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ilk ve tek tamamlanmış ürün ailesi.^{†1*}

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† Kaynak: 2025 GFK satış verileri, 12 global pazar.

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The Use of Citicoline in Ophthalmology: A systematic review

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Abstract

Objectives: Citicoline is a chemical molecule, and it plays a crucial role in the biosynthesis of cell membranes and has many functions in the human body. This compound, which increases the amount of neurotransmitters, is used in the treatment of various diseases in ophthalmology, neurology, and psychiatry. Its use as a supplement to improve cognitive functions is also widespread. In this review, we aim to shed light on the neuroprotective effects of citicoline and its applications in the field of ophthalmology, based on data obtained from published studies.

Methods: In the literature, the effects of citicoline in various ophthalmological diseases have been mentioned; however, there is no clear consensus regarding its dosage, duration of use, or efficacy due to the limited number of published studies and designs of these studies. Upon reviewing the current studies, we found evidence suggesting that citicoline supplementation may be effective in amblyopia, glaucoma, and non-arteritic ischemic optic neuropathy.

Conclusion: This review aims to evaluate and summarize the current evidence on the neuroprotective effects of citicoline in ophthalmologic diseases. Findings from various clinical studies suggest that it may have a beneficial effect on the treatment of conditions including amblyopia, glaucoma, and non-arteritic ischemic optic neuropathy.

Keywords: Amblyopia, CDP-choline, citicoline, glaucoma, non-arteritic ischemic optic neuropathy

Introduction

Citicoline is a mononucleotide that comprises ribose, cytosine, pyrophosphate, and choline. It serves as a precursor to phosphatidylcholine, a key component of mitochondrial and neuronal membranes. Citicoline is a water-soluble compound with a bioavailability exceeding 90% (1).

The term citicoline refers to cytidine-5'-diphosphocholine (CDP-choline, CDPCho). This compound is a naturally occurring endogenous chemical. Citicoline is available in many countries as a dietary supplement and medication. When administered in oral or injectable form, citicoline undergoes hydrolysis and dephosphorylation, resulting in the breakdown into cytidine and choline. These components are then thought to act as substrates for the synthesis of

phosphatidylcholine and CDP-choline within neurons. The metabolism of citicoline's function has not yet been fully understood in all aspects (2).

Citicoline exhibits negligible toxicity. When the compound is taken, it is rapidly metabolized and converted into cholinergic and pyrimidinergetic metabolites. The resulting products can then be used for various biosynthetic pathways and are ultimately excreted as carbon dioxide. It has been repeatedly confirmed in previous studies that citicoline does not have any side effects in the acute and chronic phases (3).

Citicoline, which serves as a substrate for phosphatidylcholine formation, is also an inhibitor of phospholipase A2 (PLP-A2) and directly affects the membrane of damaged neurons that are still alive. With its neuromodulatory ef-

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fect linked to the dopamine system, citicoline is effective in Parkinson's disease. Dopamine is a major neurotransmitter effective in the retinal and post-retinal areas (1). In addition to dopamine, this compound also affects the levels of acetylcholine and norepinephrine. It is currently used in the treatment of Alzheimer's disease and stroke due to its brain-stimulating effects (4).

Citicoline may help preserve sphingomyelin, a membrane component essential for neuronal signal transmission. CDP-choline enhances the concentration of dopamine, norepinephrine, and serotonin within the central nervous system. It has neuroprotective effects in hypoxia and ischemia. It also exhibits neuroprotective anti-aging effects on the brain. It has been demonstrated that CDP-choline restores mitochondrial ATPase and membrane Na/K ATPase activities in various experimental models, inhibits PLP-A2 activation, and accelerates the reabsorption of brain edema (5,6).

On the other hand, the neuroprotective effects of citicoline have been documented in dopaminergic mesencephalic neurons, neuroblastoma cells, and cultured retinal cells in *in vitro* models (7).

In conclusion, studies have determined that citicoline is effective in the regeneration of neurons and in the increase of various neurotransmitter levels. This study aims to evaluate the efficacy of citicoline treatment in improving visual function in ophthalmologic diseases compared to placebo or standard treatment.

