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## Features of the condition of the perilimbal tissues of the eye during the surgical treatment of patients with open-angle glaucoma

**Olha Sas, Iryna Shargorodska**

Department of Ophthalmology and Optometry of Postgraduate Education, Bogomolets National Medical University, Kyiv, Ukraine

**Address for correspondence:**

Sas Olha

+380964341835

E-mail: [kvolha30@gmail.com](mailto:kvolha30@gmail.com)

**Abstract:** *primary open-angle glaucoma is a multifactorial chronic neurodegenerative disease characterized by acquired loss of retinal ganglion cells and subsequent optic nerve atrophy, and is often associated with increased intraocular pressure (IOP). As the leading cause of blindness and vision loss, glaucoma affects more than 70 million people worldwide (Tang et al., 2021), and unfortunately, there is no downward trend. Most currently available glaucoma treatments tend to target the formation of the aqueous humor or the uveal-scleral outflow pathway. They do not affect the primary outflow pathway, which is usually responsible for 70–90% of aqueous humor drainage into the circulatory system. However, dysfunction and blockage of this major pathway can lead to increased outflow resistance, increased IOP, and ultimately the development of glaucoma. Purpose: to investigate the condition of the perilimbal tissues of the eye during the surgical treatment of patients with open-angle glaucoma. Materials and methods: 22 patients with primary open-angle glaucoma who underwent combined treatment for glaucoma and age-related cataract were included in the examination and made up the main group of the examination. The comparison group, which consisted of 7 patients, included patients who had age-related cataracts and did not have glaucoma. The main group of patients was divided into two subgroups. In the first subgroup of the main group, the Tenon's sheath of the area where anti-glaucomatous intervention was performed was studied. Trabecula examination was performed in patients of the second subgroup of the main group. Results: on the histological preparations of the patients of the main group, unlike the comparison group, signs of a chronic inflammatory process were revealed: neovascularization with proliferation of endotheliocytes. It was established that the nuclei of cells of fibrous tissue are changed, namely, they are increased in size and more intensely colored. Significant swelling of the surrounding tissue was observed, which pathologically changed the very structure of the tissue. Pathological deposition of diffusely located pigment was noted extracellularly in tissue structures. Conclusions: The results obtained during the study of changes in the perilimbal tissues of the eye in patients with primary open-angle glaucoma will open new ways of personalized management of this category of patients, which will make it possible to formulate additional criteria for the diagnosis and treatment of glaucoma, aimed at overcoming the inflammatory process and prolonging the postoperative result.*

**Keywords:** [Glaucoma](#); [Histology](#); [Intraocular Pressure](#); [Surgery](#); [Trabecular Meshwork](#).

## Introduction

Glaucoma is the leading cause of irreversible blindness worldwide. Glaucoma is characterized by chronic neuropathy of the optic nerve, which leads to vision loss. The disease is associated with characteristic structural damage to the optic nerve and associated visual dysfunction, which can be caused by various pathological processes and in which intraocular pressure (IOP) is a key factor (Tang et al., 2021). Glaucoma is a major public health concern because it is the second leading cause of blindness in the world after cataracts, and blindness caused by glaucoma is usually irreversible. An estimated 57.5 million people worldwide have primary open-angle glaucoma (POAG) and this number is expected to reach 111.8 million by 2040 (Allison, Patel, & Alabi, 2020).

Although the pathogenesis of glaucoma is not fully understood, it is known that the level of IOP is interrelated with the death of retinal ganglion cells. The balance between the secretion of aqueous humor by the ciliary body and its drainage occurs through 2 independent pathways – the trabecular meshwork and the uveoscleral outflow pathway, which determine the level of IOP (Miller & Tsai, 2023). However, while most currently available glaucoma treatments target aqueous humor formation or the uveal-scleral outflow pathway, they do not affect the primary outflow pathway, which is typically responsible for 70–90% of aqueous humor drainage into the circulatory system. Dysfunction and blockage of this major pathway can lead to increased outflow resistance, increased IOP, and ultimately the development of glaucoma. Although pathogenetically, the mechanisms that lead to an increase in IOP are still unclear, previous studies have identified a section of the inner wall of Schlemm's canal in combination with the juxtacanal tissue (JCT) – a section of the trabecular meshwork – as the main site of outflow resistance (Tang et al., 2021).

