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REVIEW

Literature review and meta-analysis of translaminar pressure difference in open-angle glaucoma

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Abstract

There is increasing evidence in the literature regarding translaminar pressure difference's (TPD) role in the pathophysiology of glaucoma. The optic nerve is exposed not only to intraocular pressure in the eye, but also to intracranial pressure (ICP), as it is surrounded by cerebrospinal fluid in the subarachnoid space. Although pilot studies have identified the potential importance of TPD in glaucoma, limited available data currently prevent a comprehensive description of the role that TPD may have in glaucomatous pathophysiology. In this review, we present all available qualified data from a systematic review of the literature of the role of TPD in open-angle glaucoma (OAG). PubMed (Medline), OVID Medline, ScienceDirect, SpringerLink, and all available library databases were reviewed and subsequent meta-analysis of pooled mean differences are presented where appropriate. Five papers including 396 patients met criteria for inclusion to the analysis. Importantly, we included all observational studies despite differences in ICP measurement methods, as there is no consensus regarding best-practice ICP measurements in glaucoma. Our results show that not only TPD is higher in glaucoma patients compared with healthy subjects, it is related to structural glaucomatous changes of the optic disc. Our analysis suggests further longitudinal prospective studies are needed to investigate the influence of TPD in OAG, with a goal of overcoming methodological weaknesses of previous studies.

Eye (2015) **29,** 1242–1250; doi:10.1038/eye.2015.127; published online 17 July 2015

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Received: 2 February 2015
Accepted in revised form: 10 June 2015
Published online: 17 July 2015

Introduction

Glaucoma is the second leading cause of blindness worldwide.[1] Quigley *et al* reported that there are 60.5 million people suffering from glaucoma in the world and it is predicted that in 2020 this number will increase to 79.6 million, with 74% having open-angle glaucoma (OAG).[2] The prevalence of glaucoma, which increases with age, is increasing primarily as the population ages. According to the World Health Organization (WHO) there is about 2.65% of the global population over 40 years of age who has glaucoma.[3] The global disability adjusted life years of glaucoma has risen for the past 20 years: from 443 000 years in 1990 to 943 000 years in 2010.[4,5] Glaucoma is characterized by structural optic nerve head (ONH) and visual field changes that may occur at any intraocular pressure (IOP) level, depending on each person's individual susceptibility. Although lowering IOP helps to decelerate or stabilize the disease, vast numbers of patients still develop and progress in glaucoma, despite an IOP within normal range.[6] It has been shown that in addition to high IOP there are many additional risk factors including: lower ocular perfusion pressure; reduced ocular blood flow; low blood pressure (BP); myopia; and several others.[7–10] Evidence confirms that these non-IOP factors lead to apoptotic processes associated with glaucoma.[11] Recently, researchers have began to focus on intracranial pressure (ICP) and translaminar pressure difference (TPD) as having a potential role in glaucomatous optic neuropathy.[12,13] The optic nerve is exposed not only to IOP in the eye, but also to ICP, as it is surrounded by cerebrospinal fluid (CSF) in the subarachnoid space (SAS). The lamina cribrosa demarcates these two pressurized zones and the pressure difference between them is called TPD (TPD = IOP – ICP).[14] Physiologically, the difference between IOP (14.3 (2.6) mm Hg) and ICP (12.9(1.9) mm Hg, in the supine position) is small.[15] A higher TPD may lead to abnormal function and damage of the optic nerve due to changes in axonal