Methods

The primary literature search was performed in PubMed (January 2025), and additional searches were conducted using open-access academic search engines, including Google Scholar and CrossRef to enhance the sensitivity of the search and reduce potential publication bias. Articles on the use of citicoline in the treatment of ophthalmological diseases were reviewed. The keywords "citicoline," "CDP-choline," "glaucoma," "amblyopia," "non-arteritic ischemic optic neuropathy," and "ophthalmology" were used to find the articles. The process of study identification, screening, and inclusion is illustrated in the preferred reporting items for Systematic Reviews and Meta-Analyses 2020 flow diagram (Fig. 1). Studies in which citicoline was combined with other neuroprotective agents, abstracts, reviews, comments, and letters were excluded from the study. Studies involving animals, biomechanics, computational models, *in vitro* research, and cadaveric studies were deemed ineligible. Two ophthalmologists conducted the analysis. Table 1 provides a summary of the inclusion and exclusion criteria. A three-stage analysis was conducted, including the title, abstract, and full text. The variables examined by the authors include study design, sample size, total number of participants, average age and gender of the study partici-

Table 1. Inclusion and exclusion criteria of the study

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> Articles in English Clinical studies, multicenter studies, in humans. 	<ul style="list-style-type: none"> Publications written in languages other than English Reviews and case reports Studies conducted on subjects other than humans

pants, average duration of diagnosis, disease severity, outcome measures, citicoline dosage, and number of patients. Since this study did not involve direct human or animal participation, ethical approval was not required.

Results

A total of 2498 records were identified through PubMed, Google Scholar, and CrossRef searches. After removal of duplicates and title-abstract screening, 196 full-text articles were assessed for eligibility, and 30 studies met the inclusion criteria and were included in the qualitative synthesis.

Application of Citicoline in Amblyopia

The application of citicoline in amblyopia has attracted attention due to its potential to improve visual function and stimulate neural plasticity. Citicoline, a compound that enhances phospholipid synthesis and promotes neuronal repair, has been investigated as a potential adjunctive treatment in amblyopia. Citicoline may enhance retinal and post-retinal visual pathways by stimulating the dopaminergic system. It has been shown to improve contrast sensitivity, visual acuity (VA), visual evoked responses, and the effectiveness of part-time occlusion therapy (8). While the exact mechanisms and optimal dosages for citicoline in amblyopia remain subjects of ongoing research, preliminary findings have shown promise, particularly in conjunction with other therapies such as occlusion or vision training. However, further large-scale, controlled trials are needed to confirm its efficacy and establish definitive treatment protocols. Key clinical studies are summarized in Table 2. In their 1995 study, Campos *et al.* presented preliminary results from a trial investigating citicoline in amblyopia. The open-label study, initiated in 1991, included 50 patients with amblyopia treated with citicoline. In addition, a randomized and double-blind study was conducted involving 10 patients, who were allocated to either the treatment or placebo group and followed prospectively for 6 months. The double-blind study confirmed these findings, with no reported adverse effects throughout the observation period (9). In children, Campos *et al.* showed that oral CDP-choline, either alone or combined with part-time occlusion, produced significant VA improvement over 1 year, with the combined regimen providing the most stable long-term effect (10).

