness worldwide [3]. The global prevalence of primary open-angle glaucoma (POAG) is estimated at approximately 2.4%, affecting nearly 68 million people in 2020 [3,4]. In Indonesia, glaucoma also represents a significant public health concern [5]. POAG is typically asymptomatic in its early stages, leading to delayed diagnosis until substantial visual function loss has occurred [3]. An Asian population study reported that the majority of glaucoma patients present for the first time at moderate to advanced stages [6].

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POAG occurring at a younger age (between 4 and 40 years) is classified as juvenile open-angle glaucoma (JOAG) [7]. JOAG is a rare form of primary glaucoma, but tends to be more severe than adult-onset POAG [7,8]. Muma et al. (2020) reported that JOAG is associated with higher IOP and more extensive structural damage, compared with POAG [8]. It has been proposed that ocular inflammatory activity is more pronounced in younger individuals. Lai et al. (2020) demonstrated that children undergoing ocular surgery exhibit higher postoperative aqueous humor cytokine levels in younger age groups, indicating a stronger inflammatory response early in life [9]. This may explain why JOAG, which develops at a younger age, often progresses more aggressively.

The mechanisms of RGC death in glaucoma are complex. Although elevated IOP plays a significant role, it is not the sole trigger of RGC degeneration. Additional neurodegenerative processes contribute to optic nerve damage, including oxidative stress and neuroinflammation. Recent studies emphasize that oxidative stress and inflammation are key factors in the pathogenesis of primary glaucomatous optic neuropathy [10,11]. In glaucoma, retinal glial cells become activated and contribute to neuronal injury. Activated microglia, astrocytes, and macrophages in retinal tissue release various pro-inflammatory mediators, including TNF-α, which can accelerate RGC apoptosis [12–14]. Tumor necrosis factor alpha (TNF-α) in particular has been identified as a major proinflammatory cytokine involved in glaucomatous optic nerve damage. TNF-α is produced by retinal microglia in response to stress, ischemia, or elevated IOP. Increased TNF-α levels have been reported in glaucoma patients in both animal and human studies, compared with nonglaucomatous controls [15,16]. Kondkar et al. (2018) found a significant association between elevated TNF-α levels and POAG [15], and Dammak et al. (2023) also reported significantly higher intraocular TNF-α concentrations in POAG patients compared with controls [16].

TNF-α induces apoptosis of retinal ganglion cells through its binding to the TNF-R1 receptor on the RGC membrane, activating the caspase-mediated cell death signaling pathway [17]. This activation triggers an apoptotic cascade that ultimately results in RGC loss. In addition to this direct effect, TNF-α may exacerbate neuronal injury indirectly. This cytokine modulates excitatory neural signaling by disrupting glutamate homeostasis in the retina. TNF-α has been shown to modify the composition of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) -type glutamate receptors in RGCs, particularly by reducing the GluA2 subunit, which normally prevents excessive calcium influx. Consequently, elevated TNF-α levels allow excessive Ca^{2+} entry into neurons, leading to excitotoxicity and accelerating RGC death. Other intracellular pathways, including activation of proinflammatory transcription factors, such as nuclear factor kappa B (NF-κB), are also triggered by TNF-α and contribute to glaucomatous optic nerve injury [17,18].

To date, no study has specifically compared aqueous humor TNF-α levels between JOAG and POAG patients, nor evaluated the relationship between TNF-α concentration and RGC layer thickness. Based on the above rationale, this study was conducted to analyze differences in AH TNF-α levels between JOAG and POAG and to assess the correlation between TNF-α concentrations and RGC thickness in both groups.

MATERIAL AND METHODS

Study Design and Subjects: This research was an analytical observational study with a cross-sectional design. The study population consisted of patients with primary open-angle glaucoma who received treatment between November 2024 and March 2025. Two groups were recruited: 15 JOAG patients (≤ 40 years) and 15 POAG patients (> 40 years). Inclusion criteria were a confirmed diagnosis of POAG or JOAG by a glaucoma subspecialist, age 7–70 years, IOP < 30 mmHg with or without antiglaucoma therapy, eligibility for filtration surgery (trabeculectomy), and provision of informed consent. Exclusion criteria included a history of prior ocular surgery, secondary glaucoma, other ocular diseases (e.g., uveitis, keratitis), or systemic comorbidities, such as diabetes mellitus, autoimmune disease, or uncontrolled hypertension.

