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Aqueous humor TGF-β2 levels in patients with open-angle glaucoma: A meta-analysis

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Introduction: Elevated intraocular pressure (IOP) in glaucomatous eyes is often due to increased resistance to aqueous outflow. Previous studies have shown that increased extracellular material deposition in outflow pathways leads to increased resistance to aqueous outflow, and transforming growth factor (TGF)-β seems to play a role in the deposition of extracellular material. TGF-β2 is the predominant isoform in ocular tissue. Hence, comparison of the aqueous humor TGF-β2 level between patients with open-angle glaucoma (OAG) and controls would provide direct evidence for the role of TGF-β2 in the etiology of OAG. Hence, we performed this meta-analysis to develop an accurate estimate of the changes in aqueous humor TGF-β2 levels among OAG patients.
Methods: We undertook the meta-analysis of data from all available studies that had a case-control design and investigated the aqueous humor levels of TGF-β2 (total, active, or both) in OAG patients. OAG included primary OAG (POAG), secondary glaucoma, pseudoexfoliation syndrome, and exfoliation glaucoma (EXG).
Results: We selected a total of eight studies that measured TGF-β2 levels in the aqueous humor of glaucomatous eyes. The studies included in this meta-analysis clearly demonstrated that in OAG eyes, total TGF-β2 levels are significantly elevated, whereas in POAG eyes, both the total and active TGF-β2 levels are significantly higher than in controls.
Conclusions: The analysis of pooled data showed that aqueous humor TGF-β2 levels are elevated in patients with OAG and POAG.

Glaucomatous optic neuropathy, characterized by loss of retinal ganglion cells and visual fields, is the leading cause of irreversible blindness. Glaucoma is classified as primary or secondary. Primary glaucoma is further classified based on the anatomic details of the drainage angle of the eye as primary open-angle glaucoma (POAG) or primary angle-closure glaucoma (PACG). Based on whether POAG is associated with elevated intraocular pressure (IOP) or not, it can be of two types, namely high-tension glaucoma (HTG) and normal-tension glaucoma (NTG). Exfoliation glaucoma (EXG) is a type of secondary glaucoma. Among the different types of glaucoma, OAG, including HTG, NTG, and EXG, is the most common form and may account for up to 90% of glaucoma cases [1].

Despite the existing knowledge regarding the characteristics of different types of glaucoma, the treatment options generally have a common approach involving the reduction of IOP. Furthermore, the currently used drugs for lowering IOP mainly act by modifying the aqueous humor dynamics without altering the underlying pathophysiological processes leading to high IOP, which is often due to increased resistance in the aqueous humor outflow pathways [2]. The pathophysiological processes leading to increased resistance in outflow pathways remain debatable. However, it is important to identify the potential targets that may help in developing pharmacological strategies that will not only lower IOP, but also prevent or retard the underlying pathological process and hence the disease progression.

Studies have shown that in glaucomatous eyes, increased resistance to aqueous outflow is associated with increased deposition of extracellular matrix (ECM) in outflow pathways [3-5]. An imbalance between the rate of ECM synthesis and its breakdown leads to increased ECM deposition in aqueous outflow pathways. The mechanisms involved in the increased ECM deposition in glaucomatous eyes and role of several cytokines has been evaluated [6,7]. Among all of these, transforming growth factor (TGF)-β seems to play a significant role [6].

TGF-β2, a 25 kDa polypeptide, is synthesized by the tissue in the anterior segment of eye. It is a component of normal aqueous humor and can be detected in many mammalian eyes [8-11]. Three isoforms that are expressed in human ocular tissue are TGF-β1, TGF-β2, and TGF-β3 [12]. Among these, TGF-β2 is regarded as the major isoform in ocular

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tissue [12,13]. It is mainly secreted in a biologically inactive form. Activation results from dissociation of a dimeric active TGF-β2 from the latent form [14,15]. This is a multifunctional growth factor involved in several cellular activities such as cell migration, cell proliferation, cell death, and protein synthesis [16]. It promotes ECM production and suppresses cell proliferation. Several studies have been carried out in humans to evaluate the aqueous humor level of TGF-β2 in patients with OAG. Therefore, we undertook this meta-analysis of all eligible studies to develop an accurate estimate of the changes in aqueous humor TGF-β2 levels among patients with OAG.

METHODS

Strategy for literature search: For this study, we carried out a computerized search of three databases, namely ISI Web of Knowledge, Scopus, and PubMed. Keywords such as transforming growth factor-β2 (TGF-β2), aqueous humor, serum, and glaucoma were used in combination. Relevant studies were also searched manually from the reference lists of reviews and clinical trials. The literature search was updated on 31/01/15.

Selection criteria: The selection criteria were as follows: (1) studies that investigated the aqueous humor levels of TGF-β2 (total, active, or both) in OAG patients and (2) a case-control design. All selected studies were carefully and independently reviewed by two investigators to assess their suitability for inclusion in this study.

