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REDUCTION OF THE RISK OF GLAUCOMATOUS OPTIC NEUROPATHY PROGRESSION AFTER COMPLEX NEUROPROTECTION

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The problem of glaucomatous neurodegeneration with progressive death of retinal ganglion cells (RGCs) and development of visual field defects can lead to irreversible blindness. In this regard, there is a need to search for effective strategies for neuroprotection of RGCs.

Objective. To study the risk of glaucomatous optic neuropathy (GON) progression in patients with primary open-angle glaucoma (POAG) after complex neuroprotection by photobiomodulation (PBM) and nutraceutical formula AREDS2 with ω-3 polyunsaturated fatty acids (PUFA) enhancement and resveratrol for a 12- month follow-up.

Material and methods. A total of 137 patients (137 eyes) diagnosed with early or advanced POAG were examined. The main group (group 1) included 74 patients, the control group (group 2) – 63 patients. All patients underwent PBM therapy. Patients of group 1 were additionally recommended the nutraceutical formula AREDS2, enriched with ω-3 PUFA and resveratrol 60 mg (Resvega® Forte; Théa, France; 2 capsules per day) for 12 months. Using Cox regression, the relative risk (cumulative risk function) for predicting the progression of GON was calculated.

Results. After 12 months of observation, the median POAG in group 1 exceeded the initial level by 15%. Stabilization and a tendency to improve the parameters of retinal morphometry, Humphrey computer perimetry, as well as an improvement in intraocular blood volume by 24% (p = 0.001) were noted. In the control group, deterioration in all parameters was noted.

Conclusions. Complex neuroprotection using PBM and taking the AREDS2 nutraceutical with ω-3 PUFA and resveratrol (60 mg) for 12 months in patients with POAG can reduce the relative risk of progression of GON by 2.27 times (95% DI 1, 38–3.75).

Keywords: glaucomatous optic neuropathy, neuroprotection, photobiomodulation, nutraceutical, resveratrol.

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ЗНИЖЕННЯ РИЗИКУ ПРОГРЕСУВАННЯ ГЛАУКОМНОЇ ОПТИЧНОЇ НЕЙРОПАТІЇ ПІСЛЯ КОМПЛЕКСНОЇ НЕЙРОПРОТЕКЦІЇ

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Статтю присвячено актуальній проблемі глаукомної нейродегенерації та пошуку ефективних стратегій нейропротекції. Фотобіомодуляція (ФБМ) з антиоксидантною дією ресвератролу є перспективним методом нейропротекції, що дає змогу обгрунтувати його застосування за глаукомної оптичної нейропатії (ГОН) як комплексної нейропротекторної терапії. Використання ФБМ сітківки / диска зорового нерву з 12-місячним прийманням нутрицевтика формули AREDS2, посиленого ω-3 ПНЖК і ресвератролом (60 мг), у хворих на первинну відкритокутову глаукому дає можливість у 2,27 раза знизити відносний ризик прогресування ГОН (95 % DI

1,38–3,75), завдяки покращенню об'ємного внутрішньоочного кровообігу, підвищенню провідності в нервових волокнах зорового нерву з покращенням загальної світлової чутливості зорового аналізатора, та стабілізувати морфометричні показники зорового аналізатора й максимально кориговану гостроту зору.

Ключові слова: глаукомна оптична нейропатія, нейропротекція, фотобіомодуляція, нутрицевтик, ресвератрол.

Introduction. Primary open-angle glaucoma (POAG) is prevalent mainly among people aged 60 years and older, and one of the proven factors contributing to the progression of glaucoma is elevated intraocular pressure (IOP) [2]. Despite various methods of IOP stabilization, the death of retinal ganglion cells (RGC) continues, and glaucoma remains the main cause of irreversible vision loss. RGCs are very sensitive to ischemic and reperfusion injury [2], which leads to a decrease in the thickness of the RGC complex and the peripapillary nerve fiber layer (RNFL) [18]. Early changes in the RGC dendrites provide a gap for neuroprotective therapy and prevention of further damage [18]. To improve cell survival, reduce apoptosis, oxidative stress and restore mitochondrial function, photobiomodulation (PBM) of the retina/optic nerve is effective, with proven anti-edematous, anti-inflammatory and antioxidant effects, and PBM stimulates neurogenesis and synaptogenesis, reducing apoptosis [9, 11, 13]. These effects justify the use of PBM in complex neuroprotective therapy in the treatment of patients with glaucomatous optic neuropathy (GON) [9].