Sampling Procedure and Examinations: All subjects underwent Optical Coherence Tomography (Cirrus HD-OCT, Carl Zeiss) preoperatively to measure retinal ganglion cell layer thickness, specifically the ganglion cell layer plus inner plexiform layer, using the macular cube 512×128 protocol. Examinations were performed in a dark room under standard fixation and positioning. During trabeculectomy, before creating the surgical incision, approximately 0.1 mL of aqueous humor was aspirated from the anterior chamber, using a 30G needle via gentle paracentesis and transferred into sterile microtubes. AH samples were stored at 0–4°C in a portable cooling system and subsequently frozen at -80°C until analysis. TNF-α concentrations were measured using a TNF-α-specific enzyme-linked immunosorbent assay (ELISA). All samples were processed in duplicate at the Biomedical Laboratory, Faculty of Medicine, and results were expressed in pg/mL.

Data Analysis: Demographic and clinical characteristics were summarized descriptively. The Shapiro-Wilk test was used to assess normality. Since the data were normally distributed ($p > 0.05$), differences in mean TNF-α levels between JOAG and POAG were analyzed, using the independent t-test. Differences in mean RGC thickness were assessed similarly. Pearson's correlation was used to examine the relationship between TNF-α levels and RGC thickness in both groups. The correlation coefficient (r) and significance (p) values were recorded, with $p < 0.05$ considered statistically significant. Statistical analyses were performed, using the IBM Statistical Package for the Social Sciences (SPSS) version 26. Ethical approval was

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obtained from the Research Ethics Committee of the Faculty of Medicine, Universitas Andalas/RSUP Dr. M. Djamil Padang, and written informed consent was obtained from all participants.

RESULTS

This study included 30 eyes from 30 patients with open-angle glaucoma, consisting of 15 JOAG patients (mean age 23.4 ±8.7 years; 8 males and 7 females) and 15 POAG patients (mean age 58.6 ±9.3 years; 9 males and 6 females). At baseline, all JOAG subjects were receiving maximal topical antiglaucoma therapy (a combination of two or three medications), yet their IOP remained suboptimal (mean IOP 32.4 ±5.1 mmHg). Most POAG patients were also on topical therapy, with a mean IOP of 24.7 ±3.8 mmHg. The indication for trabeculectomy in all subjects was failure to achieve target IOP or clear evidence of disease progression, despite maximal medical treatment.

Aqueous Humor TNF-α Levels in JOAG vs. POAG (Table 1): The mean AH TNF-α concentration in JOAG patients was 179.02 ±27.04 pg/mL (range 127.28–231.83 pg/mL), whereas in POAG patients the mean level was 130.17 ±18.62 pg/mL (range 91.74–155.86 pg/mL). The difference in mean TNF-α levels between the two groups was statistically significant (independent t-test, $p < 0.001$), indicating that intraocular TNF-α concentrations were substantially higher in JOAG compared with POAG. Individual data distribution showed that most JOAG patients had TNF-α levels exceeding 150 pg/mL, whereas the levels in POAG patients predominantly ranged between 100–150 pg/mL.

Retinal Ganglion Cell (RGC) thickness in JOAG vs. POAG (Table 2): The mean RGC layer thickness in the JOAG group was 42.87 ±8.29 µm (range 30–55 µm),

Table 1. Mean Aqueous Humour TNF-α Levels in JOAG and POAG Patients

JOAG			POAG		
Sample	**TNF-α**	**Mean ±SD**	**Sample**	**TNF-α**	**Mean ±SD**
J1	154.91		P1	91.74	
J2	127.28		P2	133.34	
J3	179.76		P3	118.70	
J4	151.50		P4	124.38	
J5	223.84		P5	98.37	
J6	181.85		P6	118.07	
J7	194.50		P7	140.49	
J8	170.03	179.02 ±27.04	P8	155.86	130.17 ±18.62
J9	186.05		P9	145.27	
J10	165.20		P10	155.15	
J11	188.16		P11	133.98	
J12	156.96		P12	126.87	
J13	177.67		P13	136.58	
J14	195.92		P14	148.43	
J15	231.83		P15	125.37	

TNF-α – Tumor Necrosis Factor-Alpha, POAG – Primary Open-Angle Glaucoma, JOAG – Juvenile Open-Angle Glaucoma, SD – Standard Deviation

Table 2. Mean RGC Thickness in JOAG and POAG Patients

JOAG			POAG		
Sample	**RGC *Thickness***	**Mean ±SD**	**Sample**	**RGC *Thickness***	**Mean ±SD**
J1	49		P1	71	
J2	55		P2	57	
J3	46		P3	70	
J4	48		P4	60	
J5	31		P5	72	
J6	45		P6	71	
J7	33		P7	55	
J8	40	42.87 ±8.29	P8	36	58.13 ±14.86
J9	42		P9	50	
J10	54		P10	39	
J11	53		P11	54	
J12	36		P12	78	
J13	45		P13	60	
J14	36		P14	28	
J15	30		P15	71	

RGC – Retinal Ganglion Cell, POAG – Primary Open-Angle Glaucoma, JOAG – Juvenile Open-Angle Glaucoma, SD – Standard Deviation