As the final barrier to aqueous humor drainage, the cells of the inner wall of Schlemm's canal are in constant dynamic thanks to their microenvironment, this is due to both shear flow and aqueous humor flow from the basal-apical canal through Schlemm's canal endothelial cells (Hann et al., 2022; Karimi et al., 2023; Xu et al., 2022). Basal-apical flow for the cells of the Schlemm

canal creates a large transcellular mechanical load, which leads to the formation of fluid-filled intracellular cavities or “giant vacuoles” that fuse with other membrane cells (Xu et al., 2022; Martin & Johnstone, 2022). These are pressure-dependent protrusions into the canal lumen accompanied by transcellular and/or paracellular pores that allow aqueous humor to pass without disrupting the blood barrier (Lewczuk, Jabłońska, Konopińska, Mariak, & Rękas, 2022). In glaucomatous eyes, the contractile ability of the cells of the Schlemm canal and the rigidity of the basement membrane change significantly. This prevents the formation of giant vacuoles and pores, and leads to increased outflow resistance and increased IOP (Karimi et al., 2023). Understanding the underlying mechanism and role of Schlemm's canal cells in modulating IOP may lead to the development of effective targets for future pharmacology (Vincent et al., 2021). The role of the biomechanical influence of the perilimbal tissues of the eye on the drainage pathway of the aqueous humor, including the distal venous outflow system, and the regulation of IOP is not fully understood. Preliminary studies in recent years indicate that the number of necessary reoperative interventions in glaucoma patients is about 50% (Jia et al., 2022). However, to date, the pathogenetic mechanisms that lead to the overgrowth of channels have not been fully elucidated, and the development and implementation of modern devices (valves) does not solve the problem.

Thus, the search and research of new methods of treatment for patients with POAG is relevant, since untimely and ineffective treatment can have significant negative consequences for individual and public health. All this determined the relevance of conducting research and determined the goal and task of this work.

### Aim

To investigate the state of perilimbal tissues of the eye during surgical treatment of patients with open-angle glaucoma

### Materials and Methods

The examination included 22 patients with primary open-angle glaucoma, who underwent combined treatment for glaucoma and age-related cataracts and made up the main group of the examination. Patients who had age-related cataracts and did not have glaucoma were included in the

comparison group, which consisted of 7 patients. The main group of patients was divided into two subgroups. In the first subgroup of the main group, the Tenon's sheath of the area where anti-glaucomatous intervention was performed was studied. Trabecula examination was performed in patients of the second subgroup of the main group. In the patients of the comparison group, we examined both the Tenon's sheath and the trabeculae.

The research used the following selection criteria:

- age from 50 years and older;
- a clinically established diagnosis of primary open-angle glaucoma (main group) or its absence (comparison group);
- age-related cataract;
- informed written consent of the patient (the patient's representative) to conduct research and participate in dynamic observation;
- the patient's ability to adequately cooperate in the research process.

The exclusion criteria:

- age is less than 50 years;
- impossibility of visualization of the posterior segment of the eye (ophthalmoscopy, OCT, angio-OCT, etc.);
- the presence of concomitant ophthalmological diseases that can reduce visual functions;
- operated detachment of the retina;
- presence in the anamnesis of a craniocerebral injury;
- presence of endocrine diseases in the anamnesis (diabetes, etc.);
- presence of autoimmune diseases in the anamnesis;
- the presence of mental illnesses and neurological disorders that will prevent the patient from understanding the conditions of participation in the study.

Criteria for excluding subjects from the study:

- refusal of patients to undergo certain stages of diagnostic studies or non-compliance with the deadlines for conducting studies.

According to the research objectives, all patients who were examined within the framework of this dissertation work were divided into groups.

Patients underwent standard examinations, which included assessment of visual acuity, Humphrey perimetry, tonometry, gonioscopy, biomicroscopy, optical coherence tomography of the optic disc, ganglion cells, and retina.

