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CLINICAL STUDY

Factors associated with topographic changes of the optic nerve head induced by acute intraocular pressure reduction in glaucoma patients

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Abstract

Purpose To investigate factors associated with changes in optic nerve head (ONH) topography after acute intraocular pressure (IOP) reduction in patients with primary open-angle glaucoma (POAG).

Methods Untreated POAG patients (IOP >21 mm Hg) were prospectively enrolled. Systemic and ocular information were collected, including central corneal thickness (CCT) and corneal hysteresis (CH). All patients underwent confocal scanning laser ophthalmoscopy and tonometry (Goldmann) before and 1 h after pharmacological IOP reduction. The mean of three measurements was considered for analysis. Changes in each ONH topographic parameter were assessed (one eye was randomly selected), and those that changed significantly were correlated with patient's systemic and ocular characteristics.

Results A total of 42 patients were included (mean age, 66.7 ± 11.8 years). After a mean IOP reduction of 47.3 ± 11.9%, significant changes were observed in cup area and volume, and in rim area and volume ($P<0.01$), but not in mean cup depth ($P=0.80$). Multiple regression analysis (controlling for baseline IOP and magnitude of IOP reduction) showed that CH ($r^2=0.17$, $P<0.01$) and diabetes diagnosis ($r^2 \geqslant 0.21$, $P<0.01$) were negatively correlated with the magnitude of changes in ONH parameters, whereas the cup-to-disc ratio was positively correlated ($r^2=0.30$, $P<0.01$). Age, race, disc area, and CCT were not significant ($P \geqslant 0.12$). Including all significant factors in a multivariable model, only the presence of diabetes remained significantly associated with all ONH parameters evaluated ($P<0.01$).

Conclusions Different systemic and ocular factors, such as diabetes, CH, and the relative size of the cup, seem to be associated with the magnitude of changes in ONH topography after acute IOP reduction in POAG patients. These associations partially explain the ONH changes observed in these patients and suggest that other factors are possibly implicated in an individual susceptibility to IOP.

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Introduction

Elevated intraocular pressure (IOP) remains the most important known risk factor for glaucomatous optic neuropathy (GON).[1,2] Although obstruction to axoplasmic flow may be involved in glaucoma pathophysiology, it is still not clear how mechanical, vascular, and cellular mechanisms would participate in this process.[3–6] Basically, the mechanical theory of damage postulates that elevated IOP causes lamina cribrosa (LC) distortion, resulting in the damage of retinal ganglion cell axons at the optic nerve head (ONH).[6] Previous studies, using confocal scanning laser ophthalmoscopy, have found changes in ONH topography in patients with glaucoma after IOP variation. The reduction in IOP was associated with an

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increase in the neural rim area and a decrease in the cup size, probably due to anterior shifting of the LC.[7–12] The inverse mechanism was observed after IOP elevation.[13]

Susceptibility to glaucomatous damage varies among patients and seems to be related to several individual ocular and systemic characteristics. Although some factors such as age[1,14–16] and central corneal thickness (CCT) are better established,[1,14,16] others such as corneal hysteresis (CH)[17] and diabetes mellitus (DM)[11,18–21] remain controversial.

The mechanical damage in glaucoma involves the biomechanical properties of the ONH, mainly related to the stiffness of the LC, scleral canal wall, and peripapillary sclera, as demonstrated in studies based on ONH modelling.[6,22–26] Previous studies have suggested that systemic and ocular factors, such as ageing,[27–29] chronically elevated IOP,[30–32] level of glaucomatous damage,[1,17,33] and disc size (scleral canal diameter),[34] could influence the susceptibility of an individual ONH to a given level of IOP. More recently, it has been suggested that other factors could be either directly or indirectly related to ONH response to pressure-induced damage, such as corneal parameters (both CCT and CH)[13,35–37] and diabetes.[1,37,38] In glaucoma management, it is important to identify which factors are significantly related to an individual response to pressure-induced damage. Once these factors are known, it is possible to identify patients at a greater risk for disease progression and to set a patient's target IOP. Therefore, we designed this clinical study to investigate possible factors associated with pressure-induced changes in ONH topography in patients with primary open-angle glaucoma (POAG).

