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Comparative study of factors associated with the progression of primary open-angle and angle-closure glaucoma

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ABSTRACT

Purpose — to compare the factors associated with the progression of primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG).
Material and methods. This prospective study analyses clinical data of POAG and PACG patients followed up for 6 years. The progression of glaucomatous optic neuropathy (GON) was determined using perimetry and spectral optical coherence tomography (OCT). The value of each diagnostic indicator (z-value) was calculated using the Wilcoxon-Mann-Whitney test and the area under the ROC-curve (AUC) to identify the parameters reliably associated with the progression in both groups of patients.
Results. According to OCT, 47.3% of PACG patients and 52.46% of POAG patients had GON progressing, while according to perimetry, these figures were 21.8% and 23%, respectively. The common factors associated with progression of these glaucoma forms were age (AUC 0.7, z –1.9 in PACG and AUC 0.7, z –2.9 in POAG) and maximum IOP (0.7; –2.7 in PACG and 0.79; –5.4 in POAG). The progression of PACG is associated with lens size (0.7; –2.4), subfoveal choroidal thickness (AUC 0.8, z –3.3) and peripapillary choroidal thickness (0.79; –3.2), resistive index in the vortex veins (0.81; –3.3) and their end diastolic blood flow velocity (0.83; 3.2). The progression of POAG is associated with a thin peripapillary (0.75; 2.6) and subfoveal choroid (0.74; 2.5), increased resistive index in the posterior short ciliary arteries (0.8; –2.3), and initial retinal nerve fiber layer (RNFL) thickness: 0.69; 2.9.
Conclusion. The progression of POAG and PACG has only two common factors — age and maximum IOP. The progression of PACG is mainly related to the lens size, venous dysfunction and the choroid expansion, while the progression of POAG is related to the initial RNFL thickness, reduced arterial blood flow and choroid thinning.

Keywords: *primary angle closure glaucoma, primary open angle glaucoma, glaucoma progression, ocular blood flow, choroid, optical coherence tomography.*

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Detection of progression and its rate is the most topical task of glaucoma monitoring, especially in terms of the quality of life of patients and preventing irreversible loss of visual functions and blindness.

The main studies on glaucoma progression are devoted to primary open-angle glaucoma (POAG) [1—5], but for a long time its progression was detected only using perimetry [1, 2] and/or the results of an optic disc fundus study [3—5]. According to recent data, optical coherence tomography (OCT) significantly increases the accuracy of progression detection as it allows to detect thinning of retinal ganglion cell layer (RGC) and peripapillary retinal nerve fiber layer (RNFL) [6] at early stages. Moreover, efficiency of progression detection increases significantly with simultaneous use of perimetry and OCT [7].

Progression of primary angle-closure glaucoma (PACG) is not studied enough. There are only two publications on this topic in the literature, where the progression of glaucomatous optic neuropathy (GON) was evaluated only using perimetry [8, 9]. It is noteworthy that OCT is generally used in this form of glaucoma only to assess the condition of the anterior eye segment [10] in order to identify anatomical risk factors for PACG development. We could not find any study on the use of OCT of RNFL and RGC for assessing the progression of PACG. Meanwhile, PACG is the form of glaucoma with the highest risk of blindness [11].

Based on the different pathogenesis of POAG and PACG, it can be assumed that the factors associated with the progression of GON in these two forms of glaucoma are also different. However, the studies devoted to the rate of progression of GON and to the GON-associated factors in the specified forms of glaucoma have not been carried out in a comparative aspect before.

The **purpose** of this study is to compare the factors associated with the GON progression in POAG and PACG.

Material and methods

The study included 55 eyes (55 patients) from 73 PACG and 61 eyes (61 patients) from 73 POAG with initial glaucoma after excluding eyes with phacoemulsification and intraocular lens implantation at the end of the follow-up period (17 eyes (23.29%) in PACG and 11 (15.07%) in POAG), and the eyes with anti-glaucoma surgery.

The study was conducted in accordance with Good Clinical Practice within the tenets of the Declaration of Helsinki. The study protocol was approved by the Ethical Committee of the Russian State Research Center – Burnasyan Federal Medical Biophysical Center of Federal Medical Biological Agency of Russia.

Patients were enrolled in the study from April 2010 to May 2012. The follow-up period lasted until June 2018.