Data collection: Two independent investigators collected the data using a predetermined datasheet and both investigators reached a consensus on all items included for analysis. The items that were extracted from each study included name of the first author, year of publication, number of cases and controls, number of eyes as cases or controls, age of included subjects, type of glaucoma, mean IOP, and aqueous TGF-β2 levels (total, active, or both).

Statistical methods: The meta-analysis was based on the data retrieved from individual studies selected using the inclusion and exclusion criteria. Only the original data, not the analyzed data, were retrieved. The purpose of the analysis was to estimate the population's mean difference based on a larger sample size. In this study, we used the random effect model. The assumptions underlying the use of this model are that (i) heterogeneity is present among the participant studies due to difference in populations' characteristics, data collection methods, and research setting; and (ii) the effect size is estimated from a distribution of true effects based on study sample size—hence, the true effect could vary from study to study [17,18].

Hedge's standardized mean difference with its 95% confidence interval (CI) was used to assess the difference in active and total TGF-β2 between cases and controls. A forest plot was used to show the individual study and pooled effect size. The Z statistic with the corresponding p value was used to assess the significance of the effect size. Weighting of studies was carried out by computing the inverse of variance of each effect size of individual participant studies. Under the random effect model, studies with a larger sample size would have smaller standard error, and hence greater weight. Heterogeneity was assessed with Q statistics and I^2, which reflect percentage of variation in the effect size of studies that is not due to sampling error. A p value of less than 0.05 was indicative of significant heterogeneity among the studies. Sensitivity analysis was performed by sequential omission of individual studies in every comparison. Publication bias was assessed through Begg's funnel plot and Egger's regression.

RESULTS

Characteristics of the included studies: The literature search based on the keywords yielded 12 studies; of these, eight were selected based on the inclusion and exclusion criteria described above [11,19-25]. The number of eyes included in each of these studies, the mean age of subjects, and IOP values are presented in Table 1. The types of OAG patients in the included studies were POAG, secondary open-angle glaucoma (SOAG), pseudoexfoliation syndrome (PXS), and EXG. The study done by Min et al. [19] included POAG and SOAG patients, while that of Inatani et al. [25] included PXS patients besides POAG and SOAG. Picht et al. and Ozcan et al. [20,23] included POAG and EXG patients, while the other three studies included POAG only. The control subjects in all studies had cataract with no other ophthalmic abnormalities. The presence of cataract may affect the composition of aqueous humor; however, these samples represent the closest to normal aqueous humor that can be possibly obtained from age-matched normal subjects.

All studies included in this meta-analysis measured the TGF-β2 levels in aqueous humor using enzyme-linked immunosorbent assay (ELISA). Yamamoto et al. [24] measured only the total TGF-β2; Ozcan et al. [23] measured only active TGF-β2; and the rest of the studies, measured both the total and active TGF-β2. The total TGF-β2 was measured after activation of the latent form by acidification, whereas intrinsically active TGF-β2 was measured before acidification.

Association of total and active TGF-β2 with OAG: The mean values for total and active TGF-β2 in the aqueous humor of different types of OAG in eight of the included studies are shown in Table 2. The standardized mean difference (SMD)

Table 1. Subject characteristics (number of eyes, age and IOP) of the included studies.

Study	Type of glaucoma	OAG			Control (cataract)	
		Number of eyes (n)	Age (years)	IOP (mmHg)	Number of eyes (n)	Age (Years)
Tripathy et al., 1994 (USA) [11]	POAG	15	76±7.13	NA	10	73.2±7.58
Inatani et al., 2001 (Japan) [19]	POAG	40	67.4±8.9	21.5±5.2	24	77.3±6.2
	PXS	18	72.9±5.4	21.3±6.8		
	SOAG	7	64.2±7.6	33.3±13.4		
Picht et al., 2001 (Germany) [20]	POAG	29	71.14±9.71	34.32±9.85	29	NA
	EXG	17	72.17±6.77	36.08±8.78		
Schlotzer-Schrehardt et al., 2001 (USA) [21]	POAG	27	-	-	27	-
	PXS	27	71.4±6.7	-		
	EXG	27	74.4±6.9	-		
Ochai et al., 2002 (Japan) (For total TGF-β2) [22]	POAG	8	66.6±6.9	21.8±2.7	10	76.7±/6.6
Ochai et al., 2002 (Japan) (For active TGF-β2) [22]	POAG	11	74.5±7.1	20.6±4.9	15	71.6±8.1
Ozcan et al., 2004 (Turkey) [23]	POAG	11	61.09±9.20	37±11.76	6	57.5±9.8
	EXG	4	62±9.09	23.5±4.72		
Yamamoto et al., 2005 (Japan) [24]	POAG	8	58 to 72	18 or less	5	42 to 78
Min et al., 2006 (Korea) [25]	POAG	14	49.88±17.58*	21.8±5.7	20	49.88±17.58*
	SOAG	15		27.3±4.7		

*Mean age of all patients from both the POAG and SOAG groups. OAG: open angle glaucoma; IOP: Intraocular pressure; POAG: Primary open angle glaucoma; PXS: Pseudoexfoliation syndrome; SOAG: Secondary open angle glaucoma; EXG: Exfoliation glaucoma

is represented by Hedges' g statistic. The SMDs for total and active TGF-β2 in all subtypes of OAG were 2.20 and 0.56, respectively. The difference was found to be highly significant with the random model for total TGF-β2 ($p<0.001$), but not for active TGF-β2 ($p=0.21$). The test of heterogeneity showed that there was significant heterogeneity among studies (Table 3).