transportation, deformation of the lamina cribrosa, altered blood flow or a combination thereof leading to glaucomatous damage.[16] Furthermore, it is considered that the TPD may be a primary pressure related factor for glaucoma, as the ONH is located at the junction between the intraocular and retrobulbar spaces.[17] However, the role of TPD in glaucoma pathogenesis and its progression remains unclear as the gold standard for ICP evaluation is an invasive measurement of the pressure in the CSF via lumbar puncture or via implantation of a pressure sensor into a cerebral ventricle.[18–20] Importantly, this invasiveness includes the potential risk for intracranial hemorrhages and infection.[21] To overcome these invasive limitations, several approaches have been proposed to estimate ICP noninvasively including: transcranial Doppler ultrasonography; tympanic membrane displacement; ophthalmodynamometry; and measurement of optic nerve sheath diameter.[22] For instance, Xie *et al* estimated mathematical ICP formula based on three parameters: diastolic BP; age and body mass index ($ICP = 0.44 \times$ body mass index $(kg/m^2) + 0.16 \times$ diastolic BP (mm Hg) $- 0.18 \times$ age (years) $- 1.9$); and Bland–Altman analysis revealed that 40 of 42 measurements were within the 95% limits of agreement.[23] All of these approaches are based on correlation of anatomical or physiological parameters of the human head and brain with ICP. Unfortunately, correlation-based approaches are not accurate for real-quantitative ICP value measurement. To the best of our knowledge, this is the first review and meta-analysis to present all available qualified data from a systematic review of the literature of the role of TPD in OAG.

Materials and methods

A comprehensive literature search was performed via electronic databases of PubMed (Medline), OVID Medline, ScienceDirect, SpringerLink, and all available library databases with reference cross-matching to identify all observational studies evaluating TPD in patients with OAG. In our literature search we included a combination of keywords, such as 'translaminar pressure difference', 'translaminar pressure gradient', or 'translamina cribrosa pressure difference' and 'glaucoma'. Search strategy was carried out on articles published over the past 10 years (from November 2004 to November 2014). The search was performed by two independent researchers (AD and LB) until all relevant articles were identified. The completeness of searches was validated by the primary author (LS) using all available library databases. We included all observational studies despite differences in ICP measurement methods (invasive or noninvasive) as there is no consensus regarding best-practice measurements of ICP in glaucoma.

Study quality assessment was based on the following criteria:

- The study type and number of subjects.
- Information on the characteristics of the studied population.
- Information on the inclusion criteria.
- Data processing quality.
- Approval of the Ethics Committee.

Data including age, IOP, ICP, and TPD were collected and statistical analysis was performed using the statistical analysis program (SPSS version 22, 'Insight Solutions', Vilnius, Lithuania). The analysis of the quantitative variables included calculation of the weighted averages mean and SD (×(SD)). Two articles subdivided data into categories based on the form of primary open-angle glaucoma (POAG), thus weighted averages of all data points and SD were calculated.[15,24] One article presented data of IOP and ICP, while TPD was used just in correlations; the data were converted to numerical values using formula $TPD = IOP - ICP$.[25] The hypothesis of equality among groups was analyzed using *t*-test. The level of significance $P < 0.05$ was considered significant.

Results

A total of 135 articles were identified from the search strategy and five studies that reported quantitative TPD parameters directly were deemed appropriate for inclusion.[12,15,24–26] Figure 1 shows the article selection process for studies included in the final meta-analysis. Ninety-two papers including case reports, comments, letters, editorials, abstracts, and review papers/chapters were excluded, as this systematic review was sought observational studies. For clinical applicability, only data from human subjects were included, thus eliminating articles[27–33] that used experimental models. Twenty-five papers were excluded because there was no evaluation of TPD.[34–58] Three papers were eliminated because glaucoma patients were not analyzed in these studies.[59–62] Three articles which did not present quantitative TPD values in OAG group were also excluded[62–64] Table 1 shows the characteristics of papers (including 181 POAG patients and 215 healthy subjects) included to systematic review.[12,15,24–26]

Two retrospective studies[25,26] and three prospective studies[12,15,24] matched all search criteria. One study evaluated ICP noninvasively using a two-depth transcranial Doppler (TCD) device (Vittamed UAB, Kaunas, Lithuania),[24] based on simultaneous measurements of blood-flow parameters in intracranial and extracranial segments of the ophthalmic artery (OA).