Inclusion criteria were the following: patients with initial POAG and PACG, ametropia ⩽ 0.5, anterior chamber open angle confirmed OCT (at least 30°), and the absence of concomitant pathology of organ of vision, except for cataracts.

The diagnosis of glaucoma was made on the basis of the presence of the optic disc excavation, thinning of neuroretinal rim, wedge-shaped defects of RNFL adjacent to the optic disc edge, vertical asymmetry of the cup/disc ratio > 0.2 between eyes (not associated with different sizes of the optic disc), determined using Visucam 500 stereoscopy (Zeiss, Germany), and hemorrhages at optic disc edges.

The results of SAP 24—2 were considered abnormal if pattern standard deviation (PSD) was P < 5% or the result of glaucoma hemifield test was determined to be "outside normal limits". The stage of glaucoma was determined according to the Mills classification [12].

The diagnosis of angle-closure glaucoma was made on the basis of the presence of the anterior eye chamber closed angle (if at gonioscopy the posterior pigmented part of the trabecular network was not visible at least at 180° when a patient looked directly) according to the Foster classification [13], the presence of GON, defined as narrowing of a neuroretinal rim with vertical optic disc excavation > 0.7 and/or with an asymmetry of vertical optic disc excavation > 0.2 and visual field defects indicating the presence of glaucoma, or based on a combination of all abovementioned characteristics.

Initial stage of glaucoma was established according to the Hodapp-Parrish-Anderson classification based on severity of visual dysfunction detected using 24—2 SITA STANDARD visual field protocol: groups of patients with mean deviation (MD) > −6 dB, less than 25% of points below 5 %, less than 10 points at the level of 1 % pattern deviation, provided that all points in the central zone of visual field of 50 have 15 dB sensitivity.

The exclusion criteria included the following: normal-tension glaucoma, pigmentary glaucoma, insufficiently transparent ocular media, lack of stable fixation, medically induced myosis, sphero-equivalent ± 6.0 diopters, astigmatism ± 2.0 diopters, history of surgeries on visual organs (including antiglaucoma surgeries and phacoemulsification), the presence of chronic autoimmune diseases, diabetes mellitus, Parkinson disease, Alzheimer disease, or dementia, systemic chronic diseases required the administration of glucocorticoids, as well as the presence of any other concomitant ophthalmic pathology.

Tonometry at all stages was performed at the same time: from 10 am to 12 am using ORA (Ocular Response Analyzer) (Reichert, USA). Initial intraocular pressure (initial IOP) and its average, maximum (maximum IOP) and minimum (min. IOP) values for the whole follow-up period were measured. Selective laser trabeculoplasty (SLT) was performed and/or hypotensive regimen was increased in case of increased IOP or detection of glaucoma progression.

Retinal ganglion cell layer (RGC) and retinal nerve fiber layer (RNFL) were analyzed using FD-OCT RTVue spectrograph (Optovue, USA). Three scans of RGC layer and optic disc were performed during each visit. Only the scans of optic disc and RGC with a signal strength index (SSI) above 45 were selected for the analysis, as it is recommended in the literature [6]. RGC scanning was carried out in the macula area of 7×7 mm with centering at 0.75 mm temporally from the fovea. RGC layer refers to a combination of RNFL, the ganglion cell layer, and the inner plexiform layer in the specified scanning area.

Optovue software was used to get the RGC thickness map of 6 mm in diameter with a center at 0.75 mm temporally from the foveal region. Peripapillary RNFL was measured using the ONH and 3D Disc protocols. The scans were centered manually at the exit zone of blood vessels from the optic disc. A set of radial and concentric optic disc scans (1.3—4.9 mm in diameter) was used to construct a peripapillary RNFL thickness map. RNFL map also showed thickness of the nerve fiber layer section in a circle with 3.45 mm diameter with centering in accordance with the identified center of optic disc. RTVue software (version 6.12) was used to make following measurements based on OCT images: average RGC thickness and average RNFL thickness. These both parameters were used to track structural changes, which are considered to be GON predictors. If any of these parameters indicated a trend of significant ($p<0.05$) thinning over time, then this eye was classified as having OCT progression. A series of OCT thickness parameters was found out at each follow-up visit, starting from the initial one and ending with the current visit. Progression was diagnosed when there was a significant ($p<0.05$) negative slope of RNFL or RGC thickness (thinning tendency).