All clinical studies were conducted in compliance with the basic bioethical norms and requirements of the Declaration of Helsinki, the Council of Europe Convention on Human Rights and Biomedicine (1977), the relevant provisions of the WHO, the International Council of Medical Scientific Societies, the international code of medical ethics (1983) and the Order of the Ministry of Health of Ukraine No. 690 of 09/23/2009.

Statistical processing of the results was carried out using the SPSS 61 11.0, MedStat and MedCalc v.15.1 software package (MedCalc Software bvba). In all cases, the differences were considered statistically significant at  $p < 0.05$ . The distribution of studied patients in groups depending on gender and age is shown in Table 1.

According to the data in Table 1, the study was mainly attended by women, the average age of which was  $65 \pm 9$  years. There was no statistically significant difference in the distribution of patients by gender in the main and comparison groups.

After the combined surgical intervention, we conducted histological studies of the perilimbal tissues of the eye (Tenon's membrane and trabeculae) of the patients. The material was taken and fixed, followed by dehydration and compaction of the samples. Next, the samples were placed in a mixture of xylene and paraffin

**Table 1.** Distribution of patients by group, n=29 (29 eyes)

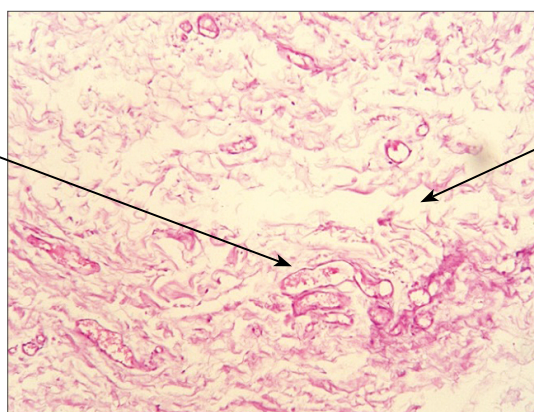
Indicator		Sex		Average age, years
		Men	Women	
Abs. / %	Main group I subgroup, n= 12 (12 eyes)	4 / 18,2 %	8 / 36,3 %	65±7
	Main group II subgroup, n= 10 (10 eyes)	4 / 18,2 %	6 / 27,3 %	63±9
	Comparison group, n= 7 (7 eyes)	2 / 28,6 %	5 / 71,4 %	65±9
The level of significance of the difference, p		P<0.05		–



and in pure liquid paraffin, which hardens when cooled. Sections were sequentially deparaffinized in xylene, alcohols, and placed in water before staining. Sections were stained with hematoxylin-eosin, after which the sections were washed again, illuminated and sealed in balsam.

**Results**

Histological studies of the perilimbal tissues of the eye (Tenon’s membrane) of patients with POAG revealed certain differences and features of the tissue structure compared to the histological structure of the tissue in the comparison group. Signs of neovascularization were established and edema was located around it, which pathologically changed the structure of the tissue (Picture 1).



**Pic. 1.** Histological preparation of Tenon’s membrane of a patient with POAG.

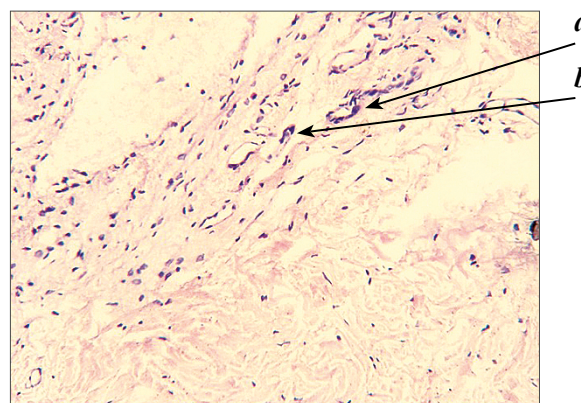
Hematoxylin-eosin staining. *a* – a row of vessels in a state of dilation; *b* – loose structure of the tissue with illumination

Also, in the tissue structure of patients with POAG, changed nuclei of fibrous tissue cells were found, namely, increased in size and more intensely colored, which is a sign of proliferation in such patients (Picture 2).

