Review

Is Glaucoma a Two-Pressure-Related Optic Neuropathy? A Systematic Review and Meta-Analysis

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Abstract

Objectives: To review the current literature related to the correlation between translaminar pressure difference (TLPD) and glaucoma.

Materials and Methods: In this article, we conducted a literature review using MEDLINE via PubMed, Cochrane Eyes and Vision, and Google Scholar from 01/01/2010 to 31/12/2022. Search terms included "glaucoma", "intraocular pressure", "translaminar cribrosa pressure gradient/difference", "intracranial pressure", and "cerebrospinal fluid pressure". Of 471 results, 8 articles were selected for the meta-analysis.

Results: Our meta-analysis demonstrated significantly higher intraocular pressure, lower cerebrospinal fluid pressure (CSFp), and greater TLPD in high-tension and normal-tension glaucoma groups compared to healthy groups.

Conclusion: The differences in CSFp and TLPD between glaucoma and healthy people detected in current studies suggests a potential relationship between TLPD and glaucoma.

Keywords: Glaucoma, intraocular pressure, translaminar cribrosa pressure gradient/difference, cerebrospinal fluid pressure, intracranial pressure

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Introduction

Glaucoma is a chronic, irreversible optic neuropathy characterized by damage to retinal ganglion cells with or without elevated intraocular pressure (IOP). The current global prevalence of glaucoma is 3.5% in the 40- to 80-year-old population. In 2013, the number of people in this age group suffering from glaucoma was 64.3 million and was predicted to rise to 76 million in 2020 and 112 million in 2040.[1]

Elevated IOP has long been considered the main and only modifiable risk factor in the pathogenesis of glaucoma. Nonetheless, patients may be diagnosed with normal-tension glaucoma (NTG) or exhibit disease progression even with well-controlled IOP and in the absence of cardiovascular risk factors.[2,3] Because IOP exerts its force at the anterior lamina cribrosa and is theoretically countered by the cerebrospinal fluid pressure (CSFp) within the optic nerve sheath which exerts force at the back of the globe, researchers have explored the potential relationship between glaucoma and CSFp.[4,5,6,7] CSFp can be calculated by invasive (lumbar puncture) and non-invasive (formula,[8,9,10,11] transcranial Doppler[12]) methods. The resulting translaminar pressure difference (TLPD = IOP - CSFp)[13] may be normal/balanced or abnormal/imbalanced in either direction. If the intraocular force (IOP) is in excess, glaucoma may result. On the other hand, a TLPD with excessive CSFp and normal IOP has been implicated in the optic disc swelling and posterior globe flattening that may be seen in disorders of elevated intracranial pressure (idiopathic intracranial hypertension) and in astronauts after long-duration spaceflight.[14,15] The reverse effect of the TLPD theory can also be seen in ocular hypotony, in which low IOP and normal CSFp can cause optic disc edema.[16] Some animal and experimental studies have suggested the possible role of TLPD in glaucoma.[17,18,19] We conducted this review because a

potential intervention to increase CSFp, reduce IOP, or alter the gradient might have implications in the broader management of glaucoma.

In 2015, Siaudvytyte et al.[20] published the first systematic review and meta-analysis about the correlation between CSFp and glaucoma. Their study showed a higher TLPD in subjects with glaucoma compared to healthy controls, as well as a correlation between TLPD and glaucomatous optic neuropathy.[20] Most current reviews are qualitative literature searches without any quantitative analysis. Therefore, we conducted this study to systematically evaluate the current evidence that links glaucoma development and progression to alterations in the TLPD.

Materials and Methods

Literature Search

This systematic review and meta-analysis followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline. We searched MEDLINE through PubMed, Cochrane Eyes and Vision, and Google Scholar from 01/01/2010 to 31/12/2022. Keywords included "glaucoma", "intraocular pressure", "translaminar cribrosa pressure gradient/difference", "intracranial pressure", and "cerebrospinal fluid pressure". Two independent reviewers (T.T.H. and V-A.B.) independently reviewed all PubMed, Cochrane Eyes and Vision, and Google Scholar abstracts to assess eligibility.