Drugs that improve retinal antioxidant defense (citicoline, resveratrol) play an important role in neuroprotective therapy [4, 7, 17]. The recommendations of the 5th edition of the European Glaucoma Society state that the goal of therapeutic treatment of glaucoma is to preserve the patient's visual field and quality of life [5].

Objective. To evaluate the risk of GON progression in patients with POAG after complex neuroprotection by using PBM and nutraceuticals of the AREDS2 formula, enhanced with ω-3 polyunsaturated fatty acids (PUFAs) and resveratrol, for 12 months.

Material and Methods. The open prospective study of patients with GON was a fragment of the research work "Optimization of diagnostics, treatment and prevention of degenerative and inflammatory diseases of the organ of vision" (2020–2024; state registration number 0119U003573) of Odesa National Medical University. The basis for the study complies with the Helsinki Declaration for the Moral Regulation of Medical Research, the Council of Europe Convention on Human Rights and the laws of Ukraine. The bioethical expertise of the study was confirmed by the conclusion of the ONMU Bioethics Commission (Protocol No. 44 of May 01, 2024).

We examined 137 patients (137 eyes) with clinical signs of GON (i.e., thinning of the peripapillary nerve fiber layer, narrowed neuroretinal rim, visual field defects), with the following visits: V0 – before treatment, V1 – after 1 month, V6 – after 6 months and V12 – after 12 months. The information consent was signed by all participants.

Inclusion criteria: patients with target IOP achieved by medication (75 eyes) or surgery (63 eyes) and no neuroprotective treatment for 6 months.

Exclusion criteria: severe lens opacification, poor quality of retinal visualization according to optical coherence tomography (OCT), macular degeneration, vascular diseases of the retina and optic nerve, diabetic retinopathy, high degree of refractive anomaly, severe somatic pathology.

Patients were divided into 2 groups: Group 1 (main) – 74 patients and Group 2 (control) – 63 patients. Both groups of patients were representative in terms of the main clinical parameters. All patients received 10 sessions of PBM of the retina and optic disc (λ = 650 nm, W = 0.4 mW/cm², t = 5 min). For 12 months, patients in Group 1 (main) were additionally recommended to take a nutraceutical of the AREDS2 formula, fortified with ω-3 PUFA and resveratrol 60 mg (Resverga® Forte; Théa, France), 2 capsules once daily. Ophthalmologic examination included maximum corrected visual acuity (BCVA), biomicroscopy, gonioscopy, Goldmann applanation tonometry, fundus examination with a VolkSuper aspheric lens, computerized static perimetry on a Humphrey 750i visual field analyzer, 30-2 SITA program; rheo-ophthalmography (ROG; Reocom, Ukraine) – to determine the characteristics of intraocular volume circulation (RQ index). Optical coherence tomography (OCT) (SOCT Copernicus OPTOPOL Technology S.A., Poland) assessed the thickness of the peripapillary nerve fiber layer (RNFL), as well as the thickness of the ganglion cell layer + inner plexiform layer (GCL-IPL). Patient adherence to the treatment and instillation regimen was noted, and the presence of side effects was clarified.

STATISTICA 10.0 (StatSoft Inc., USA) was used for calculations and MedCalc v.15.1 (MedCalc Software, Belgium) for graphical representations of the data. The normality of the continuous data distribution was tested using the Shapiro-Wilk test. Since all the variation series had a distribution other than normal, the median (Me) and the 25% and 75% quartiles (Q 25–75%) were used for descriptive statistics. Qualitative data were described with numbers and percentages using frequency tables. Comparison of predicted and observed frequencies of features was performed using the χ^2 test with Yates' correction. When comparing several independent samples, the Mann-Whitney U test was used, and the Kruskal-Wallis test was used to test the equality of the medians of several samples (V0–V12). For repeated within-group comparisons, the Wilcoxon signed-rank test was used. Using Cox regression, the relative risk (Cumulative Hazard Function) and 95% confidence interval were calculated to predict the progression of GON depending on the treatment group. The critical level of significance for testing statistical hypotheses was $p < 0.05$.

Results. The duration of glaucoma disease in the 137 patients examined ranged from 12 months to 12 years, with a median of 4 (3–6) years (Table 1). Early POAG was diagnosed in 97 eyes (mean deviation (MD) ≥ –6.00 dB) and advanced in 40 eyes (–12.00 ≤ MD < –6.00 dB). The age of the patients was 60 (54–77) years, and 39% (54/137) were men.