Patients and methods

This prospective protocol adhered to the tenets of the Declaration of Helsinki and was approved by The Ethics Committee of The Federal University of São Paulo. In addition, written informed consent was obtained from all subjects.

Patients

We prospectively enrolled consecutive untreated newly diagnosed POAG patients, with and without type II DM, from the general clinic of the Ophthalmology Department of the Federal University of São Paulo. Patients who met our inclusion criteria were promptly directed to the glaucoma clinic, where a complete ophthalmological examination was conducted. Exclusion criteria were systemic collagen diseases,[39] history of using oral or topical steroids, spherical equivalent $> \pm 4.0$ D, previous ocular surgery or trauma, secondary glaucomas, and any ocular disease other than glaucoma (including diabetic retinopathy). All diabetic patients were under medical (insulin or oral hypoglycaemic) treatment. POAG was defined as characteristic GON and visual field loss, with IOP >21 mm Hg on two separate occasions and a widely open angle.

Typical GON was defined as a vertical cup-to-disc ratio >0.5, asymmetry of the cup-to-disc ratio ≥ 0.2 between the eyes, the presence of localized RNFL defects, and/or neuroretinal rim defects in the absence of any other abnormalities that could explain such findings. A glaucomatous visual field defect in the standard automated perimetry (Humphrey SITA—Standard 24–2, Carl Zeiss Meditec, Dublin, CA, USA) was defined as three or more points in clusters with a probability of $<5\%$ (excluding those on the edge of the field or directly above and below the blind spot) on the pattern deviation plot, a pattern SD index with a probability of $<5\%$, or a glaucoma hemifield test with results outside the normal limits.

Procedures

Baseline data included systemic (age, gender, self-described race, and diabetes diagnosis) and ocular (CCT and CH) factors. The ocular response analyzer (ORA; Reichert Inc., Depew, NY, USA) was used to assess CH values. The ORA is a non-contact tonometer that measures IOP calibrated to Goldmann and corneal-compensated IOP, taking into account corneal biomechanical properties. It also measures other parameters, including CH, which is an estimate of the viscoelastic (time-dependant) material properties of the cornea.[40,41] CH is correlated with CCT, and seems not to be associated with refractive error or axial length.[42,43] CH as measured by the ORA is described in greater detail elsewhere.[40,41,44] For this study, four measurements were obtained for each eye and the average was considered as the final value for analysis. Readings from the ORA required consistent and smooth raw signal morphology (clean, sharp, well-defined raw signal peaks, with repeatable characteristics for multiple measurements). If the measurements differed by >2 mm Hg, an additional measurement was taken and the two extreme values were excluded from the analysis.[44]

Confocal scanning laser ophthalmoscopy using the Heidelberg retina tomograph III (HRT; Heidelberg Engineering, Heidelberg, Germany) and Goldmann applanation tonometry were performed before and 1 h after pharmacological IOP reduction (topical timolol maleate 0.5% + brimonidine tartrate 0.2%, topical bimatoprost 0.03%, and oral acetazolamide 500 mg). All patients were refracted before the first HRT examination, and whenever the cylinder was ≥ 1.00 D, correction for corneal astigmatism was performed. The following stereometric parameters were investigated: rim area, cup area, rim volume, cup volume, and mean cup depth. The mean of three measurements was used for all tests, and quality control of the scans was set to $<30\,\mu$m SD. Three patients were excluded from the analysis because of poor quality scans. The same examiners performed all the HRT (LMG), tonometry, and ORA (TSP) examinations, and both were masked for patient's data. All tests were performed on the same day. After the last test, glaucoma treatment was initiated, confirmatory/ancillary examinations were scheduled, and patients were followed up regularly.

Statistical analysis

Descriptive analysis was used to present demographic and clinical data. D'Agostino–Pearson's test was performed to determine whether the HRT data had a normal distribution. As it rejected normality ($P<0.05$), we used a non-parametric test (Wilcoxon's signed-rank test) to compare baseline and post-IOP reduction values for each HRT parameter. The ONH parameter chosen for sample size calculation was cup area. Considering a mean difference in cup area values before and after IOP reduction of 0.05 mm^2 and a mean SD of the differences of 0.1 mm^2, for an α-error of 0.05, it would require 37 patients (1 eye per patient) to reach a statistical power of 80%. After assessing changes in each ONH topographic parameter, those that changed significantly were correlated with patient's systemic (age, race, and presence of diabetes) and ocular characteristics (disc area, cup-to-disc ratio, CCT, and CH) using multiple regression analysis. In the regression analysis, the presence of diabetes was taken as '1' and the absence of diabetes as '0'. First, each variable was analyzed separately, controlling for baseline IOP and amount of IOP reduction. All variables with a statistically significant result (P-value was adjusted for multiple comparisons using Bonferroni's correction) were then included in the multivariable model. Computerized analysis was performed using MedCalc software (MedCalc Inc., Mariakerke, Belgium).