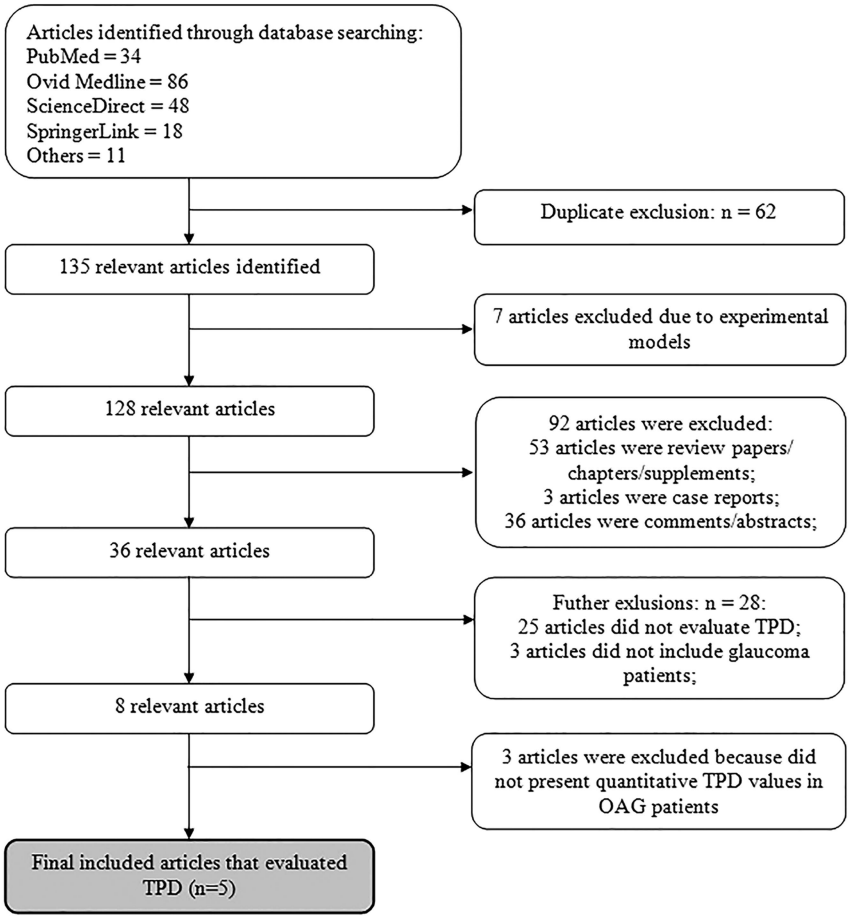

Figure 1 Summary of article selection process. TPD, translaminar pressure difference; OAG, open-angle glaucoma.

Table 1 Characteristics of the studies

Authors	*Ren* et al[12]	*Ren* et al[15]	*Siaudvytyte* et al[24]	*Berdahl* et al[25]	*Berdahl* et al[26]
Study type	Observational, prospective	Observational, prospective	Observational, prospective	Observational, retrospective	Observational, retrospective
Included groups	POAG (NTG+HTG), OH	NTG, HTG, healthy	NTG, HTG, healthy	POAG and healthy	POAG (NTG+HTG), NTG, OH, healthy
ICP measurement method	Invasive	Invasive	Noninvasive	Invasive	Invasive
Other data					
Day of IOP and ICP measurements	Same day	Same day	Same day	Maximum IOP before lumbar puncture	Maximum IOP before lumbar puncture
Wash-out period	1 month for NTG, HTG – did not include	1 month for NTG, HTG – did not include	Did not include	Did not include	Did not include
Neurologist consultation	+	+	—	+	+
Approval of the Ethics Committee	+	+	+	+	+

Abbreviations: HTG, high-tension glaucoma; ICP, intracranial pressure; IOP, intraocular pressure; NTG, normal tension glaucoma; OH, ocular hypertension; POAG, primary open-angle glaucoma.