Eligibility Criteria

Peer-reviewed English papers with cross-sectional, case-control, or cohort designs including high-tension glaucoma (HTG) (primary open-angle glaucoma [POAG] or angle-closure glaucoma [PACG]) and NTG participants in the case group and healthy individuals in the control group were selected. Variables such as glaucoma type, IOP, CSFp, and TLPD must have been clearly described. We excluded literature or narrative reviews, animal and computer model studies, and studies not analyzing IOP, CSFp, and TLPD in glaucoma patients. Eligible full-length articles were finally selected by two reviewers (T.T.H. and V-A.B.). The Newcastle-Ottawa Scale, a collaborative project between Newcastle University, Australia and Ottawa, Canada, was applied to assess the quality of non-randomized studies in meta-analysis.[21]

Outcome Measures

Data extracted for the meta-analysis included IOP, CSFp, TLPD, and CSFp measurements and glaucoma type.

Definitions

Validated CSFp measurements were both invasive (lumbar puncture) and non-invasive (formula,[8,9,10,11] transcranial Doppler[12]). TLPD was defined as IOP - CSFp.[3]

Statistical Analysis

The data were analyzed using RevMan 5.3 (Cochrane Collaboration). A random effects model was employed to calculate effect size due to the heterogeneity of the studies. A p value less than 0.05 was considered statistically significant.

Results

We found 471 results through database searches. After removing duplicated records, we screened 90 studies. Of these screened studies, 25 abstracts met the selection criteria for full-text assessment; 15 of them were excluded with reasons shown in Figure 1, leading to a final inclusion of 8 articles (Table 1).[5,9,10,11,22,23,24,25] Quality assessment and extracted data for meta-analysis of the included studies can be found in Supplementary Tables 1 and 2.

Glaucoma patients in the HTG group had significant higher IOP (Z=2.65, p=0.008), lower CSFp (Z=5.9, p<0.0001), and higher TLPD (Z=3.9, p<0.0001) than the healthy participants (Figure 2A, B, C). Similarly, the NTG group also had significant higher IOP (Z=93.89, p<0.00001), lower CSFp (Z=2.06, p=0.04), and higher TLPD (Z=2.41, p=0.02) compared to controls (Figure 2D, E, F). Table 2 includes studies supporting the correlation between TLPD and glaucoma progression in terms of structure and function.

Discussion

At the time of the first review in 2015, only 3 prospective studies were available for analysis. Since then, additional prospective studies have been carried out to explore the potential relationship between TLPD and glaucoma risk and progression. Our study found significant differences between glaucoma patients and healthy people in terms of IOP, CSFp, and TLPD in both the HTG and NTG groups. These findings are consistent with the meta-analysis of Siaudvytyte et al.[20] as well as most of the included studies, and further contribute to our knowledge of this topic.

In our study, the NTG group had a higher mean IOP than healthy controls (p<0.00001), which was similar to a recent study of Deimantavicius et al.[26] This could be because the studies by Ren et al.[5] and Lee et al.[9] included NTG patients whose IOP was higher on average than in other studies in this systematic review.

Our results also showed that CSFp was significantly lower in both the HTG (p<0.0001) and NTG (p=0.04) groups compared to control groups. According to Wang et al.[27], NTG patients had the narrowest orbital optic nerve subarachnoid space (SAS) on magnetic resonance imaging (MRI), suggesting a lower CSFp in comparison to POAG patients and healthy participants. Employing computed tomographic cisternography, Pircher et al.[28] indicated that contrast-loaded CSF gradually decreased along the optic nerve of NTG patients while no similar reduction was found in normal subjects. Boye et al.[29] measured the flow-range ratio between the intracranial cavity and SAS of the optic nerve in MRI diffusion images and demonstrated that this ratio was significantly lower in NTG compared to healthy people, indicating abnormal CSFp in NTG. In the study by Deimantavicius et al.[26], CSFp determined by two-depth transcranial Doppler (TCD) ultrasonography was lower in both the HTG and NTG groups than in healthy participants.