At the first visit (V0), IOP was 16.5 (16.0–19.0) and 18.0 (16.0–19.0) mm Hg in groups 1 and 2, respectively. At subsequent visits (V1–V12), there were no significant

Table 1

Clinical characteristics of the study cohort (137 patients – 137 eyes)

Indications for treatment	Group 1 (main), n = 74 eyes	Group 2 (control), n = 63 eyes	p
Age (years)	62.0 (56–67)	63 (59–66)	p = 0.02[a]
Men/women	33 (45%) / 41 (55%)	21 (33%) / 42 (67%)	p = 0.18[b]
POAG stage: initial / advanced	45 eyes (61%) / 29 eyes (39%)	52 eyes (82.5%) / 11 eyes (17.5%)	p = 0.01[b]
Anti-glaucoma surgery, yes	37 (50%)	25 (40%)	p = 0.23[b]
Duration of glaucoma, year	4.0 (3–6)	3.0 (2–5)	p = 0.34[a]
Cataract / pseudophakia	35 eyes (47.3%) / 27 eyes (36.5%)	24 eyes (38.1%) / 29 eyes (46%)	p = 0.28[c] p = 0.26[b]
IOP, mm Hg	16,5 (16,0–19,0)	18 (16,0–19,0)	p = 0.31[a]
BCVA	0,65 (0,45–0,8)	0,8 (0,6–0,8)	p = 0.21[a]
CCT, µm	527 (516–545)	532 (523–547)	p = 0.06[a]
RNFL, µm	78 (76–87)	76 (74–83)	p = 0.03[a]
GCL+IPL, µm	74.5 (67–79)	72 (64–78)	p = 0.04[a]
RQ, ‰	2.1 (1.9–2.5)	2.5 (2.1–2.5)	p = 0.16[a]
Cardiovascular pathology, yes	25 (34%) patients	34 (54%) patients	p = 0.02[b]
Smoking, yes	18 (24%) patients	16 (25%) patients	p = 0.88[b]
Observation time, days	338 (330–353)	330 (325–330)	p = 0.000[a]

Note: p – the level of significance of the difference between the indicators: *a* – by the Mann-Whitney test with Me (Q 25–75%), *b* – by the Fisher's exact test with n (%).

Abbreviations: POAG – primary open-angle glaucoma; IOP – intraocular pressure; BCVA – maximum corrected visual acuity; CCT – central corneal thickness; RNFL – thickness of the peripapillary nerve fiber layer; GCL+IPL – thickness of the retinal ganglion cell complex and the inner plexiform layer; RQ – intraocular volume circulation index.

differences in IOP in the groups (p > 0.05). The BCVA after the PBM course (V1) increased in both groups by 15% and 16% (p = 0.34), at the examination at V6 in Group 1 there was a tendency to further improvement to 0.83 (0.6–1.0), while in Group 2 the BCVA was already close to the baseline data (p = 0.001). After 12 months of observation, it was found that the median BCVA was 0.75 (0.5–0.9) and was 15% higher than the baseline values, while in the V12 control group this indicator showed a 12.5% lower level than the baseline of 0.7 (0.55–0.7; p = 0.02), as shown in Figure 1.

The dynamics of static perimetry parameters after 12 months of follow-up was as follows. The deviation of the total light sensitivity (MD) in patients of Group 1 improved in 36 eyes (49%), remained unchanged in 32 eyes (43%) and worsened in 6 eyes (8%), while in the control group, improvement was noted in 14 eyes (22.4%), remained unchanged in 33 eyes (52.2%) and worsened in 16 eyes (25.4%) ($\chi^2 = 6.32$, p = 0.01). The same trend was observed for the visual field index (VFI) ($\chi^2 = 9.36$, p = 0.002) and the local defect index (PSD) ($\chi^2 = 7.73$, p = 0.005) (Table 2).

A representative case. In Figure 2, a case of advanced glaucoma of the eye before treatment demonstrates a pronounced depression in the superior nasal quadrant of the nasal step type in the central 30° in the 30-2 program (Fig. 2, *A*). After treatment, the visual field was improved by perimetric parameters compared to the previous study (Fig. 2, *B*). According to OCT, the thickness of retinal nerve fibers (RNFL) in the inferior sector was outside the normal range (43 µm), and in the temporal sector was borderline (Fig. 2, *E*).

