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Rates of macular volume changes in different stages and courses of primary open-angle glaucoma

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Purpose: *To examine macular volume changes as assessed by optical coherence tomography (OCT) and rates of these changes in different stages and courses of primary open-angle glaucoma (POAG).*

Material and Methods: *Totally, 123 patients (191 eyes; 54 men and 69 women; age, 48 to 69 years) with POAG were included in the study and underwent examination. Of these eyes, 67 were found to have pre-perimetric glaucoma and 124, perimetric POAG. At 5 years after enrollment in the study, the rate of macular volume change was assessed in 118 eyes. Examination included routine eye examination, static automated perimetry and OCT. POAG was classified as progressive or stabilized on the basis of annual rate of mean deviation (MD) change. The control group comprised 27 healthy individuals (54 eyes).*

Results: *Macular volume was smaller in patients with perimetric glaucoma than in those with pre-perimetric glaucoma and decreased with an increase in the stage of glaucoma. We found macular volume to be positively moderately correlated with the annual rate of MD change ($r = 0.6649$, $p < 0.05$). Throughout a five-year study period, there was a reduction in the macular volume in 52.8% of eyes with pre-perimetric glaucoma and 59.7% of eyes with perimetric glaucoma ($p > 0.05$). A reduction in the macular volume was seen significantly more frequently among eyes with progressive perimetric POAG than among eyes with stabilized POAG (67.8% versus 45.9%; $\chi^2 = 4.46$; $p < 0.05$).*

Conclusion: *Macular volume positively moderately correlated with the annual rate of MD change in eyes with POAG. Macular volume was significantly smaller in eyes with perimetric POAG than in controls and eyes with preperimetric POAG, and significantly decreased with an increase in the stage of glaucoma. A reduction in the macular volume over time was almost 1.5 times more common in eyes with progressive perimetric POAG than in eyes with stabilized perimetric POAG.*

Keywords:

glaucoma, primary open-angle glaucoma, macular pathophysiology, primary open-angle glaucoma pathophysiology, primary open-angle glaucoma diagnosis

Introduction

Glaucoma is a leading cause of loss of vision and irreversible blindness globally, and a majority of glaucoma cases are attributed to primary open-angle glaucoma (POAG) [1, 2].

In 2020, the number of people with glaucoma was estimated to be 68.56 million, increasing to 111.8 million in 2040 [3, 4]. The global prevalence of POAG is 2.2% [5]; however, it differs greatly from country to country and increases with age [4, 5].

A crucial element in the pathophysiology of all forms of glaucoma is the death of retinal ganglion cells (RGCs), a population of central nervous system (CNS) neurons with their stroma in the inner retina and axons in the optic nerve. This is associated with reduced neurotrophic protection of neurons, impaired transport of cerebral trophic factors to RGCs, and the involvement of the neuroglia into the pathological process [6, 8, 9, 10, 11].

Optical computed tomography (OCT) studies have shown a reduction in retinal macular thickness [12, 13] and macular volume [12, 13, 14, 15] in POAG and a trend of decreasing macular volume in eyes with more advanced disease [13, 14].

Ganglion cell complex (GCC) abnormality ratio (GCC SAR) is a macular parameter representing the surface area over which the macular thickness is decreased. GCC SAR had a better ability to diagnose perimetric glaucoma compared to the OCT software provided global GCC parameters [16].

Macular changes in POAG are, however, a subject of debate. A study by Liesegang [17] provided histological and electrophysiological evidence that RGCs are the only neurons affected by glaucoma. The outer plexiform layer (OPL) contains synapses among and between retinal photoreceptors, horizontal cells and bipolar cells, whereas the outer nuclear layer (ONL) contains photoreceptor nuclei; the thicknesses of the OPL and ONL are decreased in POAG patients [18]. It has been reported that experimental glaucoma resulted in prolonged severe loss of cone

photoreceptors [19]. Most researchers believe a reduction in retinal macular thickness in glaucomatous eyes to be associated with ganglion cell death [20, 21]. However, GCC was found to decrease with age in normal human eyes [22, 23], whereas the total macular volume did not show a significant difference with age in eyes with no known retinal disease [24]. Obviously, the cause of macular changes in glaucoma needs to be clarified. In addition, rates of macular volume changes in eyes with different stages of POAG have not been sufficiently investigated. To the best of our knowledge, there have been no reports on the macular volume in progressive versus stabilized glaucoma.

The purpose of the study was to examine macular volume changes as assessed by OCT and rates of these changes in different stages and courses of POAG.