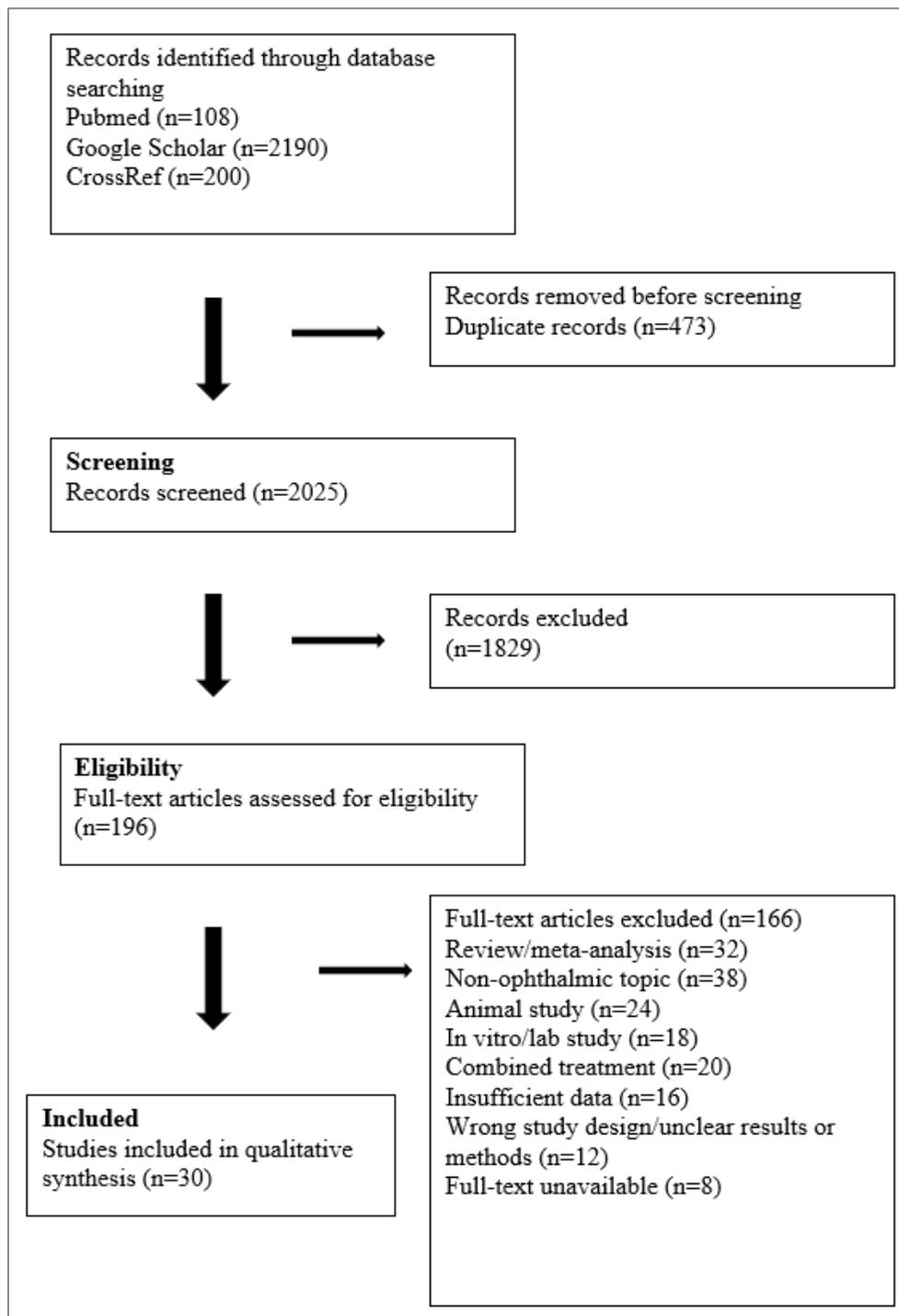


Figure 1. PRISMA 2020 flow diagram of the study selection process.

Porciatti *et al.* reported that intramuscular CDP-choline in adults improved VA, contrast sensitivity, and VEP parameters, supporting a functional neuroenhancing effect (11).

More recent pediatric data are heterogeneous. A retrospective series from Indonesia suggested that citicoline is particularly effective in mild to moderate refractive amblyopia, with treatment durations of 3–6 months (12).

Pawar *et al.* investigated the effectiveness of adding citicoline to patching therapy for amblyopia in children. During phase I, no notable disparity in the average VA was observed between the two groups until a plateau was reached. In phase 2, VA showed no considerable variation between the groups during the first 4 months. However, starting from the 5th month through the twelfth, a significant improvement was noted in Group I compared to Group II. This trend was con-