Association of active aqueous humor TGF-β2 with POAG: Since all included studies involved POAG patients but not other types of OAG, we further performed pooled analysis for POAG cases. The results of pooled analysis for the association of active aqueous humor TGF-β2 levels with POAG are shown in Table 4 and Figure 1. The mean difference was significant for all studies included in the analysis. Inatani et al. [19] showed the largest mean difference, while Tripathy et al.[11] showed the smallest difference. The pooled mean difference was found to be highly significant with the random model. The test of heterogeneity showed that there was also significant heterogeneity among studies.

Association of total aqueous humor TGF-β2 with POAG: The SMD for total TGF-β2 between cases of POAG and controls was significant for all studies. The highest values were observed by Inatani et al. [19] and the lowest by Min et al.[25]. The mean difference between the POAG and control groups was significantly high. The Q statistics showed that there was a significant heterogeneity beyond the sampling error (Table 5, Figure 2).

Sensitivity analysis and publication bias: The data showed that no study significantly influenced the pooled effects, as any study could be omitted without significantly affecting the results. The findings showed an absence of publication bias for the active TGF- β 2 for OAG ($p>0.05$) or total and active TGF-β2 for POAG ($p>0.05$; Figure 3B, Figure 4A,B). Although the funnel plot was symmetric for the total TGF- β 2 for OAG, Egger's regression indicated a significant publication bias ($p=0.02$; Figure 3A).

DISCUSSION

To investigate whether TGF-β plays an important role in the etiology of OAG, comparison of the aqueous humor TGF-β levels between patients with OAG and controls can provide direct evidence. Therefore, in the present study, we performed a meta-analysis and summarized the studies that investigated presence of TGF-β in the aqueous humor in patients with OAG, as well as in control subjects. TGF-β2 is considered the

Table 2. Total and active TGF b2 in the aqueous humor of OAG and control eyes.

Author; year	Type of glaucoma	OAG			Control (cataract)		
		Number of eyes (n)	Total TGFβ2 (picogm/ml)	Active TGFβ2 (picogm/ml)	Number of eyes (n)	Total TGFβ2 (picogm/ml)	Active TGFβ2 (picogm/ml)
Tripathy et al., 1994 [11]	POAG	15	2700±760	450±280	10	1480±680	200±240
Inatani et al., 2001 [19]	POAG	40	1647±124.5	293.6±33.6	24	1094.1±91.5	181.8±26.1
	PXS		1442.7±187.8	135.8±30.2			
	SOAG		1929.0±367.6	41.0±10.7			
Picht et al., 2001 [20]	POAG	29	1874.5±1205.7	205.4±96.8	29	762.1±3 45.5	127.4±4
	EXG	17	1046±409.3	133.5± /77			
Schlotzer-Schrehardt et al., 2001 [21]	POAG	27	1877.9±415.7	699.78±39.8	27	1043.5± 158.4	335.4± 80.8
	PXS	27	1428.5±195.7	393.7±62.1			
	EXG	27	1436.1±558.6	259.7±59.6			
Ochai et al., 2002 [22]	POAG	8	1699.4±346.31	-	10	1001.4±444.1	-
	POAG	11	-	822.5±484.41	15	-	321.2±197.91
Yamamoto et al., 2005 [23]	POAG	8	2,203.2±128.2	-	5	1,107.7±311.73	-
Ozcan et al., 2004 [24]	POAG	11	-	3200±1330	6	-	1670±302
	EXG	4		1900±260			
Min et al., 2006 [25]	POAG	14	3824±890	397±147	20	1392±177	233±66
	SOAG	15	1984±539	277±136			

OAG: open angle glaucoma; IOP: Intraocular pressure; POAG: Primary open angle glaucoma; PXS: Pseudoexfoliation syndrome; SOAG: Secondary open angle glaucoma; EXG: Exfoliation glaucoma

Table 3. Analysis of pooled data (random model) for total and active TGF b2 in OAG eyes.

Type of TGFβ	Hedges	SEM	Variance	lower limit	upper	z	p
Total TGFβ	2.20	0.34	0.11	1.54	2.86	6.55	<0.001
Active TGFβ	0.56	0.44	0.20	−0.31	1.43	1.26	0.21

Table 4. Analysis of pooled data for active TGF b2 in POAG eyes

Author, Year	Hedges	SEM	Variance	lower limit	upper	z	p
Schlotzer-Schrehardt et al. 2001	4.98	1.39	1.93	2.26	7.70	3.59	<0.001
Inatani et al. 2001	3.56	0.41	0.16	2.77	4.35	8.79	<0.001
Min et al. 2006	1.50	0.39	0.15	0.75	2.26	3.89	<0.001
Ochai et al. 2002	1.40	0.43	0.19	0.55	2.24	3.25	0.001
Ozcan et al. 2004	1.32	0.53	0.28	0.28	2.36	2.48	0.013
Picht et al. 2001	1.12	0.28	7.80E-02	0.58	1.67	4.02	<0.001
Tripathy et al. 1994	0.91	0.42	0.17	9.80E-02	1.73	2.20	0.028
Random	1.83	0.41	0.17	1.03	2.63	4.49	<0.001

Table 5. Analysis of pooled data for total TGF b2 in POAG eyes.