Choroid thickness was studied using RTVue-100 spectral tomograph (Optovue, USA) in the RetinaCrossLine mode, as it was described previously [14]. Scanning was carried out in tracking mode. The choroid thickness was measured at 13 points in the 6x6 mm area in horizontal and vertical sections. The choroid was identified as the dis-

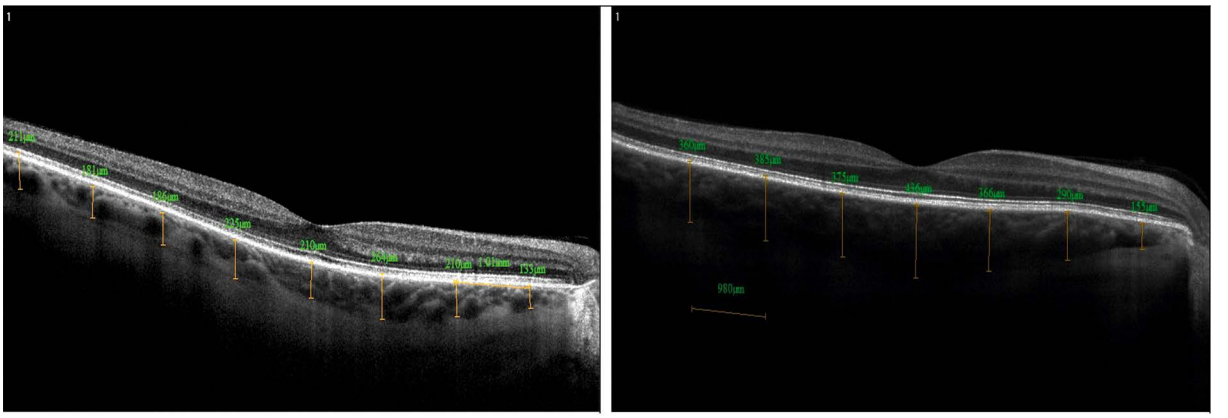

Fig. 1. **Scan protocols of the choroid.**

a — in a 59 year old patient with initial POAG; b — in a 58 year old patient with initial PACG.

tance between the area of hyperreflective line from the pigmented epithelium to sclera or to lamina fusca sclerae, if it was visualized **(Fig. 1)**.

Retrobulbar blood flow was studied using VOLUSON 730 Pro (Kretz, Austria) color Doppler mapping of the ocular vessels and retrobulbar space with a 10 to 16 MHz linear sensor in accordance with the previously described method [14].

GON progression rate was measured on the basis of visual field index (VFI) or perimetry index MD with the use of Guided Progression Analysis (GPA) software of Humphrey II visual field analyzer (Zeiss, USA), as well as by the method of event analysis [16]. Probability levels were considered statistically significant when p was less than 0.05 for the slope of whole 24—2 area. Only reliable values were selected to calculate the average progression values. Standard automated perimetry (SAP) was performed every 6 months. The endpoint corresponding to the "progression" conclusion was determined when either an event analysis or a trend analysis indicated a significant degree of progression. To exclude the influence of cataracts on visual field indicators, the eyes with reliable progression of cataracts were excluded, when visual acuity decreased by two or more lines at two or more visits as a result of lens opacification. Only follow-up visits with perimetry and OCT data were considered.

Statistical data processing

We applied Mann-Whitney U test and Pearson chi-squared test to compare two independent groups by one characteristic. Wilcoxon rank sum test was used to compare eyes with progression and non-progression eyes. To determine the parameters associated with progression, area under receiver operating characteristic curve (AUC) and the z-value of Mann-Whitney U test were calculated.

Cut-off value was determined by means of Youden's index. The numerical data are represented as the mean ± standard deviation. Parameters with $p<0.05$ were considered statistically significant. Statistical processing of the obtained results was carried out using SPSS version 16.0 and MedCalc version 11.5.1 for Windows.

Results

The studied groups differed significantly only in size of anterior-posterior axis, spherical equivalent, depth of the anterior chamber and the degree of opening of anterior chamber angle upwards. The clinical characteristics of patients are presented in **Table 1**.