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Table 3. Pearson Correlation Between Aqueous Humour TNF-α Levels and RGC Thickness in JOAG and POAG

Variable	JOAG			POAG		
	Mean ±SD	Pearson Correlation (r)	p-value	Mean ±SD	Pearson Correlation (r)	p-value
TNF-α (pg/mL)	179.02 ±27.04	-0.726	0.02	130.17 ±18.61	-0.807	0.00
RGC thickness (μm)	42.87 ±8.29			58.13 ±14.85		

TNF-α – Tumor Necrosis Factor-Alpha, RGC – Retinal Ganglion Cell, POAG – Primary Open-Angle Glaucoma, JOAG – Juvenile Open-Angle Glaucoma, SD – Standard Deviation

whereas the mean RGC thickness in the POAG group was 58.13 ±14.86 μm (range 28–82 μm). The RGC layer in JOAG was significantly thinner than in POAG (independent t-test, $p = 0.004$). In the JOAG group, 80% of subjects had an RGC thickness of < 50 μm, while in the POAG group, most measurements were above 50 μm. This finding is consistent with the more severe optic nerve damage typically observed in JOAG. In addition, one POAG case demonstrated an extremely low RGC thickness (28 μm), probably representing a patient with very advanced glaucoma.

Association Between TNF-α Levels and RGC Thickness (Table 3): Pearson's correlation analysis demonstrated a strong and significant negative association between aqueous humor TNF-α levels and RGC thickness. In the JOAG group, the correlation coefficient was $r = -0.726$ with $p = 0.02$, indicating that higher TNF-α levels were closely associated with thinner RGC layers. Similarly, in the POAG group, a very strong negative correlation was observed ($r = -0.807$; $p < 0.001$), confirming that elevated TNF-α levels corresponded to more pronounced RGC thinning. This relationship is illustrated in the scatter plot (not shown), where patients with higher TNF-α concentrations consistently exhibited lower RGC layer thickness. These findings support the hypothesis that elevated intraocular TNF-α is associated with more severe RGC damage in both JOAG and POAG.

DISCUSSION

The findings of this study demonstrate that aqueous humor TNF-α levels in juvenile open-angle glaucoma are markedly higher than those in adult primary open-angle glaucoma. While elevated IOP is the traditional hallmark of glaucoma, our results suggest that JOAG is not merely a pressure-dependent neuropathy, but is driven by a profound "inflammatory burden" that distinguishes it from the adult-onset disease [9]. This aligns with our observation that JOAG patients exhibited significantly thinner retinal ganglion cell layers compared to POAG patients, confirming that the disease process in younger individuals is both biologically distinct and structurally more aggressive.

The mean TNF-α concentration in JOAG in our study was considerably higher than the values previously reported in normal eyes or adult POAG, which rarely reach triple-digit concentrations [19,20]. For context, previous literature by Balaiya et al. established that normal eyes typically maintain AH TNF-α levels of approximately 1.59 ±0.46 pg/mL [19]. The discrepancy observed suggests a substantially more active intraocular inflammatory process in glaucoma presenting at a young age. Two key factors probably drive this hyperactivation: the first is an age-dependent immune response, in which younger individuals exhibit more robust inflammatory reactions to stress than adults [9]. The second is higher mechanical stress in JOAG, characterized by very high IOP and significant pressure fluctuations. Studies in adult glaucoma have shown that mechanical stress from IOP fluctuations triggers the release of inflammatory cytokines. In the context of JOAG, extreme mechanical strain possibly induces a vicious cycle of microglial activation and massive TNF-α release [21].

The significantly thinner RGC layer, along with its fibers and the inner plexiform layer observed in JOAG rather than in POAG in this study, confirm that optic nerve damage in JOAG is more severe. JOAG patients experience greater RGC loss, consistent with the aggressive disease progression commonly seen in younger individuals. Gupta et al. found that JOAG patients exhibit substantial visual disability during their productive years, due to rapid glaucomatous damage [22]. This aligns with our findings, in which the mean RGC thickness in JOAG was approximately 43 μm, already within the range of advanced structural loss, whereas the mean thickness in POAG was 58 μm.