Table 2. Clinical studies evaluating citicoline in the treatment of amblyopia

First author (year)	Study design	Population	Citicoline regimen	Comparator/co-treatment	Follow-up	Main outcomes&key findings
Campos (9) (1995)	Open-label study+randomized double-blind placebo-controlled sub-study	50 patients with amblyopia, beyond critical period of visual development; additional 10 patients in RCT	1000 mg IM daily for 5 days	RCT: Citicoline vs. placebo	Up to 6 months	In the open-label cohort, VA improved significantly in both amblyopic and fellow eyes in 92% of patients, with effect maintained ≥ 4 months. The double-blind trial confirmed VA improvement without reported adverse events.
Campos (10) (1996-1997)	Prospective comparative study	45 children (5-9 years) with unilateral amblyopia	Group 1: CDP-choline 500 mg/day for 10 days every 6 months; Group 2: same regimen+ 1 h/day occlusion; Group 3: 1 h/day occlusion alone	Three arm comparison	12 months	All groups showed significant VA gains. Group 1 had initial improvement with partial regression by month 4 but further gain after retreatment. In Group 2, VA improvement occurred within 10 days and remained stable. Group 3 improved after 1 month and remained stable for 8 months.
Porciatti (11) (1998)	Prospective pre-post interventional study	10 adults with amblyopia	(CDP-choline) 1 g IM Daily for 15 days	None	Assessment pre-treatment and 1 day post-treatment	Mean VA gain of 1.4 to 1.5 lines in amblyopic eyes and 0.4 lines in fellow eyes. CS increased by ~ 3 dB in both eyes. VEP amplitude increased by $\sim 30\%$ with phase shift; overall improvement in VA, CS and VEP parameters. Citicoline was effective in mild-moderate amblyopia and treatment durations of 3 and 6 months.
Loebis (12) (2021)	Retrospective chart review	34 eyes; mainly 5-6 years old; mild (61.8%), moderate (20.6%); severe (5.9%) amblyopia	Various citicoline regimens; 3-8 months	No standardized control group	3-8 months	Citicoline was effective in mild-moderate amblyopia and treatment durations of 3 and 6 months.

Table 2. Clinical studies evaluating citicoline in the treatment of amblyopia

First author (year)	Study design	Population	Citicoline regimen	Comparator/co-treatment	Follow-up	Main outcomes&key findings
Pawar (4) (2014)	Randomized controlled trial	4-13 years with amblyopia	Phase 2: Group I received citicoline 250 mg/day(<5 years) or 500 mg/day (≥5 years) plus patching	Group II: patching alone	Phase I: until VA plateau; Phase 2: 12 months	During phase I VA improvement was similar between groups. In phase 2, starting from the fifth month through the twelfth, a significant improvement was noted in Group I compared to Group II.
Fresina (13) (2008)	Randomized comparative study	61 children (5-10 years) with anisometropic or strabismic amblyopia	Group A: 800-1200 mg oral citicoline + 2h/day patching for 30 days	Group B: 2h/day patching only	30 day treatment-60 day follow-up	Short-term VA improvement was similar between groups. However at 90 days, VA gains were better maintained in the citicoline group, whereas BCVA tended to regress towards baseline in controls.
Sabetti (14) (2017)	Prospective comparative study	39 patients with amblyopiatreated with Bangerter filters	Oral citicoline once daily, 5 days/week, combined with Bangerter filter in one group.	Bangerter filter alone	12 months	VA improved in both groups. Filter only group: VA from 0.27 to 0.09 logMar. Filter+citicoline group: from 0.35 to 0.01 logMar.

RCT: Randomized controlled trial, IM: intramuscular.

sistent across both younger (<7 years) and older (>7 years) patients (4).

Fresina *et al.* (13) compared the combination of patching and oral CDP-choline with patching on its own. The vision improvements in the control and citicoline groups were similar. However, integrating CDP-choline with conventional amblyopia therapy led to a more pronounced medium-term effect, as evidenced by enhanced visual function stabilization at 90 days. Notably, in those receiving CDP-choline, the visual improvements obtained with patching were maintained over the next 2 months. In contrast, the control group (CG)

exhibited a tendency for BCVA to decrease, gradually approaching pre-treatment values.

Sabetti *et al.* examined the effect of choline supplementation in combination with the Bangerter filter as a treatment for amblyopia. Neither group exhibited any notable alterations in the angle of deviation throughout the study. Both therapies led to improvements in VA; however, the combination of the Bangerter filter with choline demonstrated notably greater efficacy, particularly in cases of severe amblyopia (14).

Based on the above analysis, the efficacy of citicoline in improving the clinical condition of individuals with amblyo-

Table 3. Clinical studies evaluating im citicoline as an adjunctive therapy in glaucoma