According to the results of 6 years of follow-up, SAP revealed the disease progression in 14 eyes (23%) with initial POAG and in 12 (21.8%) in PACG. OCT detected the disease progression more often: according to RNFL — in 27 (44.26%) eyes with POAG and 23 (41.82%) in patients with PACG; according to RGC analysis — in 32 (52.46%) eyes with POAG and 26 (47.3%) in eyes with PACG. Despite the fact that the number of cases with GON progression did not significantly differ between the groups, the rate of progression was higher in patients with CAP compared with POAG **(Table 2)**.

Though the number of cases with GON progression did not differ significantly between the groups, ROP was higher in patients with PACG compared with POAG **(Table 2)**.

Table 3 and **Table 4** show that the significant progression factors in both forms of glaucoma were maximum IOP and age of patient at the time of start of follow-up.

Lens size was a significant factor in PACG **(Table 3)**, and RNFL initial thickness — in POAG **(Table 4)**. In case of PACG, the factor most related to the progression of GON was venous blood flow (Table 3), while ar-

Table 1. **Clinical characteristics of patients with POAG and PACG**

Characteristics	POAG	PACG	*P*
Age, years	69,6±6,5	68,9±5,8	0,255
Follow-up period, months	71,5±22,4	75,0±19,0	0,374
Vision with correction	0,91±0,1	0,90±0,1	0,544
Equivalent spherical, Dpt	–0,32±1,18	1,5±1,4	0,000
Corneal thickness, μm	541,4±34,3	547,8±33,2	0,314
Anterior-posterior axis, mm	23,9±0,7	22,5±0,9	0,000
Anterior chamber depth, mm	3,3±0,3	2,64±0,29	0,000
Lens thickness, mm	4,7±0,1	4,8±0,2	0,100
Avg. RNFL, μm	96,0±9,6	97,7±11,6	0,436
GCC, μm	89,9±9,0	90,3±9,5	0,633
No. of OCT tests	4,9±1,9	4,6±1,6	0,531
No. of perimetries	9,5±3,7	8,6±3,0	0,168
Initial MD, dB	–2,2±2,0	–1,8±2,5	0,118
Initial PSD, dB	1,4±1,0	1,3±1,7	0,324
Initial IOP, mm Hg	21,8±2,8	22,7±3,2	0,130
IOP max, mm Hg	23,6±2,3	23,8±2,8	0,586
IOP min, mm Hg	16,4±2,8	17,2±2,0	0,086
Degree of anterior chamber angle pigmentation	2,2±0,5	2,3±0,6	0,475
Dimensions of anterior chamber angle upwards (0)	32,2±5,1	12,6±3,9	0,001
Dimensions of anterior chamber angle downwards (0)	31,5±5,2	24,3±4,3	0,084
Average amount of hypotensive eye drops	1,21±0,6	1,29±0,6	0,264
Average number of laser surgeries			
Laser iridotomy	0	100% (55)	0,000
SLT*	26,56% (17)	40% (22)	0,422

Note: P — is an indicator according to Mann-Whitney U test and Pearson chi-squared test. GCC — ganglion cell complex; MD — mean deviation; PSD — pattern standard deviation; RNFL — retinal nerve fiber layer; IOP — intraocular pressure; *SLT (selective laser trabeculoplasty), in some eyes it was performed several times during the follow-up period.

Table 2. **Rate of progression (ROP) after SLT in patients with POAG and PACG**

ROP	PACG	POAG	*p*
ROP_1 (MD), dB/year	0,11±0,49	0,04±0,44	0,027
ROP_2 (RNFL), μm/year	1,38±2,0	0,70±1,62	0,180
ROP_3 (GCC), μm/year	1,34±2,40	0,82±1,78	0,476

Note: *p* — reliability parameter according to Mann-Whitney U test; ROP — rate of progression detected using perimetry (1) and OCT, in accordance with RNFL (2) and RGC (3).

Table 3. **Diagnostic significance of the parameters in differentiating the presence/absence of GON progression in PACG patients**

Parameters	AUC±S. E.	*p*	Cutoff	Z
Age, years	0,712±0,11	0,045	>71	–1,9
IOP max, mm Hg	0,713±0,07	0,005	>24,2	–2,7
Lens thickness, mm	0,715±0,09	0,018	>5,0	–2,4
Vortex Vein, EDV, cm/s	0,83 ±0,06	0,001	<=5,7	3,2
Vortex Vein, RI	0,801±0,09	0,000	>0,33	–3,3
Peripapillary CT, μm	0,798±0,08	0,003	>281	–3,2
Foveal CT, μm	0,801±0,08	0,001	>327	–3,3

Note: AUC — area under ROC curve; S.E. — standard error; CT — choroidal thickness.

terial retrobulbar blood flow played the most important role in POAG (Table 4).