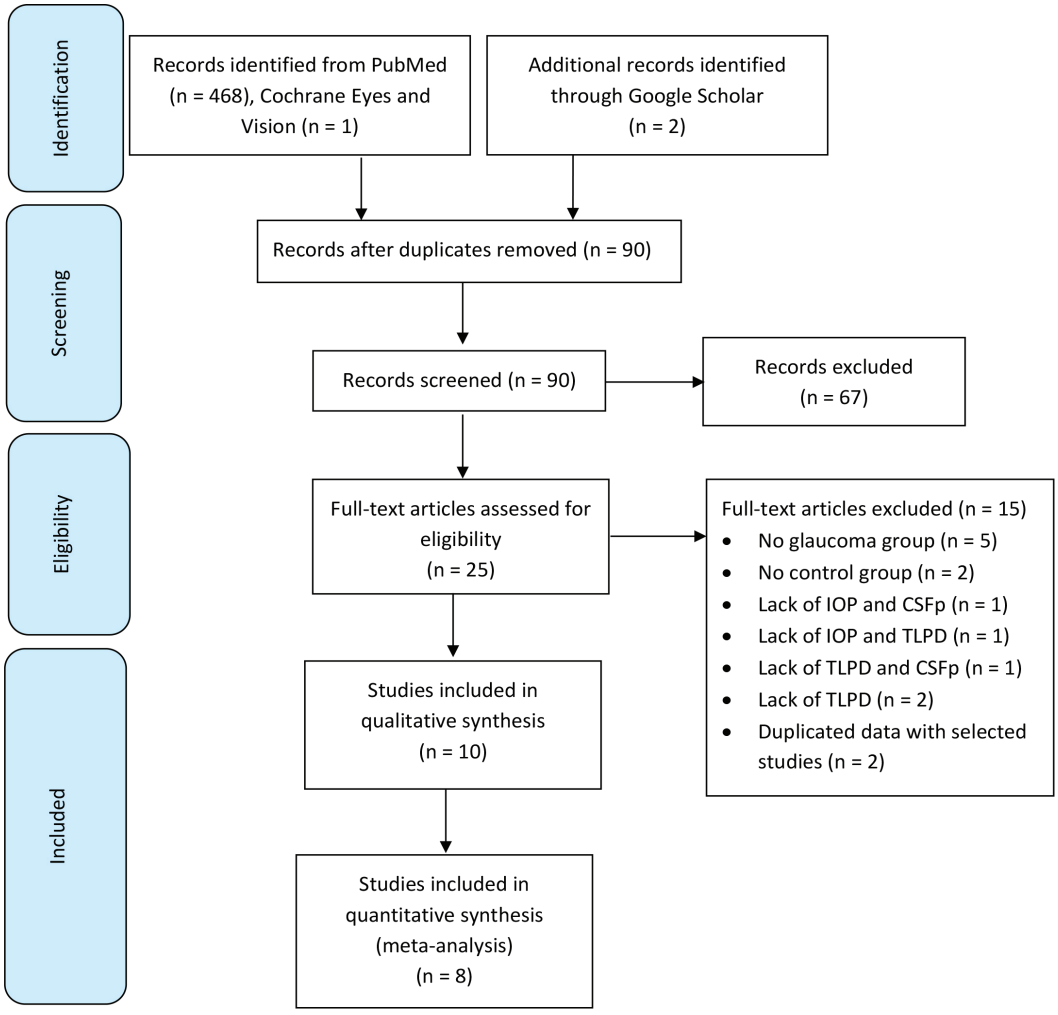

Figure 1. Systematic review flow diagram
IOP: Intraocular pressure, CSFp: Cerebrospinal fluid pressure, TLPD: Translaminar pressure difference

Table 1. Selected studies

Study	CSFp measurement	Research design	Number of patients	Glaucoma type
Ren et al.[5] 2010	Lumbar puncture	Cross-section (prospective)	114	NTG, HTG
Siaudvytyte et al.[22] 2014	Two depth TCD	Cross-section (prospective)	27	NTG, HTG
Jonas et al.[23] 2015	Formula	Cross-section (population-based)	3468	HTG (POAG, PACG)
Jonas et al.[24] 2015	Formula	Cross-section (population-based)	4711	HTG (POAG, PACG)
Lee et al.[9] 2016	Formula	Cross-section (population-based)	12743	NTG
Landi et al.[10] 2019	Formula	Cross-section (prospective)	43	HTG (POAG)
Matuoka et al.[11] 2021	Formula	Cross-section (prospective)	75	HTG (POAG)
Lindén et al.[25] 2018	Lumbar puncture	Cross-section (prospective)	24	NTG

CSFp: Cerebrospinal fluid pressure, NTG: Normal-tension glaucoma, HTG: High-tension glaucoma, POAG: Primary open-angle glaucoma, PACG: Primary angle-closure glaucoma, TCD: Transcranial Doppler

