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Assessing the impact of short-term intraocular pressure fluctuations on primary open-angle glaucoma progression

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Purpose: *To examine the impact of short-term intraocular pressure (IOP) fluctuations on the progression of glaucomatous optic neuropathy based on optical coherence tomography (OCT) data.*

Material and Methods: *Totally, 32 patients (62 eyes) with primary open-angle glaucoma (POAG) were included in the study and divided into two groups. Group 1 comprised 15 patients (30 eyes) with a standard deviation (SD) of IOP of less or equal to 3 mmHg, and group 2, 17 patients (32 eyes) with an SD of IOP greater than 3 mmHg. Patients were followed over 12 months. At baseline, at 6 and 12 months, they had a routine eye examination and OCT of the optic nerve and macula, with retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) thicknesses determined. At 12 months, the rebound tonometer ICare Home2 was used for diurnal IOP measurements, and an SD of IOP was determined.*

Results: *In group 1 and group 2, annual losses in RNFL were 3.20 ± 3.86 μm/year and 8.11 ± 9.1 μm/year, respectively (p = 0.03), and global GCC losses, 0.87 ± 3.98% and 5.24 ± 8.05%, respectively (p = 0.04). There was a statistically significant positive correlation of the SD of IOP measurements with annual loss in GCC thickness (r = 0.5161; p = 0.02) and global GCC loss (r = 0.6258; p = 0.03) for group 2, but no significant correlation for group 1.*

Conclusion: *IOP fluctuation (SD > 3 mmHg) is a factor of glaucoma progression which impacts particularly on retinal GCC losses.*

Keywords:

glaucoma, glaucoma progression, intraocular pressure, short-term fluctuations, optical coherence tomography

Glaucoma is the second leading cause of blindness globally, after cataract [1]. The disease is the major cause of irreversible blindness worldwide [2]. The first priority for the clinician is his/her capacity to assess longitudinal changes in glaucoma and predict the course of glaucomatous neuropathy because of continuous progression of primary open-angle glaucoma (POAG) and severe visual disability due to POAG. Monitoring changes in the visual field (VF) and morphological changes (like changes in optic disc area, cup-to-disc ratio, thickness of the retinal ganglion cell complex (GCC) and retinal nerve fiber layer (RNFL) thickness) is crucial for early detection and management of glaucoma. The rate of loss in these characteristics which is above the norm for a particular age group is considered as progression of optic neuropathy. It is known that higher intraocular pressure (IOP) is a major significant factor for faster disease [3]. The mean IOP in adult populations is estimated at 15-16 mmHg, with a standard deviation of nearly 3.0 mmHg. Normal IOP has been defined as two SDs above the mean, i.e. 21 mmHg, and any IOP above this level is considered to be elevated [4]. IOP reduction is the major proven strategy to prevent disease onset and slow disease progression. In addition, IOP assessment allows the physician to determine glaucoma severity, tendency for progression, and response to the treatment. Although pathological effects of elevated IOP are of no doubt, there is still a controversy regarding the effect of short-term and long-term fluctuations in IOP on the course of POAG. Short-term IOP fluctuation is defined as the IOP fluctuation that occurs over days to weeks. Long-term IOP fluctuation is defined as that which

occurs over months to years [5]. The results of previous studies are still controversial. Some studies [6, 7] showed the impact of IOP fluctuations on the development of POAG, whereas others refuted those findings [8, 9]. Arriving at a consensus is difficult partly due to variation in definitions of IOP fluctuations and the lack of standards for their measurement. Because measurements of the amount and the assessment of the parameters of short-term IOP fluctuations can be easily performed in routine clinical setting, an improved understanding of the impact of these fluctuations on the course of POAG may improve the quality of routine eye care for patients with glaucoma. In this study, we aimed to identify the parameters of short-term IOP fluctuations which have a prognostic value for POAG progression.

The purpose of this study was to examine the impact of short-term IOP fluctuations on the progression of glaucomatous optic neuropathy based on optical coherence tomography (OCT) data.

Material and Methods

Thirty-two patients (62 eyes) with POAG were included in the study and divided into two groups. Group 1 comprised 15 patients (30 eyes) with an SD of IOP of less or equal to 3 mmHg, and group 2, 17 patients (32 eyes) with an SD of IOP greater than 3 mmHg. Patients were followed over 12 months. Every 6 months, they had an OCT of the optic nerve and macula, with peripapillary RNFL thickness, ganglion cell complex (GCC) thickness, global GCC loss and focal GCC loss calculated. A loss in overall GCC thickness ≤ 0.26 μm/year and a loss in RNFL thickness ≤ 0.14 μm/year were considered normal [10].

Glaucoma progression was defined as the exacerbation of retinal thinning over a year, calculated by subtracting final overall GCC thickness from baseline overall GCC thickness, and final RNFL thickness from baseline RNFL thickness. The disease was considered progressive when the actual glaucoma progression was larger than the annual normal thickness loss.