On samples of the II subgroup (trabecula), pathological deposition of diffusely located pigment in extracellular tissue structures (accumulations of various sizes) was noted (Picture 3), which was not observed in the tissue structures of patients of the comparison group. Thinning of the tissue, unevenness of the structure with small light lumens filled with pigment is noted (Picture 4).

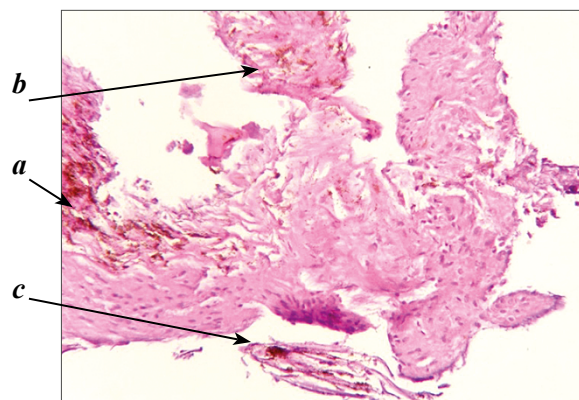
**Discussion**

On the histological preparations of patients of the first subgroup of the main group, unlike the

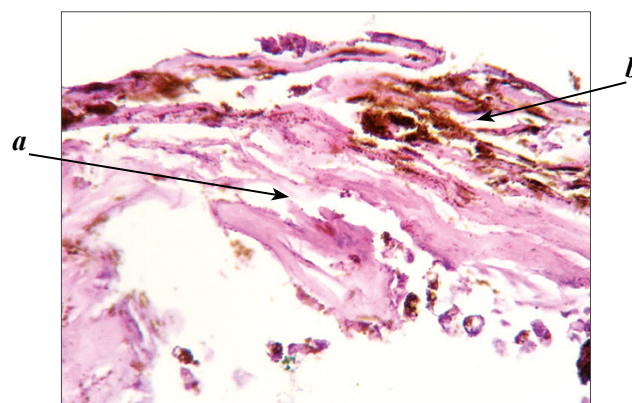


**Pic. 2.** Histological preparation of Tenon’s membrane of a patient with POAG.

Hematoxylin-eosin staining. *a* – hypertrophy of cell nuclei; *b* – increased staining intensity of cell nuclei



**Pic. 3.** Histological preparation of a trabecula of a patient with POAG. Hematoxylin-eosin staining. *a, b, c* – diffuse arrangement of pigment in tissue structures



**Pic. 4.** Histological preparation of a trabecula of a patient with POAG. Hematoxylin-eosin staining.

*a* – loose fabric structure with illumination; *b* – uneven structure of the fabric with openings filled with pigment

comparison group, signs of a chronic inflammatory process were revealed: neovascularization with proliferation of endotheliocytes, which can lead to overgrowth of the fluid outflow path and leveling of the postoperative result.

Fibrovascular proliferation of the anterior segment causes the formation of progressive peripheral anterior synechiae, which close the angle of the anterior chamber and cause an increase in IOP, and negate the postoperative outcome.

It was established that on the histological preparations of the patients of the first subgroup of the main group, in contrast to the comparison group, slightly changed nuclei of fibrous tissue cells located around them were found, namely, increased in size and more intensely colored, which may indicate changes in the functions of the cells of the tissue being studied and, in the future, as a result, it can affect postoperative scarring. Significant swelling of the surrounding tissue was also observed, which pathologically changed the very structure of the tissue, which was not noted on the histological samples of Tenon's sheath of the comparison group, this may lead to an increase in outflow resistance and an increase in IOP.

In the samples of the second subgroup of the main group, unlike the samples of the trabeculae of the comparison group, a pathological deposition of a diffusely located pigment was noted, which can also cause an increase in IOP due to the blockage of the main path of outflow of intraocular fluid and blocking of the postoperative result and, as a result, the further progression of glaucoma.