Material and Methods

Totally, 123 patients (191 eyes; 54 men and 69 women; age, 48 to 69 years; mean age, 64.4 years) with POAG were included in the study and underwent examination. Of these eyes, 67 were found to have preperimetric glaucoma and 124, perimetric POAG. POAG stage 1 was found in 47 eyes, stage 2 in 36 eyes, and stage 3 in 41 eyes.

Glaucoma was classified as progressive or stabilized before the enrollment in the study in 93 eyes with perimetric glaucoma. Of these, 56 were found to have progressive glaucoma, and 37, stabilized POAG.

At 5 years after enrollment in the study, the rate of macular volume change was assessed in 118 eyes (36 eyes with preperimetric glaucoma and 82 eyes with perimetric POAG).

Exclusion criteria were the opacities in the media and ocular structures preventing macular volume assessment; age-related macular degeneration; retinopathy; chorioretinal scarring; amblyopia; high myopia; non-compensated hypertension; diabetes mellitus; connective tissue disease; history of abnormal retinal circulation or eye globe surgery; or POAG stage 4.

Examination included routine eye examination, 30-2 full-threshold static automated perimetry (SAP) (Twinfield Version 3.15r07, OCULUS Optikgeräte, Wetzlar, Germany) and OCT (MOCEAN 4000, MOPTIM, Shenzhen Sloton Technology Co. Ltd., China; TOPCON 3D OCT-1000, Topcon Corporation, Tokyo, Japan; 3D-Macula Report, Scan 6.0 x 6.0 mm).

POAG stage was determined by a reduction in retinal light sensitivity with mean deviation (MD), and eyes were classified as those with glaucoma stage 1 (early glaucoma; MD ≥ -6 dB), glaucoma stage 1 (moderate glaucoma; MD, -6.01 to -12 dB), and glaucoma stage 3 (advanced or severe glaucoma; MD, -12.01 to -20.0 dB), based on the number of points affected, i.e., with reduced retinal light sensitivity.

POAG was classified as progressive when the annual rate of MD change over at least 6 months before the enrollment in the study was ≥0.05 dB, or stabilized when the annual rate of MD change was ≤0.04 dB.

The control group included 27 healthy individuals (54 eyes).

This study was approved by the Ethics and Bioethics Committee of Kharkiv National Medical University (Minutes of the Committee Meeting no. 21) and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all study subjects.

The study envisaged examination of patients, determination of the macular volume and the stage of glaucoma, and analysis of the data obtained.

Statistical analysis was conducted using IBM SPSS Statistics 27 software.

Results

Macular volume values for patients with different stages of glaucoma and healthy controls are presented in Table 1. In patients with pre-perimetric glaucoma, the macular volume was 7.49 ± 0.09 mm3 and was not significantly different from healthy controls (7.72 ± 0.12 mm3, $p > 0.05$).

Macular volume was smaller in patients with perimetric glaucoma than in those with pre-perimetric glaucoma (6.86 ± 0.11 mm3 and 7.49 ± 0.09 mm3, respectively; $p < 0.05$), and decreased with an increase in the stage of glaucoma. Mean macular volume was smaller in patients with glaucoma stage 1 than in healthy controls (7.3 ± 0.1 mm3 and 7.72 ± 0.12 mm3, respectively; $p < 0.05$). In patients

Table 1. Macular volume values for eyes of healthy controls and patients with different stages of primary open-angle glaucoma

Group	Macular volume (mm³)	P-value
Healthy controls	7.72 ± 0.12	—
Preperimetric POAG	7.49 ± 0.09	$p^{4,5} < 0.05$
POAG stage 1	7.3 ± 0.1	$p^{1,4,5} < 0.05$
POAG stage 2	6.85 ± 0.09	$p^{1,2,3,5} < 0.05$
POAG stage 3	6.36 ± 0.08	$p^{1,2,3,4} < 0.05$

Note: p^1, significance of difference compared to controls; p^2, significance of difference compared to pre-perimetric glaucoma; p^3, significance of difference compared to POAG stage 1; p^4, significance of difference compared to POAG stage 2; p^5, significance of difference compared to POAG stage 3

with glaucoma stage 2, macular volume was 6.85 ± 0.09 mm3, and was significantly smaller than in patients with glaucoma stage 1 (7.3 ± 0.1 mm3; $p < 0.05$) and healthy controls (7.72 mm3 ± 0.12; $p < 0.05$). In eyes with POAG stage 3, macular volume was 6.36 ± 0.08 mm3, and was significantly smaller than in eyes with POAG stage 1, eyes with POAG stage 2 and eyes in healthy controls ($p < 0.05$).