Author, year	Hedges	SEM	Variance	lower limit	upper	z	p
Inatani et al. 2001	4.82	0.50	0.25	3.84	5.79	9.71	<0.001
Min et al. 2006	4.07	0.60	0.36	2.90	5.24	6.79	<0.001
Schlotzer-Schrehardt et al. 2001	2.51	0.65	0.42	1.24	3.78	3.87	<0.001
Ochai et al. 2002	1.64	0.53	0.28	0.61	2.68	3.11	0.002
Tripathy et al. 1994	1.62	0.46	0.21	0.72	2.51	3.54	<0.001
Yamamato et al. 2005	1.54	0.39	0.15	0.77	2.30	3.96	<0.001
Picht et al. 2001	1.24	0.28	8.03E-02	0.68	1.79	4.37	<0.001
Random	2.45	0.52	0.27	1.43	3.47	4.73	<0.001

predominant form in ocular tissue, and we selected studies that measured TGF-β2 levels in aqueous humor.

A total of eight studies were included. The pooled analysis of all types of OAG showed that the difference between the control and OAG groups were significant for total but not active TGF-β2. However, when we analyzed the POAG cases, the differences were significant for both the total and active TGF-β2. Picht et al. [20] observed that there was no correlation between an increase in total TGF-β2 and an increase in the active form of TGF-β2. In the POAG cases that they studied, there were patients with significantly increased concentrations of total TGF-β2 and normal low levels of the active form of TGF-β2, and vice versa. Their data also indicated that age, gender, and IOP do not influence TGF-β2 levels. At the same time, it can also be assumed that the latent form of TGF-β2 is a source for active TGF-β2; hence, in OAG eyes, elevated levels of latent TGF-β2 represented a ready pool from which active TGF-β2 could be generated depending on the presence of stimuli and pathways for activation that have not been fully elucidated. Significantly high level of both the total and active TGF-β2 in POAG cases indicated not only increased secretion, but also the activation of latent TGF-β2. OAG is a multifactorial disease and in some types of OAG, the factors initiating the conversion of TGF-β2 to its active form may be less prominent, as they are in POAG. Hence, we observed a significant difference for active TGF-β2 in pooled analysis for POAG cases but not in OAG. Nevertheless, significantly high values of total TGF-β2 in both the OAG and POAG cases supported the hypothesis that TGF-β2 plays an important role in the etiology of OAG, and particularly the etiology of POAG.

The functional significance of TGF-β is complex [6]. Studies have shown that it inhibits cell growth of vascular endothelial cells, but augments α-smooth muscle actin

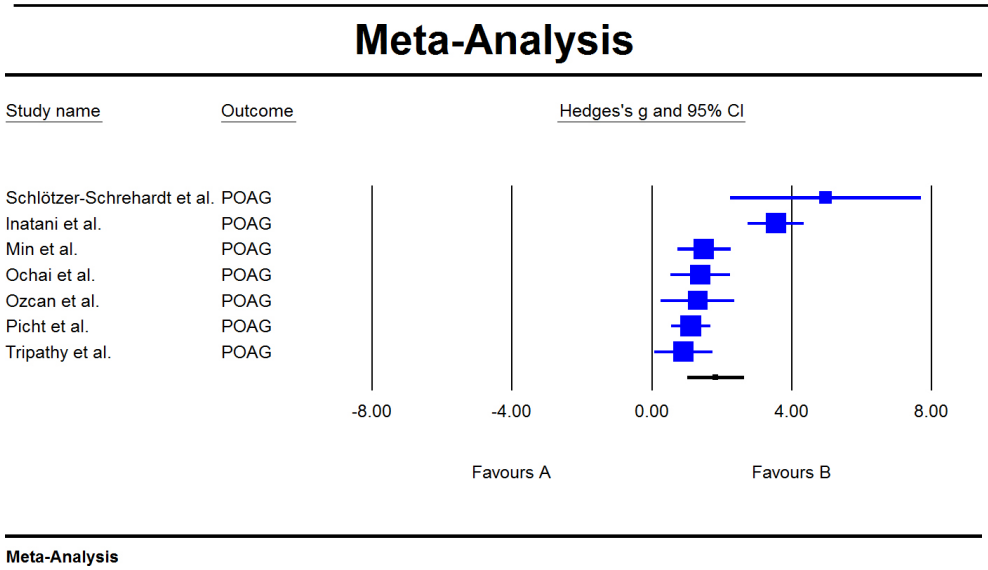

Figure 1. Forest plot of the standardized mean difference and 95% CIs of the active TGF-β2 levels in aqueous humor between the patients with POAG and the control subjects. The blue squares represent individual studies, and the size of the square represents the weight given to each study in the meta-analysis. The black square represents the pooled estimate. The horizontal lines represent 95% confidence interval (CI). The pooled results showed that patients with primary open angle glaucoma had higher active transforming growth factor (TGF)-β2 levels than the controls.