The value of external pressure, when OA blood flow in both segments was equal, was fixed and expressed automatically in absolute units mm Hg. The sensitivity, specificity, and diagnostic value of this device was proven in the previous studies with neurological patients.[65,66]

Table 2 shows the results of the included studies. A meta-analysis of 396 patients was followed out

and it was found that IOP, ICP, and TPD statistically significantly differed between POAG and healthy subjects ($P<0.001$).[12,15,24–26] Three articles[15,24,26] subdivided patients into normal-tension glaucoma (NTG) and high-tension glaucoma (HTG) categories; thus, meta-analysis of these data was also performed (Table 3). It was observed that IOP was significantly higher in HTG group than in healthy subjects or NTG groups ($P<0.001$). ICP was significantly lower in NTG group compared with HTG or healthy subjects ($P<0.001$). Evaluation of TPD revealed statistically significant differences between all groups: between HTG and NTG or healthy subjects, and NTG with healthy subjects ($P<0.001$). Importantly, HTG group was significantly younger than NTG group or healthy subjects ($P<0.05$). Some of these studies analyzed relationship between TPD and structural/functional glaucomatous changes[12,15,24,25] and found that higher TPD was associated with glaucomatous visual field loss or bigger structural glaucomatous changes. Summary of these studies is shown in Table 4.

Discussion

Although the importance of ICP and TPD in glaucomatous pathophysiology is beginning to emerge, scarce available data have greatly limited our understanding of this possible contributory mechanism. Therefore, we performed a first of its kind comprehensive meta-analysis to investigate the current state of knowledge of TPD in OAG.

Our meta-analysis found that ICP was significantly lower in patients with POAG, particularly in NTG, than in healthy subjects.[12,15,24–26] TPD was almost two times higher in patients with NTG, and nearly five times higher in patients with HTG, compared with healthy controls.[15,24,26] As the ONH is exposed both to IOP and

Table 2 Results of meta-analysis between primary open-angle glaucoma and healthy subjects

Group	*Parameters*	*Ren* et al[12]	*Ren* et al[15]	*Siaudvytyte* et al[24]	*Berdahl* et al[25]	*Berdahl* et al[26]	*Total*
POAG group	Number of patients (*N* (%))	35 (19.3%)	43 (23.8%)	18 (9.9%)	28 (15.5%)	57 (31.5%)	181 (100%)
	Age (years)	45.0 (16.0)	43.4 (4.4)	55.7 (1.0)	71.5	70.5 (12.9)	57.8 (12.7)
	IOP (mm Hg)	21.0 (5.0)	21.6 (3.9)	19.2 (5.7)	24.3 (6.1)	22.2 (6.4)	21.9 (1.4)*
	ICP (mm Hg)	11.0 (3.0)	11.0 (1.0)	8.2 (0.8)	9.2 (2.9)	9.3 (3.2)	9.9 (1.0)**
	TPD (mm Hg)	11.0 (5.0)	10.6 (2.8)	11.0 (4.8)	15,1	11.6 (11.0)	11.7 (1.5)***
Control group	Number of patients (*N* (%))	—	71 (33.0%)	9 (4.2%)	49 (22.8%)	86 (40.0%)	215 (100%)
	Age (years)	—	45.7 (11.3)	51.9 (6.6)	68.9	68.2 (8.6)	60.2 (10.8)
	IOP (mm Hg)	—	14.3 (2.6)	15.9 (2.1)	16.4 (2.8)	16.1 (2.7)	15.6 (0.9)*
	ICP (mm Hg)	—	12.9 (1.9)	10.5 (3.0)	13.0 (4.2)	11.8 (0.71)	12.7 (0.5)**
	TPD (mm Hg)	—	1.4 (1.7)	5.4 (3.3)	3.4	3.3 (4.0)	2.8 (1.1)***

Abbreviations: ICP, intracranial pressure; IOP, intraocular pressure; POAG, primary open-angle glaucoma; TPD, translaminar pressure difference.
*P, **P, and ***P are <0.05, significant difference between two groups (t-test).