Macular volume was positively moderately correlated with the annual rate of MD change ($r = 0.6649$, $p < 0.05$).

Throughout a five-year study period, there was a reduction in the macular volume in 52.8% of eyes with preperimetric glaucoma and 59.7% of eyes with perimetric glaucoma, but the difference was not significant ($p > 0.05$).

Of the preperimetric glaucoma eyes that exhibited a reduction in the macular volume, 63.2% developed visual field defects. Of the preperimetric POAG eyes that exhibited no reduction in the macular volume, only 23.5% developed visual field defects (the differences were statistically significant, $\chi 2 = 5.7$; $p < 0.05$).

A reduction in the macular volume was noted in 62.5% of eyes that developed versus 45% of eyes that did not develop visual field defects over five years (the differences were not statistically significant, $\chi 2 = 1.09$; $p > 0.05$).

In addition, a reduction in the macular volume was seen significantly more frequently among eyes with progressive perimetric POAG than among eyes with stabilized POAG (67.8% versus 45.9%; $\chi 2 = 4.46$; $p < 0.05$). The percentage of eyes that exhibited a reduction in the macular volume over five years was more than twice higher for eyes with POAG stage 2 and eyes with POAG stage 3 (82.6% and 81.8%, respectively) than for eyes with POAG stage 1 (37.5%), with a significant difference between the former eyes and the latter eyes ($\chi 2 = 16.24$; $p < 0.05$).

Discussion

Our finding of a reduction in the macular volume in patients with POAG is in general agreement with the findings of other researchers [12, 13, 14, 15].

We found no significant difference in the macular volume between eyes with preperimetric glaucoma and control eyes. This is comparable to the results of a study by Lederer and colleagues [14] who found no significant difference between the macular volume of glaucoma suspects and healthy controls.

Macular volume was smaller in perimetric glaucoma eyes than in pre-perimetric glaucoma eyes and eyes of healthy controls, which is in agreement with literature reports on reductions in macular volume and retinal thickness in the macula in POAG [12, 13, 14, 15].

Our finding of a statistically significant reduction in the macular volume in eyes with POAG stage 1 is in agreement with the finding of a decreased macular volume in a study by Ojima and colleagues [15], although others [13, 14] did not note a significant reduction in the macular volume in early glaucoma.

We found macular volume to decrease with an increase in the stage of POAG, which is in agreement with findings of other researchers [13, 15] of a more apparent reduction in the macular volume in advanced glaucoma.

In addition, we found macular volume to be positively moderately correlated with the annual rate of MD change ($r = 0.6649$, $p < 0.05$). Our results are indirectly confirmed by a study by Greenfield and colleagues [27] who found a correlation between retinal macular thickness as assessed by OCT and visual field mean defect.

Our finding of a reduction in the macular volume in POAG over time may be caused by an impairment in blood supply to the macula, which is indicated by reports on a reduced choroidal thickness in the macular area in POAG [26, 28], reduced density of choroidal vessels in eyes with POAG compared to controls [29, 30, 31, 32] and progressive macular vessel density loss in POAG [29].

Moreover, our finding of a reduction in the macular volume over time in eyes with POAG is indirectly confirmed by the results of a study by Saruhan and colleagues [33] who reported on POAG progression even in the presence of a drug-induced reduction in the IOP to 13-15 mm Hg.

Possible limitations of this study include a relatively small sample size and not sufficiently long follow-up.

Conclusion

First, we found macular volume to be positively moderately correlated with the annual rate of MD change in eyes with POAG. Second, macular volume was significantly smaller in eyes with perimetric POAG than in controls and eyes with preperimetric POAG, and significantly decreased with an increase in the stage of glaucoma. Third, a reduction in the macular volume over time was almost 1.5 times more common in eyes with progressive perimetric POAG than in eyes with stabilized POAG. Finally, the percentage of eyes that exhibited a reduction in the macular volume over five years was more than twice higher for eyes with POAG stage 2 and those with POAG stage 3 than for eyes with POAG stage 1.

The work presented not only determines the rate of change in macular volume in patients with POAG. It also demonstrates the necessity of (1) taking in account the rate of macular volume change to determine whether a patient has a progressive or stabilized POAG and (2) performing further research on retinal changes in POAG.

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Abbreviations: *MD, mean deviation of light; OCT, optical coherence tomography; POAG, primary open-angle glaucoma*