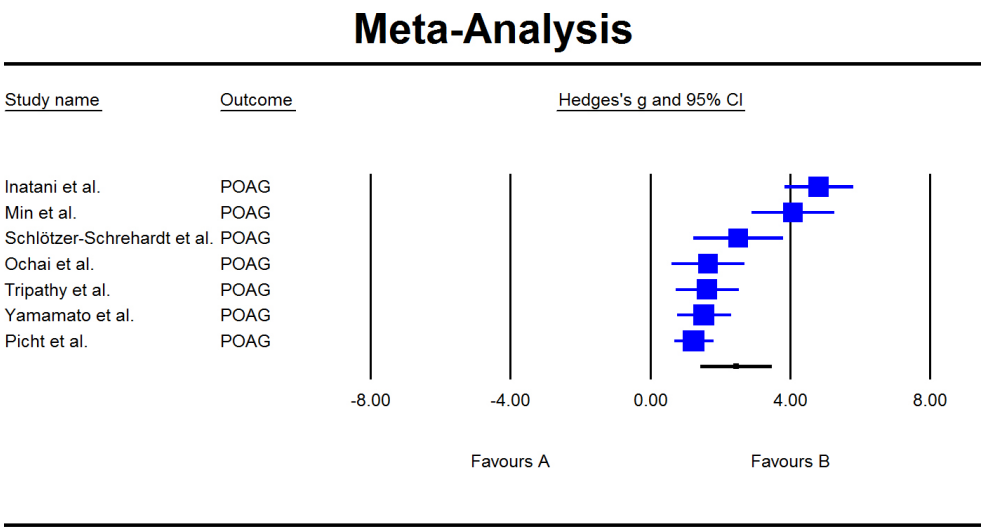

Figure 2. Forest plot of the standardized mean difference and 95% CIs of the total TGF-β2 levels in aqueous humor between the patients with POAG and the control subjects. The blue squares represent individual studies, and the size of the square represents the weight given to each study in the meta-analysis. The black square represents the pooled estimate. The horizontal lines represent the 95% confidence interval (CI). The pooled results showed that patients with primary open angle glaucoma had higher total transforming growth factor (TGF)-β2 levels than the controls.

expression [26,27]. Besides being a major molecular mediator of immunosuppression in the aqueous humor [28], it is also a potent stimulator of the synthesis of ECM components. In various tissues, it activates gene transcription and increases the synthesis and secretion of matrix proteins [29-31], fibronectin [31,32], elastin, and proteoglycans [33,34]. At the same time, it decreases synthesis of proteolytic enzymes, that degrade these proteins [13]. Fleenor et al. [35]showed that **in** cultured human anterior segments perfused with a medium supplemented with activated human recombinant TGF-β2, the

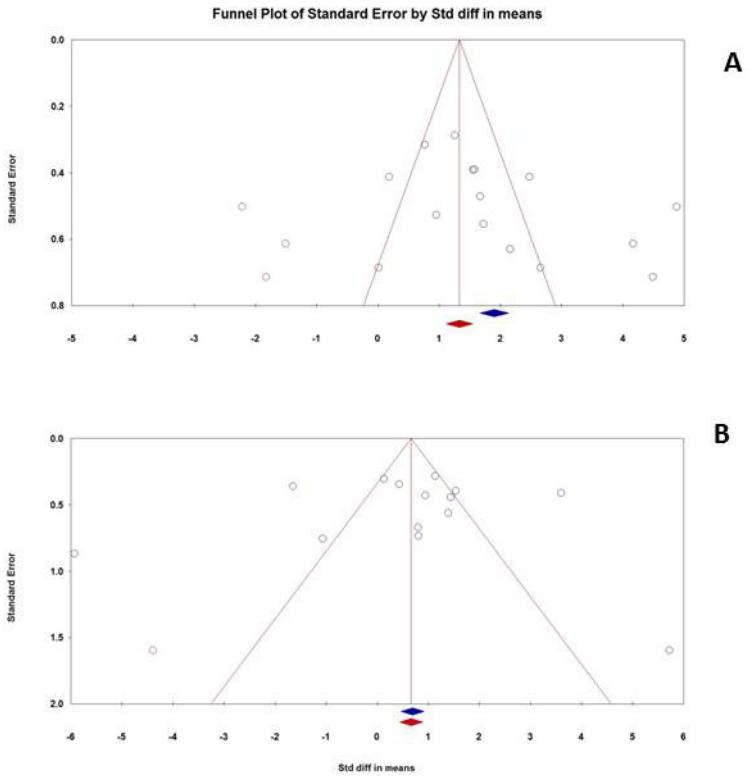

Figure 3. Begg's funnel plot with the Egger's test for publication bias for association of TGF-β levels in aqueous humor with risks of OAG. The vertical line in the funnel plot indicates the fixed-effects summary estimate, whereas the diagonal lines represent the pseudo-95% confidence interval (CI) limits concerning the effect estimate. In the absence of publication bias, studies are distributed symmetrically to the right and left of the vertical line. The blue symbols refer to the observed studies, while the red is the imputed studies, that is, expected if larger numbers of studies with negative results have been included in the analysis. **A**: Total transforming growth factor (TGF)-β2 levels in open-angle glaucoma (OAG), $P_{Egger's}$ test=0.02 **B**: Active TGF-β levels in OAG, $P_{Egger's\ test}$=0.82.