It is noteworthy that the progression was associated with the choroid thickness in both forms of glaucoma. However, progression in PACG was associated with a thicker choroid **(Table 3, Fig. 2a and 2b)**, and, on the contrary, a thin choroid was a risk factor for POAG progression **(Table 4, Fig. 2c and 2d)**. The sizes of subfeoveal and peripapillary choroid were equally significant in both forms of glaucoma.

Discussion

There is only one publication on the comparison of ROP and the factors associated with it between POAG and PACG in the literature. In that 5-year retrospec-

Table 4. **Diagnostic significance of the parameters in differentiating the presence/absence of GON progression in POAG patients**

Parameters	AUC±S.E.	*p*	Cutoff	Z
Age, years	0,710±0,07	0,001	>70	–2,9
CRA, EDV, cm/s	0,715±0,11	0,008	<=2,5	2,8
CRA, RI	0,798±0,11	0,046	>0,74	–2
TPCA, RI	0,801±0,12	0,025	>0,6	–2,3
IOP max, mm Hg	0,792±0,05	0,000	>23,8	–5,4
Peripapillary CT, μm	0,752±0,09	0,010	<=235	2,6
Foveal CT, μm	0,740±0,09	0,012	<=222	2,5
Avg. RNFL, μm	0,692±0,06	0,002	<=95,75	2,9

Note: AUC — area under ROC curve; S.E. — standard error; CT — choroidal thickness; PSCA — posterior short ciliary arteries; CRA — central retinal artery.

tive study, Lee Y. et al. revealed more rapid progression in PACG patients, and only in them, but not in POAG. The only progression factor was maximum IOP detected each year throughout the study [8]. These data coincide with our results. However, unlike Lee, maximum IOP was associated not only with PACG progression, but also with POAG progression.

The role of increased IOP as the main factor of GON progression has been noted in many works [1—5, 17]. At the same time, Verma's retrospective study did not associate increased IOP with rapid progression of PACG. PACG progression was associated only with the age of patients and optic disc excavation size at the time of monitoring [9]. The role of the age factor in the glaucoma progression has been noted by many researchers [3, 4, 17]. According to our results, patients > 70 years with POAG and patients > 71 years with PACG has higher risk of GON progression.

The initial state of RNFL in GON progression was noted by us only in case of POAG. The degree of structural changes as a risk factor for the progression of POAG has been described in other studies [18, 19].

Observing PACG patients for over 10 years, Verma et al. noted progression in 15.8% patients, with an average ROP of –0.12 dB/year [9]. These data differ from those obtained in our study. Thus, according to the GPA-analysis for a 6-year follow up, the ROP amounted to 23% in POAG and 21.8% in PACG. The data discrepancy between the study by Verma and our study may be explained by various methods for estimating progression by means of perimetry: pointwise linear regression analysis (PLR, progressor software) applied in Verma's study and the Guided Progression Analysis (GPA) applied in the present study. The progression criteria in this software are different.

Using the same software (GPA) and observing patients also for 6 years, Zhang and co-authors have revealed the progression of POAG in 18.7% cases [6]. The same authors also have found out that the glaucoma progression is detected twice often using the OCT method (38.9%, $p<0.001$), especially when analyzing the GCC changes. These data coincide with ours, because overall progression in the both groups was detected using the OCT method amounted to 36.8% (50 eyes) in comparison with SAP: 19.1% (26 eyes), $p=0.000$.

It is worth mentioning that the present study has evaluated for the first time the progression of PACG not only by SAP, but also by the morphometric assessment (OCT), moreover, in a comparative aspect with POAG.

According to the present study, the ROP in PACG was the same as that obtained by Verma [9], and was 2.5 times higher than that in POAG. These data are similar to the results obtained by Lee [8]. At the same time, the number of patients with rapid progression (more than 1.0 dB/year according to the criteria of the present work) was significantly less than in Verma's study (57%). This fact may be explained by a longer observation period, and most importantly, a more pronounced stage of PACG at the beginning of follow-up in Verma's study [9].