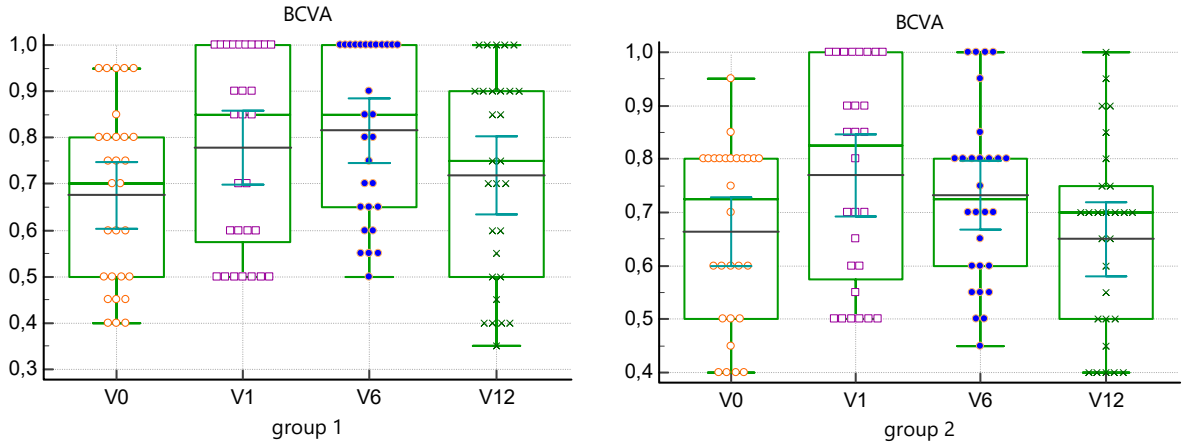


Fig. 1. Distribution of eyes with maximally corrected visual acuity, as well as the dynamics of this index during the observation period (V0-V12) in both groups

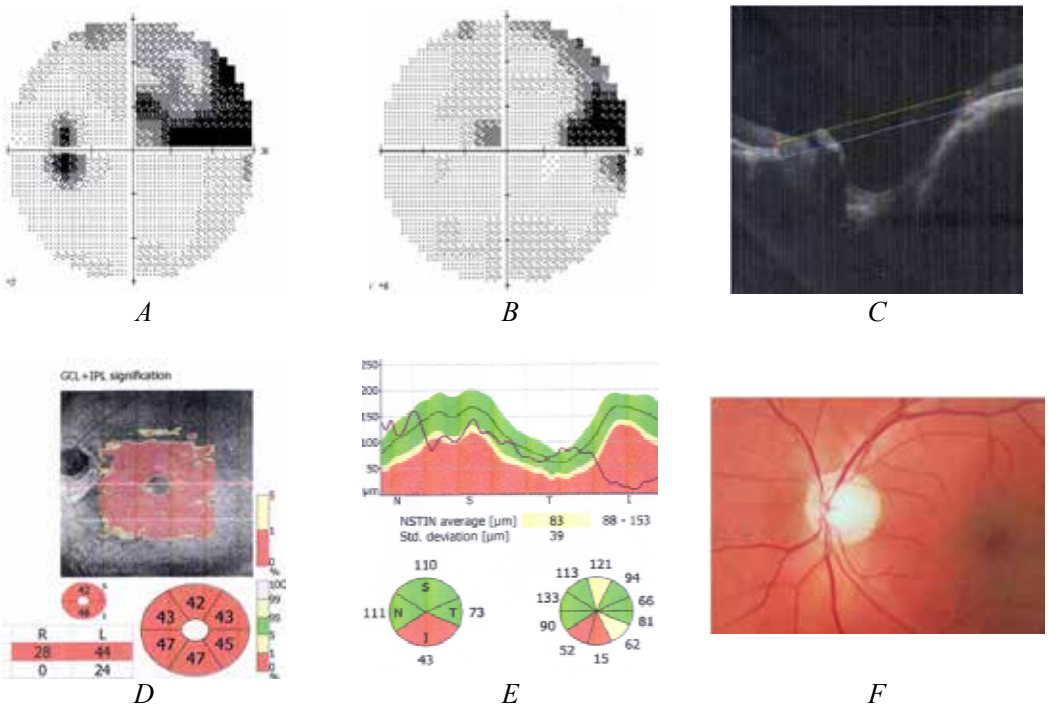
Table 2

Dynamics of computer perimetry parameters in two groups of patients with GON during the observation period