### Conclusions

The results obtained during the study will open new ways of personalized management of

patients with glaucoma. This will make it possible to formulate additional criteria for the diagnosis and treatment of glaucoma aimed at overcoming the inflammatory process and prolonging the postoperative result. The pathogenesis of glaucoma has not been fully studied to date, so the identification of new links of pathological changes in the perilimbal tissues of the eye that occur in patients with primary open-angle glaucoma may lead to the development of new effective targets for future pharmacology. Glaucoma should not become a kind of sentence for a person. The sooner we can begin to act on the main risk factors of the disease, the faster we will affect the quality and length of life of patients, which is especially important for this category of patients and necessary at the current state of development of science and technology.

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### Conflict of interests

There are no conflicts of interests.

### Consent to publication

All authors have read the text of the article and article and gave consent to its publication.

### ORCID ID and authors contribution

[0000-0002-7056-0877](https://orcid.org/0000-0002-7056-0877) ( B, C, D ) Olha Sas

[0000-0001-8958-1849](https://orcid.org/0000-0001-8958-1849) ( A, E, F ) Iryna Shargorodska

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article.

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## Особливості стану перилімбальних тканин ока при хірургічному лікуванні хворих на відкритокутову глаукому

Ольга Сас, Ірина Шаргородська

Кафедра офтальмології та оптометрії післядипломної освіти Інституту післядипломної освіти Національного медичного університету імені О.О. Богомольця, м. Київ, Україна

### Address for correspondence:

Sas Olha  
+380964341835

E-mail: [kvolha30@gmail.com](mailto:kvolha30@gmail.com)

**Анотація:** первинна відкритокутова глаукома – це багатофакторне хронічне нейродегенеративне захворювання, яке характеризується набутотою втратою гангліозних клітин сітківки та в подальшому атрофією зорового нерва, та часто асоціюється з підвищеним внутрішньоочним тиском (ВОТ). Як основна причина сліпоти і втрати зору, глаукома вражає понад 70 мільйонів осіб у всьому світі (Tang et al., 2021), і на жаль, немає тенденції до зниження. Більшість доступних на даний момент методів лікування глаукоми, як правило, спрямовані на утворення водянистої вологи або на увеально-склеральний шлях відтоку. Вони не впливають на первинний шлях відтоку, який зазвичай відповідає за 70–90% дренажу водянистої вологи в систему кровообігу. Однак, дисфункція та блокування цього основного шляху можуть призвести до підвищеного опору відтоку, підвищення ВОТ і, зрештою, до розвитку глаукоми. Мета: дослідити стан перилімбальних тканин ока при хірургічному лікуванні хворих на відкритокутову



глаукому. *Матеріали та методи:* в обстеження було включено 22 пацієнтів з первинною відкритокутовою глаукомою, які проходили комбіноване лікування з приводу глаукоми та вікової катаракти та складала основну групу обстеження. В групу порівняння, яку склали 7 пацієнтів, були внесені хворі, які мали вікову катаракту та не мали глаукоми. Основна група пацієнтів була поділена на дві підгрупи. В першій підгрупі основної групи досліджувалась тенонова оболонка ділянки, у якій виконувалося антиглаукоматозне втручання. У пацієнтів другої підгрупи основної групи проводилось обстеження трабекули. *Результати:* на гістологічних препаратах пацієнтів основної групи, відмінно від групи порівняння, було виявлено ознаки хронічного запального процесу: неоваскуляризація із проліферацією ендотеліоцитів. Встановлено змінні ядра клітин волокнистої тканини, а саме збільшені за розміром та інтенсивніше забарвлені. Спостерігався значний набряк навколишньої тканини, що патологічно змінював і саму структуру тканини. В структурах тканини позаклітинно відмічалось патологічне відкладення дифузно розташованого пігменту. *Висновки:* Отримані у ході дослідження результати зміни перилімбальних тканин ока у хворих на первинну відкритокутову глаукому відкриють нові шляхи персоніфікованого менеджменту цієї категорії пацієнтів, що дасть змогу сформулювати додаткові критерії діагностики і лікування глаукоми, направлені на подолання запального процесу і пролонгування післяопераційного результату.

**Ключові слова:** глаукома, гістологія, внутрішньоочний тиск, хірургія, трабекулярна сітка.



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