This study has revealed that there are specific factors of progression, in particular, a large lens volume, in PACG. This fact confirms the correctness of the new PACG treatment approach — early lens removal [20].

The present study was the first to identify new factors of glaucoma progression differentiating POAG and PACG. PACG progression is associated with a thick choroid and defected venous outflow from the eye. On the contrary, POAG is associated with a thinner choroid and defected arterial blood flow. The revealed correlations indicate a fundamentally different pathogenesis of these two forms of glaucoma and emphasize the role of choroid and venous blood flow in the development and progression of PACG **(Fig.2)**.

The theory of the special role of choroid in the development of PACG was formulated by H. Quigley 10 years ago [21]. According to this theory, a closed anterior chamber angle is caused by the anterior position of the lens and/or its anterior displacement under conditions of choroid increase (expansion, or effusion) that can occur even with a normal size of the anterior-posterior axis. The reasons of the choroid increase are various and are currently being studied [22]. One of them is the increased osmotic pressure in the choroid extravascular spaces. In case of choroidal effusion, the anterior chamber volume decreases [23] and IOP rises to high values. However, not all authors share this point of view, since both the choroid thickness and IOP are dynamic processes subject to fluctu-

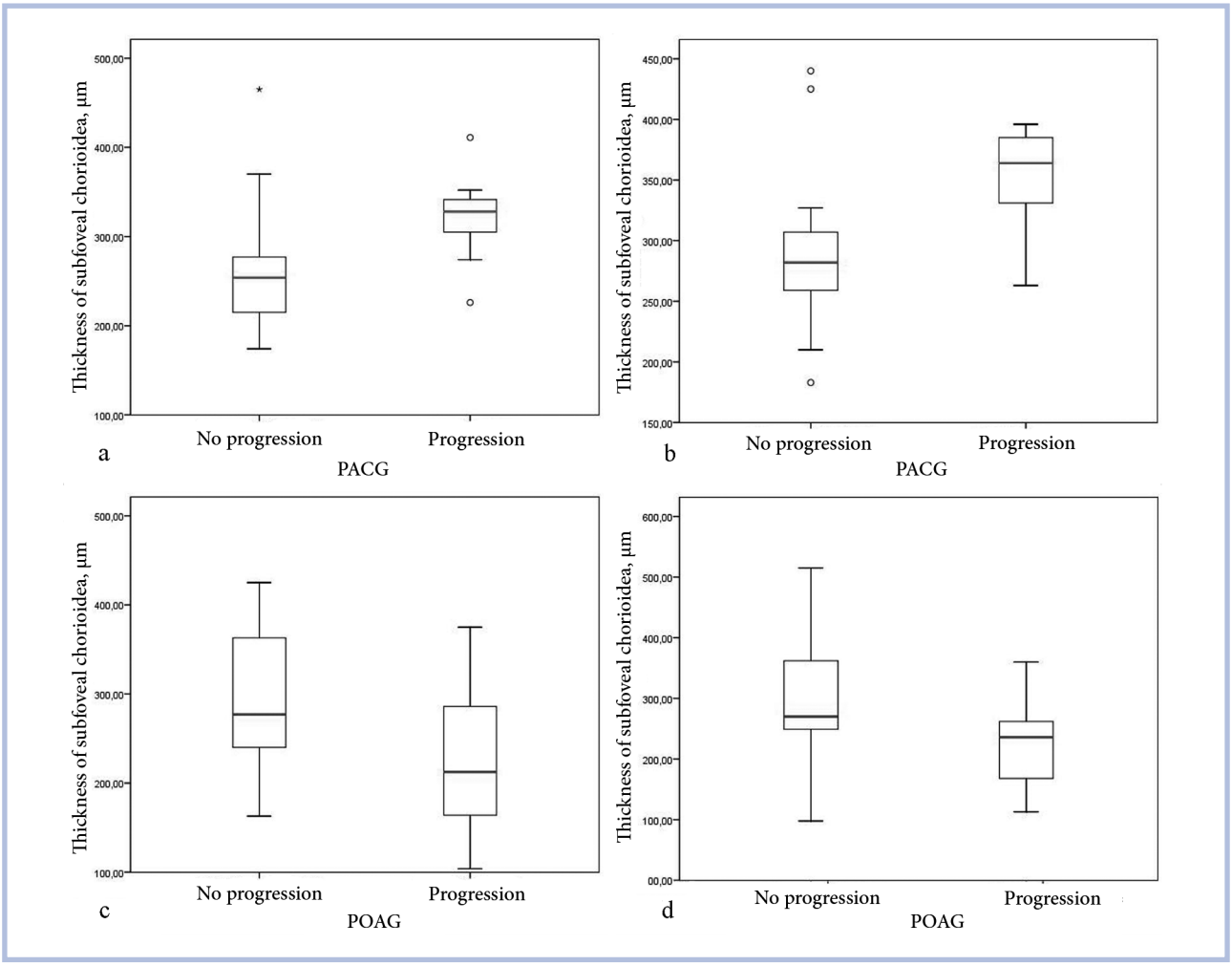

Fig. 2. **Diagrams showing the differences in thickness of peripapillary (a, c) and subfoveal (b, d) choroid as a predictor for progression of PACG (a, b) and POAG (c, d).**

ations, and there may not be a direct relation between IOP and the choroid thickness [24].

The theory of changes in choroid sizes as a cause of the PACG development has been confirmed in a number of works [21,25,26]. The advent of SD-OCT allowed carrying out a number of studies that have indicated more increased central thickness of the choroid in PACG compared to POAG and healthy eyes [25]. Moreover, it was shown that the size of subfoveal choroid increases during a PACG attack, even in the paired eye [26], and the increase in subfoveal choroid thickness is an independent PACG predictor characterizing its chronic form [27].

According to the results of our study, a violation of blood flow in the vortex veins is an important PACG progression factor. It is known that this phenomenon is closely related to choroidal effusion and manifests itself in various pathologies, for example, in retinal thrombosis. Functionally, choroidal blood flow is determined by blood flow in the vortex veins, which are the main drainage path for choroid vessels [24]. The studies on phenotypes characterizing endothelial