Indicator	Visit	Group 1 – main group (n = 74)	Group 2 – control (n = 63)	p
MD, dB	V0	–4.7 (–6.6; –2.7)	-4.3 (-5.8;-3.4)	p = 0.46
	V12	–4.1 (–6.3; –2.1)	-4.7 (-6.5;-3.5)	p = 0.045
VFI, %	V0	90.0 (84; 94)	90.0 (88; 92)	p = 0.54
	V12	93.0 (88; 96)	90.0 (88; 90)	p = 0.000
PSD, dB	V0	5.5 (4.3; 8.7)	5.3 (4.9; 6.5)	p = 0.62
	V12	5.1 (3.2; 7.1)	5.5 (4.6; 6.6)	p = 0.033

Note: p – level of significance of the difference between the indices of groups 1 and 2 according to the Mann-Whitney test with Me (Q 25%–75%).

Abbreviations: MD – deviation of the total light sensitivity; VFI – visual field index; PSD – index of local defects.



A *B* *C*

D *E* *F*

Fig. 2. Clinical data of the left eye of patient Sh., 73 years old, IOP 16 mm Hg:

A – Paracentral severe depression in the superior nasal quadrant by the type of nasal step (VFI 82%; MD –6.82 dB; PSD 10.42) before treatment; *B* – Paracentral severe depression in the superior nasal quadrant, improvement of visual field by perimetric parameters compared to the previous study (VFI 87%; MD –4.75 dB; PSD 7.92) after treatment; OCT before treatment: *C* – optic disk excavation: Area: Rim 0.31 mm^2 (N 1.09–2.08), Cup/Disc 0.89 (N 0.00–0.42); Volume: Cup 0.85 mm^3 (N0.00–0.22); Rim 0.10 mm^3 (N 0.16–0.56); *D* – complex thickness map (GCL+IPL); *E* – RNFL; *F* – ocular fundus photo

During the observation period of 12 months in Group 1, an increase in the thickness of the RNFL layer was noted in 36 eyes (48.6%) by an average of (0.88 ± 1.4) µm (p = 0.000); RNFL remained unchanged in 30 eyes (40.6%) and thinning in 8 eyes (10.8%). In the control group, RNFL layer thickening was recorded in 12 eyes (19.0%), no changes were detected in 26 eyes (41.3%) with thinning by (0.81 ± 1.75) µm (p = 0.000) in 25 eyes (39.7%) (χ^2 = 11.83, p = 0.0006) (Fig. 3). Thickening of the GCL layer + IPL in group 1 was noted in 36 eyes (48.6%) on average by (0.58 ± 0.89) µm (p = 0.000), no changes were observed in 33 eyes (44.6%) and thinning – in 5 eyes (6.8%), whereas in the control group, GCL+IPL layer thickening was recorded in 11 eyes (17.5%), unchanged in 30 eyes (47.6%), and significant thinning by (0.37 = 1.68) µm in 22 eyes (34.9%) (χ^2 = 13.43, p = 0.0003).

The intraocular volume circulation (RQ) according to ROG after the course of PBM (V1) was improved in both groups by 24% and 26% (to 2.6 (2.4–3.0) % and 3.1 (2.6–3.34) %, respectively, in groups 1 and 2; p = 0.000). After 6 months, the RQ score in Group 1 improved by another 23%, reaching almost normal values (3.2‰), in Group 2 there was a tendency to decrease this indicator (p = 0.000). After 12 months, in the main group, the RQ index remained 24% higher than the baseline values, amounting to 2.6 (2.2–3.1) %, while in Group 2 it reached the values before treatment (p = 0.001).

A graph showing the proportion of patients with a relative risk of progression (Cumulative Hazard Function) of GON during the observation period depending on the treatment group was constructed (Fig. 4).