Our study goes beyond merely documenting cytokine levels; we also demonstrate a functional consequence. We found a significant negative correlation between TNF-α and RGC thickness in both groups. This supports the hypothesis that TNF-α is a direct mediator of glaucomatous neurodegeneration. Biologically, the elevated TNF-α levels observed in the aqueous humor of JOAG patients are probably due to increased activation of microglia and intraocular immune cells. Activated microglia are known to release large quantities of TNF-α, which in turn binds to TNFR1 receptors on the surface of retinal

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ganglion cells, triggering a caspase-dependent apoptotic cascade, leading directly to cell death [17]. Beyond immediate neuronal death, TNF-α contributes to chronic inflammation within the trabecular meshwork by upregulating adhesion molecules and chemokines, promoting immune cell infiltration and trabecular fibrosis, ultimately impairing aqueous outflow and exacerbating prior IOP insult. This creates a vicious cycle that accelerates glaucoma progression. TNF-α also disrupts neurotransmitter homeostasis by increasing glutamate release, impairing glutamate reuptake, and reducing the expression of the protective GluA2 subunit of AMPA receptors on RGCs. Consequently, excessive Ca^{2+} influx occurs, leading to excitotoxic neuronal injury. This excitotoxic mechanism has been demonstrated in cultured RGC models, where TNF-α exposure induces RGC death through increased intracellular calcium [19]. These combined mechanisms explain the strong association between elevated TNF-α and reduced RGC thickness observed in our study.

The association between higher levels of this proinflammatory cytokine and greater thinning of the RGC layer suggests that the degree of neuroinflammation within the anterior segment (reflected by AH TNF-α) corresponds to the severity of retinal neurodegeneration. Previous studies have proposed that AH cytokine profiles may serve as indicators of glaucoma severity. For instance, Vidal-Villegas et al. reported distinct proinflammatory cytokine patterns between POAG and pseudoexfoliation glaucoma, suggesting that different glaucoma subtypes may possess unique inflammatory signatures [23]. Our findings expand this concept by demonstrating that JOAG, a subtype distinguished primarily by age of onset, exhibits substantially higher levels of the inflammatory mediator TNF-α than adult-onset POAG. This aligns with previous literature suggesting that microglia and chronic inflammation play central roles in retinal neurodegeneration, including glaucoma [24,25]. In a glaucomatous retina, activated microglia produce TNF-α and other proinflammatory cytokines, driving sustained axonal injury and RGC death. Moreover, Müller glial cells may undergo reactive gliosis in response to TNF-α, further exacerbating the inflammatory environment in retinal tissue [26].

The clinical reality of JOAG is often grim: patients frequently suffer substantial visual disability during their productive years, due to rapid progression. Our findings suggest this occurrence is due to JOAG eyes being subjected to a "double hit" of extreme mechanical pressure and severe neuroinflammation. This implies that standard IOP-lowering therapies, while still essential, may be insufficient to fully arrest disease progression in younger patients. The significant inflammatory component suggests that JOAG management could benefit from adjuvant therapies targeting the TNF-α mediated pathway. Preclinical studies have shown that selective TNF-α antagonists can protect RGCs in experimental glaucoma models without altering IOP. Lambuk et al. also discussed the therapeutic potential of modulating TNF-α receptors to slow neurodegeneration in glaucoma [27]. Such adjuvant strategies may, in the future, be particularly relevant for JOAG cases with markedly elevated TNF-α levels, pending confirmation of safety and efficacy through clinical trials.

Moreover, TNF-α measurement in aqueous humor may have potential as a biomarker for disease activity or prognosis, given its strong association with structural optic nerve damage. Other cytokines are also being actively investigated: for example, Burgos-Blasco et al. mapped tear film and aqueous humor cytokine profiles in POAG, reinforcing the role of inflammation in glaucoma pathogenesis [28]. A multidimensional therapeutic approach, addressing both pressure-dependent and immunological pathways, may pave the way for more comprehensive glaucoma management.

LIMITATIONS

This study has several limitations. Firstly, the sample size was relatively small, which limits generalizability. Secondly, all participants were surgical candidates scheduled for trabeculectomy, meaning most had advanced-stage glaucoma; thus, elevated TNF-α levels may reflect a population with more severe disease, introducing selection bias. Thirdly, the cross-sectional design prevents causal inference between TNF-α elevation and RGC damage, allowing only association at a single time point. Fourthly, the absence of a healthy control group limits direct comparison of TNF-α values with those of normal eyes, requiring reliance on literature-based reference values. Finally, other factors that may influence RGC thickness and cytokine expression, such as degree of myopia, axial length, or long-term topical medication use, were not evaluated. Future studies with larger samples, inclusion of normal control groups, and longitudinal designs are needed to validate these findings and further elucidate the mechanistic role of TNF-α in glaucoma progression.

CONCLUSION

Aqueous humor TNF-α levels were significantly higher in JOAG than in adult POAG. Elevated TNF-α levels were strongly and negatively correlated with retinal ganglion cell layer thickness, indicating that higher intraocular TNF-α is associated with more severe RGC loss. These findings suggest that TNF-α-mediated neuroinflammatory processes contribute to optic nerve damage in glaucoma, particularly in younger patients. Clinically, glaucoma management in younger individuals may require additional approaches targeting inflammatory components, such as TNF-α-modulating therapies, alongside standard IOP-lowering treatments.

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