Table 3 Results of meta-analysis between normal tension glaucoma, high tension glaucoma and healthy subjects

Group	*Parameters*	*Ren* et al[15]	*Siaudvytyte* et al[24]	*Berdahl* et al[26]	*Total*
NTG group	Number of patients (*N* (%))	14 (41.2%)	9 (26.5%)	11 (32.3%)	34 (100%)
	Age (years)	49.6 (12.1)	56.6 (10.4)	68.0 (17.1)	57.4 (8.0)*
	IOP (mm Hg)	16.1 (1.9)	13.7 (1.6)	17.3 (2.7)	15.9 (1.4)**
	ICP (mm Hg)	9.5 (2.2)	7.4 (2.7)	9.3 (3.2)	8.7 (0.9)***
	TPD (mm Hg)	6.6 (3.6)	6.3 (3.1)	7.4 (4.8)	6.8 (0.5)****
HTG group	Number of patients (*N* (%))	29 (76.3%)	9 (23.7%)	—	38 (100%)
	Age (years)	40.4 (16.1)	54.7 (15.6)	—	43.8 (6.2)*
	IOP (mm Hg)	24.3 (3.2)	24.7 (6.8)	—	24.4 (0.2)**
	ICP (mm Hg)	11.7 (2.7)	8.9 (1.9)	—	11.0 (1.2)***
	TPD (mm Hg)	12.5 (4.1)	15.7 (7.7)	—	13.3 (1.4)****
Control group	Number of patients (*N* (%))	71 (42.8%)	9 (5.4%)	86 (51.8%)	166 (100%)
	Age (years)	45.7 (11.3)	51.9 (6.6)	68.2 (8.6)	57.7 (11.0)*
	IOP (mm Hg)	14.3 (2.6)	15.9 (2.1)	16.1 (2.7)	15.3 (0.9)**
	ICP (mm Hg)	12.9 (1.9)	10.5 (3.0)	12.7 (3.9)	12.2 (0.7)***
	TPD (mm Hg)	1.4 (1.7)	5.4 (3.3)	3.3 (4.0)	2.6 (1.1)****

Abbreviations: HTG, high-tension glaucoma; ICP, intracranial pressure; IOP, intraocular pressure; NTG, normal tension glaucoma; TPD, translaminar pressure difference.
*P, **P, ***P and ****P are <0.05, significant difference between three groups (t-test).

Table 4 Summary of the correlations between translaminar pressure difference and structural/functional glaucomatous changes

Authors	*Number of patients*	*Subjects*	*Analyzed parameter*	*Technology*	*Correlation*	P-*value*
Ren *et al*[12]	52	POAG and OH	NRA	HRT	$r=-0.38$	0.006
			Mean defect	HFA	$r=0.38$	0.007
Ren *et al*[15]	114	NTG, HTG, healthy	Mean defect	HFA	$r=0.69$	0.005
Siaudvytyte *et al*[24]	9	NTG	NRA	HRT	$r=-0.83$	0.01
Berdahl *et al*[25]	77	POAG and healthy	Cup-to-disc ratio	Medical records	$r^2=0.399$	<0.0001

Abbreviations: HFA, Humphrey Field Analyzer; HRT, Heidelberg Retina Tomograph; HTG, high-tension glaucoma; Mean defect, Mean glaucomatous visual field defect (dB); NRA, neuroretinal rim area; NTG, normal tension glaucoma; OH, ocular hypertension; POAG, primary open-angle glaucoma.

ICP, the TPD is an important parameter, and its reduction might assist in halting the progression of glaucoma. Jonas *et al* analyzed TPD and found statistically significant difference between glaucomatous and nonglaucomatous eyes ($P<0.001$); however, glaucomatous group included not only OAG but also angle-closure glaucoma patients,[62,64] therefore, these studies were excluded from meta-analysis.