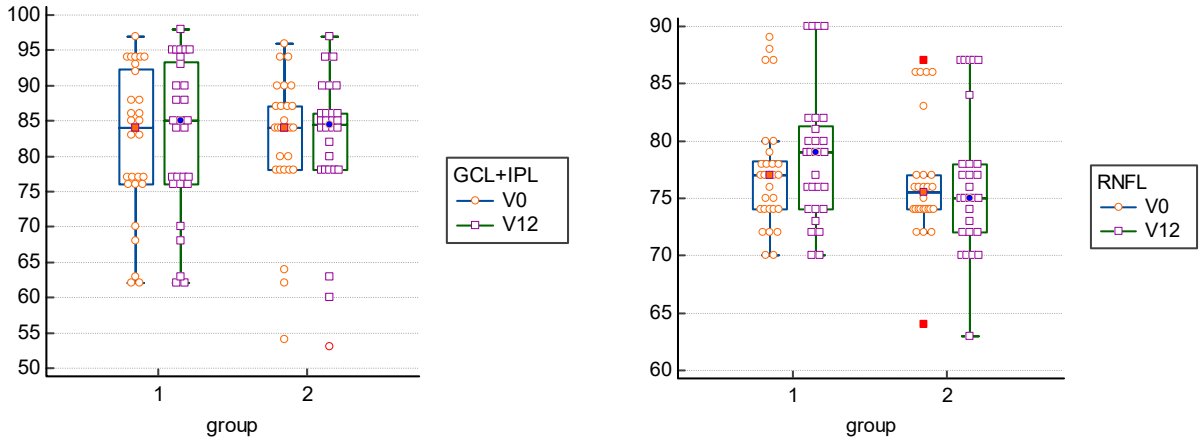


Fig. 3. Dynamics of the thickness of the ganglion cell layer + inner plexiform layer (GCL+IPL, nm) and the retinal peripapillary nerve fiber layer (RNFL, nm) in the two groups during the observation period (*p* – level of significance of the difference by the Mann-Whitney test between the groups after 12 months)

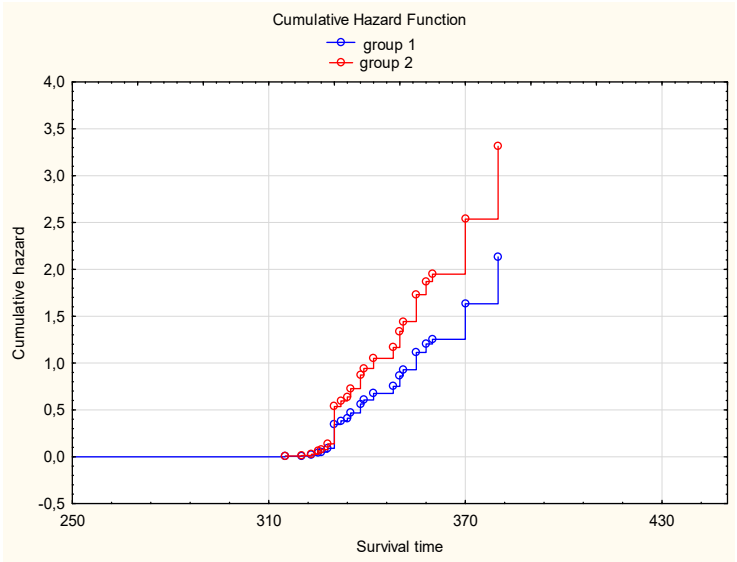


Fig. 4. Cox regression. The proportion of patients with a relative risk (Cumulative Hazard Function) of glaucomatous optic neuropathy progression after 12 months of follow-up (360 days) depending on the treatment strategy: Group 1 – on the background of complex treatment with additional intake of nutraceuticals of the AREDS2 formula with omega-3 PUFAs and resveratrol 60 mg for 12 months (HR 1.24 [95%; CI 0.921.70]), Group 2 (control (HR) 1.95 [95%; CI 1.22–3.11])

No side effects associated with complex medical treatment, PBM, and the use of nutraceuticals have been reported.

Discussion. The overall prevalence of POAG in the world is 2.4%, and its diagnosis is often performed in case of significant visual impairment, when the disease progresses to an advanced stage [20]. The classical dogma for glaucoma was irreversible neurodegeneration, but the state of parabiosis, in which some cells are located, provides a sufficient area for neuroregenerative therapy, which is now becoming a promising strategy for the functional recovery of damaged RGC [14]. And the complex neuroprotection with PBM [18] and the addition of the nutraceutical resveratrol is pathogenetically grounded and effective [4, 7, 8]. The GON is characterized by structural and functional damage to the visual analyzer. Functional damage can be assessed by visual field analysis. Structural damage is detected by thinning of the inner plexiform layer of retinal ganglion cells and the peripapillary layer of retinal nerve fibers using optical coherence tomography [18].