Results

A total of 42 POAG patients were included in the analysis (18 with and 24 without type II DM). Baseline demographics and clinical data are provided in Table 1. The mean age was 66.7 ± 11.8 years, and most patients were women ($n=29$) and White ($n=24$). After a mean IOP reduction of 47.3 ± 11.9% (13.3 ± 6.5 mm Hg), the majority of the eyes had intuitive HRT parameters changes (inward movement) in the five HRT parameters evaluated (Table 2). Significant mean changes were observed in cup area, cup volume, rim area, and rim volume ($P<0.01$), but not in mean cup depth ($P=0.80$).

With regard to the correlation between HRT parameters that changed significantly and patient's characteristics (Table 3), we chose only one volumetric (cup volume) and one bi-dimensional (cup area) HRT parameter as dependent variables, as changes in cup and rim are strongly correlated. Multiple regression analysis (controlling for baseline IOP and magnitude of IOP

Table 1 Baseline characteristics of primary open-angle glaucoma patients[a]

Variables	*Patients* (n = 42)
Age (years)	66.7 ± 11.8
Gender (female/male)	29/13
Race (White/African descent/mixed)	24/10/8
Type II diabetes diagnosis	18 out of 42
Baseline intraocular pressure (mm Hg)	27.9 ± 8.1
Intraocular pressure reduction (mm Hg)	13.3 ± 6.5
Intraocular pressure reduction (%)	47.3 ± 11.9
Central cornea thickness (μm)	541.8 ± 34.5
Corneal hysteresis (mm Hg)	8.1 ± 1.8
HRT—disc area (mm^2)	2.43 ± 0.5
HRT—linear cup-to-disc ratio	0.57 ± 0.16
HRT—mean cup depth (mm)	0.31 ± 0.1
Fundoscopy—cup-to-disc ratio	0.70 ± 0.11
Visual field mean deviation (dB)	−5.7 ± 5.2

Abbreviation: HRT, Heidelberg retina tomograph.
[a]Data are given as mean ± SD whenever indicated.

Table 2 Changes in optic nerve head topography after intraocular pressure reduction in primary open-angle glaucoma patients[a]

HRT parameters	*Mean change*[a]	*95% CI*	*Eyes with intuitive changes*[b]	P-*value*[c]
Rim area (mm^2)	0.044	0.014–0.074	32 (76%)	0.003
Rim volume (mm^3)	0.026	0.011–0.041	30 (71%)	0.001
Cup area (mm^2)	−0.046	−0.012 to −0.079	32 (76%)	0.008
Cup volume (mm^3)	−0.018	−0.004 to −0.030	30 (71%)	0.009
Mean CD (mm)		0.0005–0.003	24 (57%)	0.798

Abbreviations: CD, cup depth; HRT, Heidelberg retina tomograph.
[a]Difference between post-IOP reduction and baseline HRT values.
[b]An intuitive HRT parameter change after intraocular pressure reduction was considered when rim area and rim volume increased, and when cup area, cup volume, and mean cup depth decreased.
[c]Wilcoxon's signed-rank test (data were not normally distributed based on D'Agostino–Pearson's test).