outflow facility reduced by 27%. Meanwhile, Gottanka et al. (2004) [36] observed that TGF-β2 causes focal accumulation of fine fibrillar extracellular material under the inner wall of Schlemm's canal. They also demonstrated that Schlemm's canal was 27% shorter and the length of the inner wall apparently available for fluid flow was 33% less compared with paired control eyes. The increased deposition of ECM components seems to be attributable to TGF-β2's ability to cause increased synthesis and reduced degradation of the ECM, resulting in its net accumulation [37]. Hence, increased deposition of various components of ECM, the likely cause of increased outflow resistance and elevated IOP, could be attributed to elevated TGF-β2 activity.

Despite the clear strengths of our study, such as the larger sample size compared with the individual works, the results need to be interpreted with caution. The difference between individual studies' estimates and the pooled estimate might indicate the possibility of unaddressed confounding variables such as age, the severity of disease, progression of disease, and the pharmacotherapy administered; such variables may modify the potential role of TGF-β2. The aim of this analysis is to present scientific facts rather than suggesting an intervention. One of the limitations of the statistical method used in this study is that it does not adequately reflect the error associated with parameter estimation, especially with the small number of studies. The assumption of normally distributed random effects or between-study errors is not easily verified or justified [38].

It is worth noting that measures of publication bias using funnel plots and Egger's regression may not appear to represent the same conclusion. Symmetry of the funnel plot, which is indicative of the absence of publication bias, was not distinct in some instances, although the Egger's regression statistics indicated clear absence of such a possibility. Similarly, a significant Egger's test did not conform to the symmetric funnel plot for total TGF pooled analysis. However, neither Begg's funnel plots nor Egger's regression statistics are conclusive evidence of publication bias [39]. Nevertheless, we have taken all measures—such as extensive database search through online resources and manual search—to minimize the possibility of bias. One of the concerns in a meta-analysis with small number of studies is the possibility of false-negative results [40]. However, such results are more likely when the findings from individual studies are shown to be opposing each other [41]. The absence of publication bias for the active TGF-β2 for OAG reduces the possibility of false-negative results. Moreover, the total number of patients included in this meta-analysis is

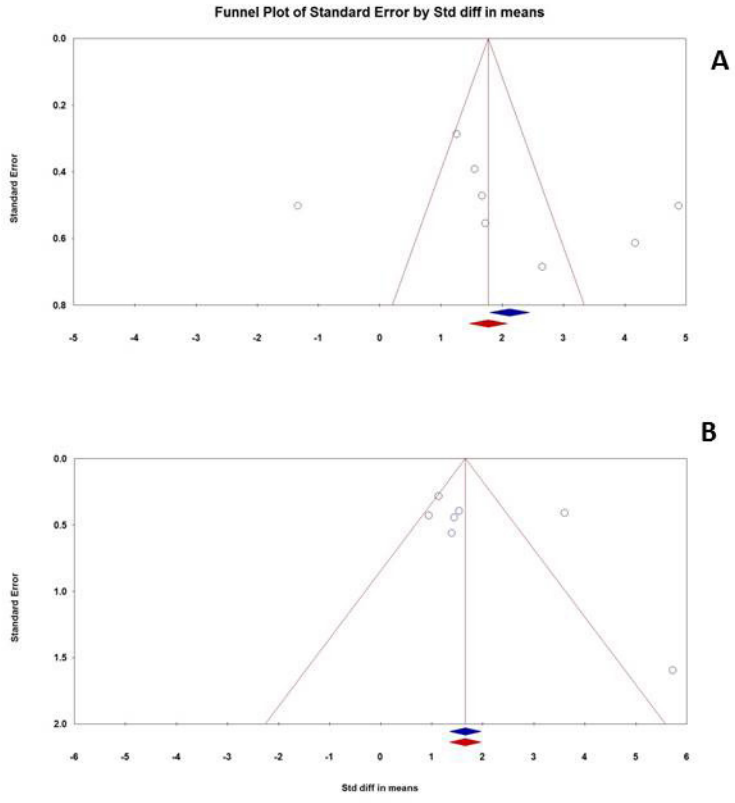

Figure 4. Begg's funnel plot with the Egger's test for publication bias for association of TGF-β levels in aqueous humor with risks of POAG. The vertical line in the funnel plot indicates the fixed-effects summary estimate, whereas the diagonal lines represent pseudo-95% confidence interval (CI) limits concerning the effect estimate. In the absence of publication bias, studies are distributed symmetrically to the right and left of the vertical line. The blue symbols refer to the observed studies, while the red is the imputed studies, that is, expected if larger numbers of studies with negative results have been included in the analysis. **A**: Total transforming growth factor (TGF)-β levels in primary open-angle glaucoma (POAG), $P_{Egger's\ test}$=0.13 **B**: Active TGF-β levels in POAG, $P_{Egger's\ test}$=0.30.

considered sufficient to provide statistical power to detect a clinically meaningful difference [42].