Siaudvytyte *et al* found that higher TPD was associated with lower neuroretinal rim area (NRA) in NTG,[24] whereas no association was found in HTG or healthy subjects. This data suggests that NTG patients are more susceptible to TPD differences. Berdahl *et al*[25] found similar results in POAG and healthy subjects. It is important to note that this study has a limitation as measurements were obtained inconsistently within 1-year period of lumbar puncture performance. Whereas Siaudvytyte *et al* did not include neurological examination to exclude neurological disorders.[24] Finally, Ren *et al*[12,15] found the relation between NRA, mean visual field defects and TPD, analyzing all study group.

There are several limitations of this meta-analysis to acknowledge. First, the limited uniformity of the available data from differing methodological approaches in the various studies makes direct comparisons difficult and the number of patients in experimental and control groups were often limited. Also, a majority of the selected studies[24–26] did not include a washout period, which may account for differing study results. Specifically, Ren *et al*[12,15] included a washout period just for NTG patients, limiting accountability for possible effects of hypotensive agents on ICP. This is especially important in subjects who may have been using carbonic anhydrase inhibitors, as they are known to have systemic effects, which may influence of CSF production and result in ICP reduction.[67]

In addition, it should be mentioned that ICP-measuring methodologies were different between studies. Four studies used golden standard invasive ICP measuring method via lumbar puncture,[12,15,25,26] whereas Siaudvytyte *et al* in their study used noninvasive two-depth TCD device, which is currently the only available method for absolute ICP value numerical and automatic measurement that does not need an individual patient-specific calibration.[24] A prospective study with 108 neurological patients showed that diagnostic sensitivity, specificity and the area under the ROC curve of this noninvasive absolute ICP method were 68.0%, 84.3%, and 0.87, respectively.[66] However, the measuring error still remains, as we can see from the results—ICP values were higher in studies that used invasive ICP measuring methods.[12,15,25,26]

Furthermore, it remains unclear whether the CSF pressure, measured by lumbar puncture, corresponds to the CSF pressure in the orbit around the optic nerve. The CSF dynamics at this area is different, as there are numerous septae present that could limit free flow of CSF. [68] In addition, unlike in other areas, the dura of optic nerve sheath contains atypical meningeal tissue with lymphoid characteristics.[69] Killer and colleagues found that patients with NTG have decreased CSF flow between the basal cisterns and the SAS surrounding the optic nerve. Such a difference has not been established in healthy subjects. This could explain why patients with NTG have lower ICP.[53] However, experimental studies on dogs showed that CSF pressure in optic nerve SAS is equal to CSF pressure in the lateral ventricle of the brain at the level of eye.[70] Moreover, it was established that the CSF pressure measured by lumbar puncture corresponds to ICP in the lateral decubitus position.[18] However, the method depends on the optic nerve path at SAS between the orbital and intracranial parts. It is not known what happens when the optic nerve canal is blocked (for example, in cases of suprasellar meningioma, tuberculous meningitis, or intracanalicular OA aneurysm).

One important consideration is that IOP, ICP, and TPD are dynamic parameters and changes in posture or individual activities might affect these measurements, respectively. In studies included in meta-analysis, the IOP was measured in the sitting position, whereas ICP was assessed in the supine or lateral decubitus positions.[12,15,25,26] Humans evolved with gravity, and gravity affects human physiology—CSF pools in the caudal spinal canal and CSF pressure at eye level is much lower than CSF pressure in the caudal spinal column in

the upright position.[18,71] However in microgravity environment, CSF is distributed throughout the SAS tending to equalize pressure in all compartments and negate any posture-induced flow, resulting in higher than normal CSF pressure at eye level.[72] Several studies have shown that changes in posture cause pressure changes in all body fluid spaces, cardiac output, peripheral resistance, and blood flow to various vascular beds.[73,74] IOP changes by 2.9 mm Hg in healthy subjects and by 3.9 mm Hg in patients with glaucoma while changing body position from sitting to supine.[75] Furthermore, head elevation decreases ICP by displacing CSF into the spinal canal and by improving cerebral venous drainage by opening alternative venous channels in the posterior circulation that remain closed while patients remain recumbent. Experimental studies showed that CSF pressure in the sitting position at the level of the occipital prominence, equivalent to eye level, ranged between 0 and −10 mm Hg.[71] One of the ways to interpret ICP values in the sitting position is mathematical modeling, whereas standard body position for ICP measuring is lateral decubitus/supine.[76]