Table 3 Factors associated with changes in optic nerve head topography after intraocular pressure reduction

Variables	*Cup area changes*			*Cup volume changes*		
	R^2	*P-value*[a]	*P-value*[b]	R^2	*P-value*[a]	*P-value*[b]
Age (years)	0.01	0.751		0.01	0.583	
Race (African descent)	0.03	0.273		0.01	0.662	
Presence of diabetes	0.34	**<0.001**	**<0.001**	0.21	**<0.001**	**<0.001**
Cup-to-disc ratio	0.08	0.042		0.30	**<0.001**	**<0.001**
Disc area (mm^2)	0.06	0.121		0.01	0.792	
CCT (μm)	0.01	0.508		0.01	0.722	
CH (mm Hg)	0.17	**0.005**	0.121	0.16	0.009	

Abbreviations: CCT, central corneal thickness; CH, corneal hysteresis; IOP, intraocular pressure.
[a]Association between mean changes in optic nerve head parameters and each patient's characteristic, controlling for baseline IOP and magnitude of IOP reduction (%). Statistical significance was set at $P<0.007$ (Bonferroni's correction).
[b]Multivariable model (only variables with a *P*-value <0.007 were entered).

reduction) showed that CH ($r^2=0.17$, $P<0.01$) and diabetes diagnosis ($r^2\geq0.21$, $P<0.01$) were negatively correlated with the magnitude of changes in ONH parameters, whereas the cup-to-disc ratio was positively correlated ($r^2=0.30$, $P<0.01$). Age, race, disc area, and CCT were not significant in this model ($P\geq0.12$). Including all significant factors in a multivariable model, only the presence of diabetes remained significantly associated with all ONH parameters evaluated ($P<0.01$). No statistically significant interactions were found between our independent variables (all *P*-values for interaction terms $\geq$0.22).

Discussion

Our results suggest that a lower CH, larger cup-to-disc ratio, and the absence of diabetes are statistically significantly related to greater ONH topographic changes after acute IOP reduction. To the best of our knowledge, this is the first study to report on both systemic and ocular factors associated with topographic changes in the ONH after acute IOP reduction in patients with POAG.

Few studies have addressed the association between corneal parameters and ONH topographic changes after IOP variation (increase or decrease) in glaucomatous patients.[13,35] We found that a lower CH (but not CCT) was correlated with greater ONH changes after IOP reduction (univariate analysis results). When other covariates were considered, this correlation lost its significance. Comparing CH values in POAG patients with and without acquired pits of the ONH, Bochmann *et al*[36] documented lower CH values in those with acquired pits. Finally, regarding other corneal parameters, Lesk *et al*[35] observed that patients with thinner corneas have greater ONH topographic changes after IOP reduction than do patients with thicker corneas. CH, which is known to be positively correlated with CCT values,[42] was not assessed in that study. On the other hand, Wells *et al*[13] correlated higher CH values (but not CCT) with greater changes in ONH topography after IOP increase. In this study, we analyzed cupping reversal (IOP reduction), which was the methodology used in the majority of previous studies,[7–12] in a study population composed of POAG patients without intraocular surgery. Wells *et al*[13] evaluated cupping distension (increasing IOP to an average of 64 mm Hg) in different types of glaucoma, some with intraocular surgery and with a lower mean age than our group. We believe that there are significant differences in study design and population between these two studies, and that further research is necessary to clarify the relationship between CH and ONH topographic changes after IOP variation (reduction or increase).

Evaluating POAG patients with moderate cupping (mean cup-to-disc ratio on fundoscopy, 0.70 ± 0.11 (95% CI, 0.66–0.73)), we found a statistically significant correlation between the cup-to-disc ratio (but not disc size) and ONH topographic changes after IOP reduction. Patients with larger cupping had greater ONH changes. There are no previous data reported on this subject. Although the correlation we found seems reasonable, the way the ONH responds to IOP variation is still not fully understood,[45] and seems to depend on both laminar and scleral canal deformation.[46] In addition, this correlation was not statistically significant for both ONH parameters (cup area and volume) in the multivariable analysis. We could also have found different results if our sample was composed of patients with more advanced damage. Chronically elevated IOP and advanced disease stage seems to produce progressive changes in the ONH, including axonal and non-axonal effects (extracellular matrix and astrocytes), possibly resulting in a stiffer and less deformable structure.[30–32,47,48]