OCT of the optic nerve head and RNFL assessment were performed in the ONH mode for a 4.5-mm-diameter circle. The GCC thickness was measured within a 6 mm x 6 mm square. At the last visit, IOP measurements with the rebound tonometer ICare Home2 were taken every 3 hours during a 72-hour period.

Inclusion criteria were age 36-70 years and the absence of history or evidence of eye disease (excluding POAG and a correctable refractive error of -4.0 D to +2.0 D). Eyes were excluded if the OCT image quality score was <7 (according to the OCT manufacturer) due to the presence of significant eye motion artifacts or significant ocular media opacity.

This study was approved by the local ethics committee. Written informed consent was obtained from all participants before enrollment and the conduct of the study adhered to the Declaration of Helsinki.

Statistical analyses were conducted using Statistica 10.0 (StatSoft, Tulsa, OK, USA) software. Data are presented as mean ± SD. The Student t test was used to assess statistical significance. The level of significance $p \leq 0.05$ was assumed. Pearson correlation coefficient was used to estimate associations between variables.

Results

Table 2 shows annual losses in RNFL and GCC, and percentages of global GCC loss, focal GCC loss, and neuroretinal rim area loss for group 1 versus group 2.

There was a significant difference between groups in terms of annual loss in RNFL thickness ($p = 0.03$) and global GCC loss ($p = 0.04$). No statistically significant correlation was found between the average daily IOP and any of the parameters under investigation such as annual loss in RNFL thickness (r=-0.04; p=0.91), annual loss in GCC thickness (r=-0.07; p=0.8), global GCC loss (r=-0.21; p=0.56), focal GCC loss (r=-0.13; p=0.64) and neuroretinal rim area loss (r=0.33; p=0.18).

In addition, we conducted a correlation analysis between SD of IOP measurements and changes in the selected characteristics of glaucoma progression separately for group 1 and group 2. The results are presented in Tables 3 and 4.

No statistically significant correlation was found between the SD of IOP measurements and any of the parameters under investigation for group 1. We found a statistically significant correlation of the SD of IOP measurements with annual loss in GCC thickness ($p = 0.02$) and global GCC loss ($p = 0.03$) for group 2.

Discussion

First of all, it should be noted that glaucomatous progression on the basis of morphological criteria

Table 1. Demographical and clinical characteristics

	Group 1 (n = 30)	Group 2 (n = 32)	p
Gender	8 women and 7 men	9 women and 8 men	
Age (M±SD)	62.3±12.70	67.2±13.23	0.51
Highest IOP, mmHg (M ± SD)	21.50±4.44	26.3±3.36	0.00
Lowest IOP, mmHg (M ± SD)	12.56±4.42	11.30±1.82	0.38
Average IOP, mmHg (M ± SD)	16.61±3.97	17.45±1.64	0.53

Note: n, number of eyes; p, significance of difference

Table 2. Losses in retinal and optic disc morphology in POAG patients with a standard deviation of intraocular pressure lower than 3 mmHg versus higher than 3 mmHg

Characteristic	Group 1 (n = 30)	Group 2 (n = 32)	p
Annual RNFL loss, μm/year (M ± SD)	3.20±3.86	8.11±9.1	**0.03**
Annual GCC loss, μm/year (M ± SD)	3.47±12.04	5.85±9.26	0.36
Global GCC loss, % (M ± SD)	0.87±3.98	5.24±8.05	**0.04**
Focal GCC loss, % (M ± SD)	0.55±2.11	0.90±1.80	0.54
Neuroretinal rim area loss, (M ± SD)	0.04±0.08	0.10±0.20	0.49

Note: RNFL, retinal nerve fiber layer; GCC, ganglion cell complex; r, correlation coefficient; n, number of eyes; p, significance of difference

Table 3. Relationship of standard deviation (SD) with annual RNFL and GCC losses, global GCC loss and focal GCC loss in POAG patients with a standard deviation of intraocular pressure lower than 3 mmHg

Characteristic	r	p
Relationship of SD with annual RNFL loss	0.2308	0.53
Relationship of SD with annual GCC loss	0.5853	0.17
Relationship of SD with global GCC loss	0.1898	0.47
Relationship of SD with focal GCC loss	0.5311	0.20
Relationship of SD with neuroretinal rim area loss	0.4022	0.31

Note: RNFL, retinal nerve fiber layer; GCC, ganglion cell complex; r, correlation coefficient; p, significance of difference

Table 4. Relationship of standard deviation (SD) with annual RNFL and GCC losses, global GCC loss and focal GCC loss in POAG patients with a standard deviation of intraocular pressure higher than 3 mmHg

Characteristic	r	p
Relationship of SD with annual RNFL loss	0.3645	0.21
Relationship of SD with annual GCC loss	0.5161	0.02
Relationship of SD with global GCC loss	0.6258	0.03
Relationship of SD with focal GCC loss	0.3896	0.51
Relationship of SD with neuroretinal rim area loss	0.1375	0.44