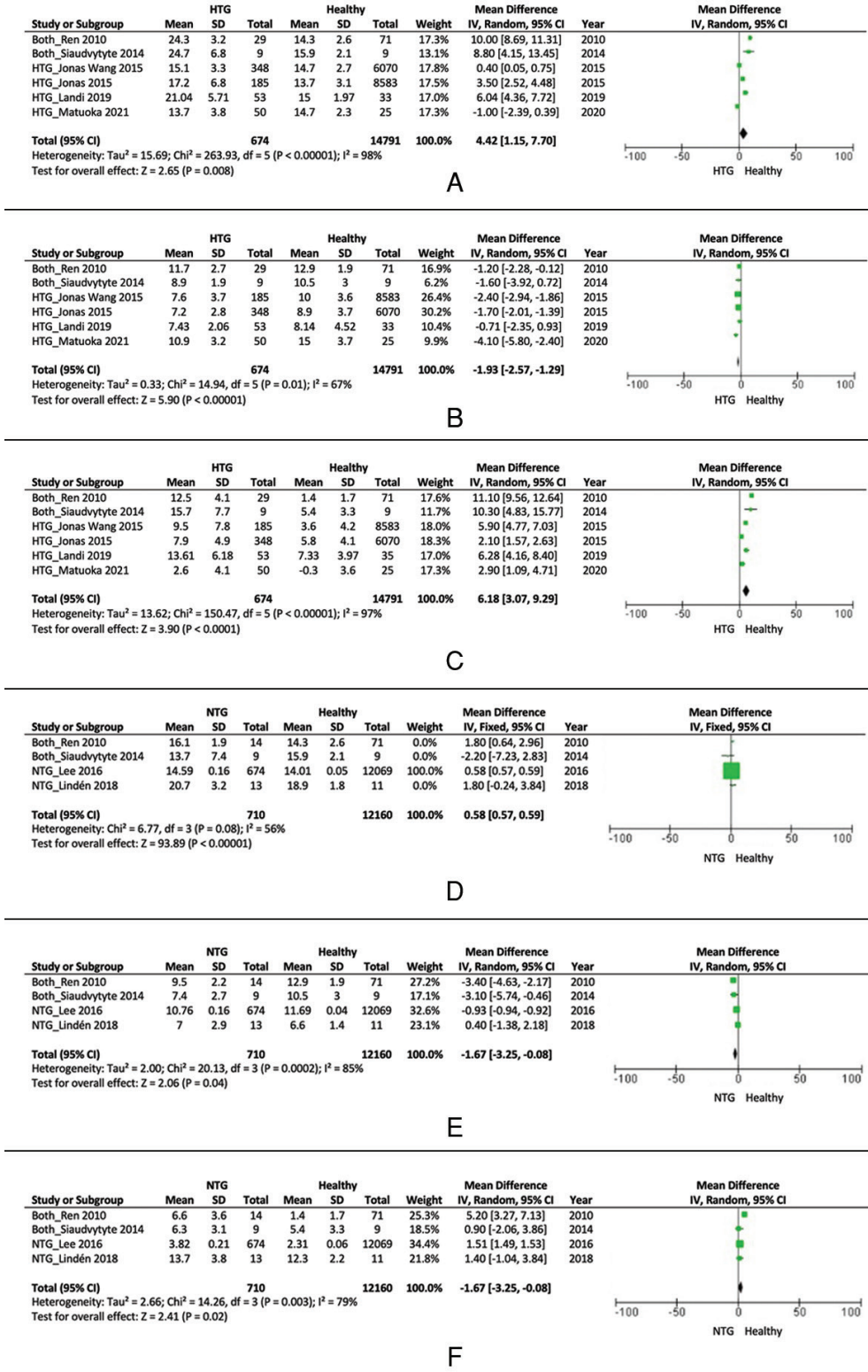

Figure 2. Meta-analysis results between high-tension glaucoma (A. Intraocular pressure, B. Cerebrospinal fluid pressure, C. Translaminar pressure difference), normal-tension glaucoma (D. Intraocular pressure, E. Cerebrospinal fluid pressure, F. Translaminar pressure difference), and healthy subjects

HTG: High-tension glaucoma, NTG: Normal-tension glaucoma, SD: Standard deviation, IV: Weighted mean difference, CI: Confidence interval, df: Degrees of freedom, I²: I-square heterogeneity statistic