In conclusion, the studies included in this meta-analysis clearly demonstrated that in OAG eyes, total TGF-β2 levels are significantly elevated, whereas in POAG eyes, both the total and active TGF-β2 levels are significantly higher than in controls. Nevertheless, the analysis of pooled data confirmed the presence of elevated aqueous humor TGF-β2 levels in patients with OAG. Further investigations into the potential use of anti-TGF-β therapy in the management of glaucoma, therefore, will be of substantial value.

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REFERENCES

1. Distelhorst JS, Hughes GM. Open-angle glaucoma. Am Fam Physician 2003; 67:1937-44. [PMID: 12751655].
2. Hynes RO. The extracellular matrix: not just pretty fibrils. Science 2009; 326:1216-9. [PMID: 19965464].
3. Lütjen-Drecoll E, Shimizu T, Rohrbach M, Rohen JW. Quantitative analysis of "plaque material" between ciliary muscle tips in normal and glaucomatous eyes. Exp Eye Res 1986; 42:457-65. [PMID: 3720864].
4. Rohen JW, Lütjen-Drecoll E, Flügel C, Meyer M, Grierson I. Ultrastructure of the trabecular meshwork in untreated cases of primary open-angle glaucoma (POAG). Exp Eye Res 1993; 56:683-92. [PMID: 8595810].
5. Gottanka J, Johnson DH, Martus P, Lütjen-Drecoll E. Severity of optic nerve damage in eyes with POAG is correlated with changes in the trabecular meshwork. J Glaucoma 1997; 6:123-32. [PMID: 9098821].
6. Agarwal R, Agarwal P. The future target molecule in antiglaucoma therapy: TGF-β may have a role to play. Ophthalmic Res 2010; 43:1-10. [PMID: 19829006].
7. Agarwal R, Agarwal P. Glaucomatous neurodegeneration.: An eye on TNF-alpha. Indian J Ophthalmol 2012; 60:255-61. [PMID: 22824592].
8. Granstein RD, Staszewski R, Knisely TL, Zeira E, Nazareno R, Latina M, Albert DM. Aqueous humor contains transforming growth factor β and a small (<3500 daltons) inhibitor of thymocyte proliferation. J Immunol 1990; 144:3021-7. [PMID: 2324494].
9. Jampel HD, Roche N, Stark WJ, Roberts AB. Transforming growth factor-beta in human aqueous humor. Curr Eye Res 1990; 9:963-9. [PMID: 2276273].
10. Cousins SW, McCabe MM, Danielpour D, Streilein JW. Identification of transforming growth factor-beta as an immunosuppressive factor in aqueous humor. Invest Ophthalmol Vis Sci 1991; 32:2201-11. [PMID: 2071334].
11. Tripathi RC, Li J, Chan WF, Tripathi BJ. Aqueous humor in glaucomatous eyes contains an increased level of TGF-beta 2. Exp Eye Res 1994; 59:723-7. [PMID: 7698265].
12. Nishida K, Sotozono C, Adachi W, Yamamoto S, Yokoi N, Kinoshita S. Transforming growth factor-beta 1, -beta 2, and -beta 3 mRNA expression in human cornea. Curr Eye Res 1995; 14:235-41. [PMID: 7796607].
13. Roberts AB, Sporn MB. The transforming growth factors-beta. In: Sporn MB, Roberts AB, editors. Handbook of experimental pharmacology. Vol 95, Heidelberg, Germany: Springer; 1990. pp. 419–72.
14. Lyons RM, Jeski-Oja J, Moses HL. Proteolytic activation of latent transforming growth factor-β from fibroblast-condition medium. J Cell Biol 1988; 106:1659-65. [PMID: 2967299].
15. Miyazono K, Hellman U, Wernstedt C, Heldin C-H. Latent high molecular weight complex of transforming growth factor β1. J Biol Chem 1988; 263:6407-15. [PMID: 3162913].
16. Yamashita H. Functions of the transforming growth factor- β superfamily in eyes. J Jpn Ophthalmol Soc 1997; 101:927-47. [PMID: 9436357].
17. Brockwell SE, Gordon IR. A comparison of statistical methods for meta-analysis. Stat Med 2001; 20:825-40. [PMID: 11252006].
18. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Introduction to meta-analysis: John Wiley & Sons; 2011.
19. Inatani M, Tanihara H, Katsuta H, Honjo M, Kido N, Honda Y. Transforming growth factor β2 levels in aqueous humor of glaucomatous eyes. Graefes Arch Clin Exp Ophthalmol 2001; 239:109-13. [PMID: 11372538].
20. Picht G, Welge-Luessen U, Grehn F, Lütjen-Drecoll E. Transforming growth factor β2 levels in the aqueous humor in different types of glaucoma and the relation to filtering bleb development. Graefes Arch Clin Exp Ophthalmol 2001; 239:199-207. [PMID: 11405069].
21. Schlötzer-Schrehardt U, Zenkel M, Küchle M, Sakai LY, Naumann GO. Role of transforming growth factor-beta1 and its latent form binding protein in pseudoexfoliation syndrome. Exp Eye Res 2001; 73:765-80. [PMID: 11846508].
22. Ochiai Y, Ochiai H. Higher concentration of Transforming growth factor β in aqueous humor of glaucomatous eyes and diabetic eyes. Jpn J Ophthalmol 2002; 46:249-53. [PMID: 12063033].
23. Ozcan AA, Ozdemir N, Canataroglu A. The aqueous levels of TGF-β2 in patients with glaucoma. Int Ophthalmol 2004; 25:19-22. [PMID: 15085971].
24. Yamamoto N, Itonaga K, Marunouchi T, Majima K. Concentration of transforming growth factor beta2 in aqueous humor. Ophthalmic Res 2005; 37:29-33. [PMID: 15637419].