The IOP was stabilized at all visits and the target pressure was achieved, and the median in both groups (n = 137) was 18 (16–19) mm Hg.

The BCVA score after the PBM course increased in both groups by an average of 15% and 16% (p = 0.34). However, after 12 months, the main group showed an increase in visual acuity by 15% from baseline values, and in the control group this index decreased by 12.5% (p = 0.02).

According to the data of computerized static perimetry, during the observation period, an increase in retinal light sensitivity, a decrease in the number, area and depth of scotomas, and an expansion of the area with normal light sensitivity in patients of the main group were noted (Table 2). After 12 months, in the control group, progression of GON

according to perimetric indices was noted 2.7 times more patients than in patients of Group 1.

Glaucoma is increasingly common in conjunction with vascular disease, as both diseases are associated with aging [15]. The analysis of blood circulation data during follow-up showed a significant improvement in RQ after the PBM course in both study groups (by 24% and 26%), which confirms the effect of PBM on the entire visual analyzer [3]. Over the next 6 months, this indicator in the main group improved further and reached the age-related norm of 3.2 (3.0–3.5) %. And the study at the last visit showed that in Group 1, the intraocular circulation volume index was 24% better than the baseline values (p = 0.000), and in the control group it was close to the baseline (p = 0.64). However, in both groups, patients with GON at 12 months had an RQ score lower than the age norm by 19% and 25%, respectively, in groups 1 and 2. Our data are confirmed by the data of other authors on the decrease in the density of peripapillary and macular vessels, which significantly affects the blood circulation of the central retina in patients with POAG [3].

The analysis of the literature shows changes in all retinal layers in the case of GON [16], with early involvement of the macular zone in the pathological process, with changes in the complex (GCL+PL) [6], which confirms the need for neuroprotective therapy. Similarly, by the end of the study, we noted significant differences in the rates of GON progression in both groups depending on the neuroprotection strategy. Studies have shown that under conditions of oxidative stress, axonal regeneration is possible, PBM improves cerebral circulation [1], and delivery of neuroprotectors to the mitochondrial membranes of the RGC [15, 12]. In our study, the thickness of the RNFL layer and the complex (GCL+PL) significantly decreased with increasing glaucoma severity, which was also noted in the results of studies by other authors [1].

According to OCT data, by the end of the 12th month, patients in the control group showed a tendency to structural loss of the complex (GCL+IPL), and in patients who were additionally prescribed a nutraceutical, stabilization and a tendency to improve morphometric parameters were noted (p = 0.0003). The same trend between the groups was observed with changes in the thickness of the RNFL layer (p = 0.0006). However, according to other authors, it is not enough to judge the progression of glaucoma only on the basis of RNFL and GCL+IPL complex data [10]. Similarly, in our study, after 12 months in the main group, in addition to stabilization of morphometric parameters, there was also an improvement in volumetric intraocular circulation, improvement in light sensitivity according to computer static perimetry and improvement in BCVA.

Significant Spearman correlations were found between the RNFL layer thickness and the indices: BCVA (r_s = 0.55), RQ (r_s = 0.42), GCL + IPL (r_s = 0.33), MD (r_s = 0.32), visual field index (VFI; r_s = 0.24), and local defect score (PSD; r_s = –0.25). Our analysis shows significant efficacy of the proposed complex neuroprotective treatment using retinal/optic disc PBM and nutraceutical AREDS2 formula, enhanced with ω-3 PUFAs and resveratrol for 12 months in patients with POAG, which allows to reduce the relative risk of GON progression 1.6 times (HR 1.24 [95%; CI 0.92–1.70] vs. control group (HR 1.95 [95%; CI 1.22–3.11]) (Fig. 4). This emphasizes the need for continuous monitoring of trophic status, taking nutraceutical supplements, correction of vascular changes, and neuroprotective therapy.

Conclusions. Comprehensive neuroprotection using photobiomodulation and taking the nutraceutical formula AREDS2, enhanced with ω-3 PUFA and resveratrol (60 mg) for 12 months in patients with primary open-angle glaucoma can reduce the relative risk of glaucomatous optic neuropathy progression 1.6 times due to improvement of intraocular blood flow and conduction in the nerve fibers of the optic nerve, which leads to stabilization of morphometric parameters of the visual analyzer, increase in overall light sensitivity and improvement of maximum corrected visual acuity.

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