Table 2. Correlation between translaminar pressure differences and glaucoma progression

Study	Number of patients	Groups	Outcome measures	Methods	Correlation
Ren et al.[5] 2010	114	NTG, HTG, control	MD	HFA	r=0.69, p=0.005
Ren et al.[31] 2011	52	HTG, NTG, OH	NRA MVFD	HFA HRT	r=-0.38, p=0.006 r=0.38, p=0.008
Siaudvytyte et al.[22] 2014	27	NTG, HTG, control	NRA	HRT	r=-0.83, p=0.01
Zhang et al.[32] 2018	6830	POAG, control	NRA	HRTII	B=-0.002, p=0.028
Landi et al.[10] 2019	43	POAG, control	MD Inferior RNFL Superior RNFL	HFA SD OCT SD OCT	r=-0.31, p<0.05 r=-0.29, p<0.05 r=-0.27, p<0.05
Matuoka et al.[11] 2021	50	POAG, control	OPP	Formula	r=-0.58, p<0.0001

NTG: Normal-tension glaucoma, HTG: High-tension glaucoma, POAG: Primary open-angle glaucoma, OH: Ocular hypertension, MD: Mean deviation, MVFD: Mean visual field defect, NRA: Neural rim area, RNFL: Retinal nerve fiber layer, OPP: Ocular perfusion pressure, HFA: Humphrey field analyzer, HRT: Heidelberg retinal tomogram, SD-OCT: Spectral domain optical coherence tomography

An analysis of 30-year clinical data performed by Knier et al.[30] also demonstrated that patients with open-angle glaucoma had significantly lower CSFp compared to the control group.

We did not include the studies of Ren et al.[31] (2011) and Xie et al.[8] (2018) despite the fact that IOP, CSFp, and TLPD were presented because they did not include any glaucoma patients. Interestingly, Ren et al.[31] found that patients with ocular hypertension had higher CSFp than healthy participants. The authors hypothesized that this could be a physiologic compensation to prevent significant imbalance at the level of the lamina cribrosa and subsequent glaucoma progression. This finding was later confirmed by Xie et al.[8], who proposed a pre-glaucoma stage in which there were only changes in TLPD with no structural or functional damage. This paved the way for further studies to investigate the TLPD threshold that differentiated normal from the pre-glaucoma stage.

Our findings showed that the TLPD was significantly higher in both the HTG and NTG groups, which was consistent with the findings of Deimantavicius et al.[26] The lamina cribrosa is exposed to both IOP and CSFp, so this finding further supports the potential relationship between TLPD and glaucoma mentioned in numerous studies.[5,10,11,22,32,33,34,35]

Study Limitations

There are some limitations related to the measurement of IOP, CSFp, and TLPD. IOP is an indirect estimation, depending on the biomechanical characteristics of cornea, and is assessed with the person in an upright position (Goldmann applanation tonometry, rebound tonometry and pneumotonometry) except for less-frequently used tonometers such as the Schiotz (indentation) or Maclakov (applanation), which can assess IOP in the supine position. CSFp is normally measured by lumbar puncture in the prone or left lateral decubitus position, and because of gravitational effects, CSFp is higher in either of these positions than in the upright position in which IOP is measured. Simplified formulas for TLPD also assume that intraorbital CSFp is similar to intracranial CSFp. However, some previous studies suggested that the orbital SAS does not communicate freely with the intracranial SAS due to trabeculae and septate structures. Therefore, CSFp measured by lumbar puncture might not represent the true CSFp behind the laminar cribrosa.[3] Recently, a study by Pircher et al.[36] demonstrated an enlarged optic nerve sheath diameter without any increase in lumbar CSFp in NTG patients, suggesting a disrupted connection between intraorbital and intracranial SAS. Our review included studies with different methods of assessing CSFp (lumbar puncture, formula and transcranial Doppler). Hence, a random effects model was used in statistical analysis to account for this heterogeneity. Additionally, TLPD was not an empirical measurement, but instead a calculation based on two variables that were assessed for significance at the same time.

Lindén et al.[25] filled this gap in the literature data by measuring CSFp in different positions and found no statistical difference in CSFp between NTG patients and healthy people. However, despite using standardized and specialized equipment for CSFp recording in the study, the study assumed a direct connection between the two SAS compartments.[25] Pircher et al.[37] was also unable to confirm either a lower lumbar CSFp or higher TLPD in NTG compared to other studies, but their retrospective study did not include a control group. For this reason, this study was not included in our meta-analysis.