dysfunction of the vortex veins in connection with a possible increase in choroid in PACG patients are currently being carried out [28]. Since choroidal effusion leads to the anteposition of the lens-iris diaphragm and occurs not only in an acute PACG attack, but also in its chronic course, it can explain the correlation between PACG progression and the choroid thickness increase and violation of venous blood flow the same time.

However, the study has revealed that GON progression in POAG, in contrast, is associated with a thinner choroid. Our previous studies demonstrated a significant decrease in the choroid thickness in patients with perimetric POAG compared to its preperimetric stage [15]. This difference was observed both in the subfoveal zone and in the peripapillary zone. Thinning of the choroid in POAG was described by other authors [29], but not all of them share this opinion [30]. Recent studies by Lee et al. with the simultaneous use of OCTA of choroid and indocyanine green angiography have shown that thinning of peripapillary choriocapillary network in POAG is associated with occlusion of capillaries as the primary factor leading to its atrophy [29]. This is an important finding that can explain the de-

crease in blood supply of the prelaminary part of the optic nerve, and as a result, GON progression.

The results of this work showed that POAG progression was also associated with decreased blood flow in CRA and PSCA, which coincides with the literature data [31,32]. The obtained results are fully within the concept of glaucoma perfusion disorders as the retinal blood supply is ensured by the retinal branches of the CRA, which also supplies the retrolaminary portion of the optic nerve. The blood supply to all other parts, including optic disc, is ensured only by PSCA.

Furthermore, the study of both the choroid thickness and retrobulbar blood flow has its limitations related to large fluctuations of the results, depending on many factors, for example, blood pressure, IOP, day time, etc. We believe that the findings of the study are useful for understanding the pathogenesis of both forms of glaucoma and can only be auxiliary in the diagnostic process. At the same time, new diagnostics methods of retinal and choriocapillary blood flow, for example, OCT-angiography, can potentially occupy its place in glaucoma monitoring.

Conclusion

According to the obtained results, the progression of POAG and PACG has only two common factors — age and maximum follow-up IOP. PACG progression is associated with such factors as the lens size, venous dysfunction and choroid expansion, and POAG progression factors are the initial state of RNFL, decreased arterial blood flow, and thinning of the choroid.

The authors declare no conflicts of interest.

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