Among systemic factors evaluated in our study, only diabetes was significantly associated with pressure-induced topographic changes in the ONH. The presence of diabetes in glaucoma patients was related to a smaller magnitude of changes in ONH topographic parameters after IOP reduction, even after adjusting for other covariates. Differently from other factors evaluated in this study, diabetes correlated not only with bi-dimensional but also with volumetric cup parameters, which involves a complex interaction between scleral (lateral displacement of ONH tissues) and laminar (vertical displacement of the LC) changes. Although no previous study has evaluated this correlation, recent reports addressing directly or indirectly the association between diabetes and glaucoma suggested that the former may influence an individual susceptibility to glaucomatous damage.[37,38] In a recent editorial, Quigley[38] commented on the presence of diabetes as a possible protective factor for mechanical damage in glaucoma and questioned why we cannot believe our own data. In a previous report, results of the Ocular Hypertension Treatment Study[1] suggested that there may be some protective effect of diabetes on the conversion from ocular hypertension to POAG. Although this finding has been much debated, our results may support it, as the presence of diabetes was independently associated with a smaller magnitude of pressure-induced cup changes in our study. The eyes of diabetic patients have more collagen cross-linking through glycation process, resulting in increased corneal stiffness and higher CH values.[37,49–51] The same processes that lead to increased corneal stiffness in diabetes may happen in other eye structures containing collagen fibres. Results from the study by Lesk *et al*[35] have suggested an association between corneal thickness and laminar stiffness. The eyes with thinner corneas would have a more compliant LC (reduced stiffness), thus allowing greater laminar displacement and increased axonal injury after IOP fluctuations. Corroborating these thoughts, collagen cross-linking was found to reduce pressure-induced laminar strain levels in porcine eyes in a recent study.[52] We therefore hypothesized that diabetic eyes not only have an increased corneal stiffness as previously documented but also have an increased laminar stiffness, which would provide protection against mechanical damage in glaucoma. However, it is important to re-emphasize that pressure-induced changes on ONH connective tissues involve not only laminar deformation. It also involves regional thinning, stretching, and deformation of both the LC and the peripapillary sclera, which were not evaluated in this study. In addition, an individual susceptibility to glaucoma is still not fully understood and axons are damaged by effects of IOP-related stress through various mechanisms.[26,33,53–59] Therefore, we believe that any conclusion whether increased tissue stiffness is a risk or a protective factor for glaucomatous injury would be a premature assumption.

There are important facts that should be considered while interpreting our results. First, age did not correlate with ONH response to acute IOP reduction in our study. However, as it has been previously demonstrated that age can alter the mechanical integrity of the LC,[27,28] a study with a wider age range could possibly detect a significant correlation. Second, although HRT provides reproducible objective and quantitative topographic measurements,[60] it has been suggested that a significant proportion of the change measured by this technology may be in the pre-laminar tissues rather than in the lamina.[23,25] In addition, the fact that the HRT parameters that changed significantly were not depth measurements (such as mean cup depth), suggests that these changes could be related to neural tissue properties rather than laminar properties. Third, CH is at present a manifestation of some aspect of the material properties of the cornea, but what those properties are remains unclear. Fourth, this study did not evaluate patients with diabetic retinopathy. Therefore, our results only apply to diabetic patients without retinopathy. As retinopathy itself could lead to different results compared with those we found, the influence of diabetic retinopathy on ONH response to IOP variation (reduction) requires further investigation. Finally, all factors significantly associated with topographic changes of ONH parameters had a weak coefficient of determination (r^2 range, 0.17–0.34). Therefore, these associations accounted for only part of the ONH changes observed in these patients. Although statistically significant, their clinical relevance is still to be determined as these associations do not explain entirely an individual (ONH) response to IOP variation (reduction in our study). These findings suggest that other factors not evaluated in this study are implicated in the ONH susceptibility to IOP.

In conclusion, our findings suggest that different systemic and ocular factors, such as diabetes, CH, and the relative size of the cup, seem to be associated with the magnitude of changes in ONH topography after acute IOP reduction in POAG patients. Whether these observations have implications in the understanding of glaucoma pathophysiology requires further investigation.

Summary

What was known before

- Acute intraocular pressure (IOP) reduction induces morphological changes in the optic nerve head—there is an individual susceptibility to these changes—these changes seem to be related to different ocular and systemic factors (only corneal properties have been studied).

What this study adds

- This is the first study to investigate both systemic and ocular factors associated with morphological changes in the optic nerve head after acute IOP reduction in primary open-angle glaucoma patients—our findings suggest that factors, such as diabetes, corneal hysteresis, and the relative size of the cup, seem to be associated with the magnitude of changes in ONH morphology after acute IOP reduction.

Conflict of interest

The authors declare no conflict of interest.

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