Another important aspect to consider is that authors analyzed simplified TPD, calculated by the following formula (TPD = IOP − ICP), and did not clarify the fact that TPD is actually the difference between IOP and the retrolaminar tissue pressure, which is largely determined by the optic nerve SAS pressure and pia mater characteristics. Furthermore, the optic nerve SAS pressure is influenced by orbital pressure from the sides.[77] Morgan *et al*, analyzed correlation between CSF pressure and retrolaminar tissue pressure in dogs and found that retrolaminar tissue pressure was basically identical to the CSF pressure in the ventricles, when CSF pressure was above 2 mm Hg. Below 2 mm Hg, the tissue pressure was approximately constant, perhaps reflecting the orbital tissue pressing against the nerve when CSF pressure is very low.[14] It would be interesting to analyze translaminar pressure gradient (defined as pressure distribution across the lamina cribrosa, altered by lamina cribrosa thickness) as the most obvious changes in glaucoma occur in the lamina cribrosa. It is estimated that lamina cribrosa is thinner and more bowed in glaucomatous eyes (201 microns) compared with normal eyes (457 microns).[78]

To answer the question whether TPD is important in glaucoma, we need longitudinal studies in addition to the retrospective and prospective studies performed thus far. Therefore, noninvasive techniques for ICP measurements would be helpful in the studies with human patients. Moreover, along with clinical studies, suitable animal models will also be helpful in understanding the role of ICP in glaucoma. Chowdhury *et al* published the study on comprehensive animal model where ICP can be manually reduced or increased over an extended period of time, that is valuable to study the balance between IOP and ICP and its role in glaucomatous optic neuropathy.[79] Moreover, there are a lot of points that need explication to further elucidate ICP role in glaucoma. As CSF dynamics are poorly ascertained, there is no clear answer whether normal cardiac variations in ICP exist or how body position or activity of the person affect it. Although it is accepted that IOP diurnal fluctuations are greater in eyes with glaucoma,[80] question is whether there are similar variations in ICP and single measurement of ICP can represent short or long-term pressure variations that could have a role in glaucoma. Furthermore, IOP fluctuations have been proposed as an independent risk factor for glaucomatous damage.[81] Wostyn *et al* arose hypothesis that ICP fluctuations may result in significant fluctuations of the TPD and could exert repetitive shear stress on the lamina cribrosa and ganglion cell axons, leading to glaucomatous damage.[82] Interestingly, other researchers found that Valsalva maneuver led to reduce or reverse of the TPD, which was associated with decreased optic cup-related parameters and enlarged neuroretinal rim-related parameters.[61] Therefore, it would be interesting to estimate if alternative treatment strategies aiming to increase ICP could be beneficial for glaucoma patients.

Conclusion

Our meta-analysis of all qualified data shows that patients with NTG and HTG have higher TPD than healthy subjects. Importantly, higher TPD is associated with larger optic disc structural changes in patients with OAG. However, our conclusions are based on the current literature data, which are limited in scope and execution and have significant differences and weaknesses in the methodologies they utilized. With acknowledgement of these weaknesses, the available data suggest that there is a need for further longitudinal prospective clinical and experimental studies investigating the influence of TPD in glaucoma.

Conflict of interest

AR is an inventor of noninvasive ICP measurement technology, which is patented in the US and EU. The remaining authors declare no conflict of interest.

Acknowledgements

This research is funded by the European Social Fund under the Global Grant measure.

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