25. Min SH, Lee TI, Chung YS, Kim HK. Transforming growth factor-beta levels in human aqueous humor of glaucomatous, diabetic and uveitic eyes. Korean J Ophthalmol 2006; 20:162-5. [PMID: 17004630].

26. Kocher O, Madri JA. Modulation of actin mRNA in cultured vascular cells by matrix components and TGF-β in vitro. Cell Dev Biol 1989; 25:424-34. .

27. Tamm ER, Siegner A, Baur A, Lütjen-Drecoll E. Transforming growth factor-β1 induces α-smooth muscleactin expression in cultured human and monkey trabecular meshwork. Exp Eye Res 1996; 62:389-97. [PMID: 8795457].

28. Streilein JW. Role of anteriorchamber-associated immune deviation in the pathogenesis of uveitis. Dev Ophthalmol 1992; 23:86-93. [PMID: 1730378].

29. Heckmann M, Aumailley M, Chu M. Timpl Ra, Krieg T. Effect of transforming growth factor-b on collagen type VI expression in human dermal fibroblasts. FEBS 1991; 310:79-82. .

30. Madri JA, Pratt BM, Tucker AM. Phenotypic modulation of endothelial cells by transforming growth factor-beta depends upon the composition and organization of the extracellular matrix. J Cell Biol 1988; 106:1375-84. [PMID: 3283153].

31. Varga J, Rosenbloom J, Jimenez SA. Transforming growth factor beta (TGF beta) causes a persistent increase in steady state amounts of type I and type III collagen and fibronectin mRNAs in normal human dermal fibroblasts. Biochem J 1987; 247:597-604. [PMID: 3501287].

32. Ignotz RA, Massague J. Transforming growth factor-β stimulates the expression of fibronectin and collagen and their incorporation into extracellular matrix. J Biol Chem 1986; 261:4337-45. [PMID: 3456347].

33. Morales TI, Roberts AB. Transforming growth factor beta regulates the metabolism of proteoglycans in bovine cartilage organ cultures. J Biol Chem 1988; 263:12828-31. [PMID: 3166454].

34. Ryynänen J, Sollberg S, Olsen DR, Uitto J. Transforming growth factor beta up-regulates type VII collagen expression in normal and transformed epidermal keratinocytes in culture. Biochem Biophys Res Commun 1991; 180:673-80. [PMID: 1953739].

35. Fleenor DL, Shepard AR, Helberg PE, Jacobson N, Pang IH, Clark AF. TGF- β2-induced changes in human trabecular meshwork: implications for intraocular pressure. Invest Ophthalmol Vis Sci 2006; 47:226-34. [PMID: 16384967].

36. Gottanka J, Chan D, Eichhorn M, Lütjen-Drecoll E, Ross Ethier C. Effects of TGF- β2 in perfused human eyes. Invest Ophthalmol Vis Sci 2004; 45:153-8. [PMID: 14691167].

37. Fuchshofer R, Yu AH, Welge-Lüssen U, Tamm ER. Bone morphogenetic protein-7 is an antagonist of transforming growth factor-beta2 in human trabecular meshwork cells. Invest Ophthalmol Vis Sci 2007; 48:715-26. [PMID: 17251470].

38. Hardy RJ, Thompson SG. Detecting and describing heterogeneity in meta-analysis. Stat Med 1998; 17:841-56. [PMID: 9595615].

39. Viechtbauer W. Publication bias in meta-analysis: Prevention, assessment and adjustments. Psychometrika 2007; 72:269-71. .

40. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; •••:1088-101. [PMID: 7786990].

41. Hajek T, Kopecek M, Alda M, Uher R, Höschl C. Why negative meta-analyses may be false? Eur Neuropsychopharmacol 2013; 23:1307-9. [PMID: 23402721].

42. Verstraete M. Value and limitation of meta-analysis. Pathophysiol Haemost Thromb 2002; 32:278-81. [PMID: 13679657].

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