Further studies are needed to investigate the communication between the two SAS compartments as well as to evaluate the interaction between IOP and CSFp in different positions, especially in the upright position as suggested by Lindén et al.[25] and Pircher et al.[37] Two-depth TCD is a non-invasive method with better reliability and stronger relationship with lumbar CSFp than optic nerve sheath diameter and CSFp measured close to the optic nerve, and as such might offer a promising approach to fill the abovementioned gaps.[26,38] Discovering the correlation between TLPD and glaucomatous optic neuropathy might enhance the current understanding of NTG pathogenesis and the natural course of glaucoma progression despite well-controlled IOP, leading to future therapeutic interventions in glaucoma.

Conclusion

Our analysis validated that a significantly lower CSFp and higher TLPD is seen in both HTG and NTG patients in comparison with healthy groups, revealing the potential

relationship between glaucoma and TLPD suggested in previous population and prospective studies.

Ethics

Authorship Contributions

Concept: V.A.B., Design: V.A.B., P.S., T.T.H., Data Collection or Processing: V.A.B., T.T.H., Analysis or Interpretation: V.A.B., T.T.H., Literature Search: V.A.B., P.S., T.T.H., Writing: V.A.B., P.S., T.T.H.

Conflict of Interest: No conflict of interest was declared by the authors.

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Supplementary Table 1. Newcastle-Ottawa scale assessing the quality of selected non-randomized studies

Study	Selection	Comparability	Exposure
Ren et al.[5] 2010	-*-*	*-	-*-
Siaudvytyte et al.[22] 2014	-*--	--	-*-
Jonas et al.[23] 2015	-**-	--	-*-
Jonas et al.[24] 2015	-**-	--	-*-
Lee et al.[9] 2016	-***	*-	-*-
Landi et al.[10] 2019	-*-*	--	-*-
Matuoka et al.[11] 2021	-*-*	--	-*-
Lindén et al.[25] 2018	**-*	--	-*-

Supplementary Table 2. Extracted data from selected studies

Study	Glaucoma type (number of eyes)	IOP (mmHg)	CSFp (mmHg)	TLPD (mmHg)
Ren et al.[5] 2010	NTG (n=14)	16.1±1.9	9.5±2.2	6.6±3.6
	HTG (n=29)	24.3±3.2	11.7±2.7	12.5±4.1
	Control (n=71)	14.3±2.6	12.9±1.9	1.4±1.7
Siaudvytyte et al.[22] 2014	NTG (n=9)	13.7±7.4	7.4±2.7	6.3±3.1
	HTG (n=9)	24.7±6.8	8.9±1.9	15.7 ±7.7
	Control (n=9)	15.9±2.1	10.5±3.0	5.4±3.3
Jonas et al.[23] 2015	HTG (n=348)	15.1±3.3	7.2±2.8	7.9±4.9
	Control (n=6070)	14.7±2.7	8.9±3.7	5.8±4.1
Jonaset al.[24] 2015	HTG (n=185)	17.2±6.8	7.6±3.7	9.5±7.8
	Control (n=8583)	13.7±3.1	10.0±3.6	3.6±4.2
Landi et al.[10] 2019	HTG (n=53)	21.04±5.71	7.43±2.06	13.61±6.18
	Control (n=33)	15.00±1.97	8.14±4.52	7.33±3.97
Matuoka et al.[11] 2021	HTG (n=50)	13.7±3.8	10.9±3.2	-0.3±3.6
	Control (n=25)	14.7±2.3	15.0±3.7	2.6±4.1
Lee et al.[9] 2016	NTG (n=674)	14.59±0.16	10.76±0.16	3.82±0.21
	Control (n=12069)	14.01±0.05	11.69±0.04	2.31±0.06
Lindén et al.[25] 2018	NTG (n=13)	20.7±3.2	7.0±2.9	13.7±3.8
	Control (n=11)	18.9±1.8	6.6±1.4	12.3±2.2

NTG: Normal-tension glaucoma, HTG: High-tension glaucoma, IOP: Intraocular pressure, CSFp: Cerebrospinal fluid pressure, TLPD: Translaminar pressure difference