Note: RNFL, retinal nerve fiber layer; GCC, ganglion cell complex; r, correlation coefficient; p, significance of difference

was present in both groups of patients. Although IOP measurements were lower in group 1 (mean IOP, 16.61 ± 3.97 mmHg; SD of IOP, ≤3 mmHg), actual annual losses in GCC (3.47 ± 12.04 μm/year) and RNFL (3.20 ± 3.86 μm/year) were substantially larger than normal annual age-related losses reported in the literature (0.26 μm/year and 0.14 μm/year, respectively) [9]. Group 2 was characterized by higher IOP measurements (mean IOP, 17.45 ± 1.64 mmHg; SD of IOP, >3 mmHg) and showed statistically significantly higher global GCC loss (5.24 ± 8.05%; p = 0.04) and annual loss in RNFL (8.11 ± 9.1 μm/year; p = 0.03) compared to group 1. The progression of the morphological changes in the retina (RFNL and GCC losses) may indicate that an increase in IOP is still the major, but not the only, factor in the development of glaucomatous opticopathy. Of note is the difference in the above characteristics between the groups. A significantly larger annual loss in RNFL in group 2 may be explained by the following: an increase in mean IOP and IOP fluctuations may result in an increased physical impact on the lamina cribrosa, leading to lamina cribrosa remodeling, failure of both anterograde and retrograde axonal transport by retinal ganglion cells (RGC), and gradual RGC death [11]. With such an injury to RGC axons, it is reasonable to expect changes in GCC parameters. Although there was no significant difference between groups 1 and 2 in the annual rate of GCC loss (p = 0.36), there was a significant difference in global GCC loss, which is of a greater informative value. Two pattern-based diagnostic indices are also calculated by the OCT analysis software. The focal loss volume (FLV) indicates the average amount of focal GCC loss divided by the map area. The global loss volume (GLV) provides the sum of the negative fractional deviation [12]. It has been found that FLV and GLV had higher diagnostic accuracy than the simple average for the diagnosis of glaucoma. For example, pattern parameters could be more sensitive in eyes that have started with an above average GCC thickness and where GCC loss is focal rather than diffuse [13, 14].

Our analysis found no significant association between mean IOP and glaucoma progression. Large retrospective studies like AGIS [15] demonstrated that high average IOP was associated with progression of VF defect. We pay attention to and do not dismiss the results of these studies,

but believe that our observations, taken together with those of others and the results of above studies, will complete the general picture for researchers. Our observations are close to those of Matlach and colleagues [16]. In a study by Matlach and colleagues [16], only the deviation and maximum short-term but not the mean IOP fluctuations were significantly associated with glaucoma progression. Glaucoma progression was defined as – if available – confirmed progression of reproducible VF defects in at least three VF examinations or increase of cup area on optic nerve imaging (Heidelberg Retina Tomograph [HRT]) with at least two images after baseline [16]. Determining the presence and rate of VF progression is critically important in the management of glaucoma [17]. However, it has been estimated that at least 25% to 35% of RGCs must be lost before producing significant abnormalities on the visual field [18]. In addition, fixation losses, false-positive and false-negative errors can contribute to the total fields [19]. Assessing glaucoma progression with the rate of change in neuroretinal rim area is also not the ultimately best choice. In a study by Alencar and colleagues [20], measurements of rates of change in RNFL thickness were superior to neuroretinal rim area in identifying eyes with progression detected by VF tests or optic disc stereophotographs.

In the current study, we observed no significant difference in the neuroretinal rim area between group 1 and group 2, and significant association between such parameters of short-term fluctuations as the mean IOP and the SD of IOP. Our correlation analysis between the SD of IOP and characteristics of retinal morphological changes (i.e., changes in GCC and RNFL) separately for both groups demonstrated a positive correlation of the SD of IOP with the loss in global GCC ($r = 0.6258$; $p = 0.03$) and annual loss in GCC ($r = 0.5161$; $p = 0.02$) for group 2, but no significant correlation for group 1. This may indicate faster RGC death and POAG progression under the impact of short-term IOP fluctuations with an SD of IOP $\geq$ 3 mmHg. Therefore, short-term IOP fluctuations are a factor for increased progression of POAG. Particularly, short-term IOP fluctuations with an SD of IOP $\geq$ 3 mmHg cause an increased loss of GCC thickness. The progression of glaucomatous neuropathy in both groups of the study may indicate that an increase in IOP is still the major, but not the only, factor in the development of glaucoma.

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Ethics Statement: *This study included human participants, was approved by the local bioethics committee and adhered to the tenets of the Declaration of Helsinki. Appropriate informed consent was obtained. This study did not include animal experiments.*

Abbreviations: *GCC, ganglion cell complex; IOP, intraocular pressure; NR, neuroretinal rim; OCT, optical coherence tomography; POAG, primary open-angle glaucoma; RNFL, retinal nerve fiber layer; SD, standard deviation; VF, visual field*