First author (year)	Study design	Population	Citicoline regimen	Comparator/ co-treatment	Main outcomes&key findings
Pecori Giraldi (15) (1989)	Prospective interventional study	POAG	IM 1 g/day for 15 days, repeated every 6 months	No citicoline	Smaller VF loss in citicoline treated eyes
Virno (16) (2000)	Long-term follow up	POAG; 11 treated vs 12 untreated	IM 1 g/day for 15 days, repeated every 6 months; 11 year follow-up	No citicoline	VF area remained more stable in the citicoline group ≥ 500 mm ² VF loss occurred in 2/11 vs 5/12 controls
Parisi (17) (1999)	Randomized double blind placebo controlled trial	OAG, n=40	IM 1 g/day for 60 days; repeated after wash out in a subgroup	Placebo injections	Significant improvement in PERG and VEP parameters in the citicoline group
Parisi (18) (2005)	Prospective electrophysiologic follow-up	OAG, long-term follow up	IM 1 g/day for 60 days; repeated after wash out in a subgroup	No citicoline	Sustained electrophysiologic benefit over 8 years with periodic treatment.
Parisi ^[20] (2008)	Prospective comparative study	OAG	IM 1 g/day vs oral citicoline 1.6 g/day for 60 days	Route comparison	Both routes produced similar improvements in PERG and VEP; benefits decreased within 4 months after discontinuation but increased again with retreatment.

POAG: Primary open angle glaucoma, IM: intramuscular, OAG: open angle glaucoma.

pia remains inconclusive. Although most studies suggest that citicoline has a substantial positive impact on clinical outcomes, definitive conclusions remain uncertain. Prospective studies with a larger number of participants are required to obtain more definitive results.

Application of Citicoline in Glaucoma

The earliest clinical experience with citicoline in primary open-angle glaucoma (POAG) dates back more than two decades and was based on repeated intramuscular cycles. In an initial series and its long-term extension, patients receiving 1 g/day intramuscular citicoline for 15 days every 6 months showed a slower loss of visual field (VF) sensitivity than untreated controls over follow-up periods of up to 10 years (15,16).

Subsequent randomized placebo-controlled work by Parisi *et al.* confirmed that similar cyclic intramuscular regimens improved pattern electroretinogram (PERG) and VEP recordings in open-angle glaucoma (OAG) with functional

gains diminishing after wash-out but reappearing when treatment was restarted, suggesting a reversible neuroenhancing effect rather than a permanent cure (17,18).

Due to the impracticality of injections for managing chronic ophthalmic conditions, a pilot study was conducted to evaluate the effects of two biweekly courses of orally administered citicoline (1 g/day), separated by a 2-week interval, on VEPs in POAG patients. Despite the small sample size (21 eyes from 11 patients), the study demonstrated a statistically significant shortening of VEP P100 latency and a notable, albeit less pronounced, increase in VEP amplitude. The prolonged latency and diminished amplitude of VEP, frequently seen in ocular hypertension and OAG, suggest a delay in neural conduction within the visual pathways. Previous investigations have shown enhanced VEP latency and amplitude after the intramuscular delivery of citicoline, known for its neuroprotective properties. This study aimed

to determine whether oral administration of citicoline could achieve similar effects. In 21 glaucomatous eyes, VEP latency and amplitude were evaluated before and after two bi-weekly regimens of oral citicoline, administered at a dose of 1 g/day. The treatment regimens were spaced 2 weeks apart, and VEP measurements were performed 2 weeks after the completion of the second regimen. In 62% of the eyes, treatment resulted in a positive response, marked by a reduction of 11.6 ms in VEP latency ($123.5 \text{ ms} \pm 3.9$ standard error of the mean (SEM) to $111.9 \text{ ms} \pm 1.9$ SEM) ($p=0.0008$) and an increase of $1.32 \mu\text{V}$ in VEP amplitude ($6.56 \mu\text{V} \pm 1.39$ SEM to $7.88 \mu\text{V} \pm 1.16$ SEM) ($p=0.04$). According to these findings, oral citicoline appears to enhance visual evoked potentials in a subset of patients with glaucoma (19).

Later studies comparing intramuscular versus high-dose oral citicoline found comparable electrophysiologic benefits, again with a tendency for the effect to decline a few months after discontinuation and to improve with retreatment (20). An overview of the studies using intramuscular citicoline in glaucoma is presented in Table 3.

Further support for the sustained benefits of oral citicoline was provided by research conducted in three university clinics in Italy. A total of 41 patients with advancing POAG, despite adequate control of intraocular pressure (IOP), were included in this study. Participants received oral citicoline solution at a dose of 500 mg daily for 4 months, with treatment cycles interspersed by 2-month no-treatment intervals. Although not randomized, this study began with a retrospective analysis of disease progression before treatment, utilizing Humphrey perimetry, before transitioning into its prospective phase. The rate of VF progression significantly improved, decreasing from -1.1 dB/year before treatment to -0.15 dB/year during citicoline therapy. Participants were selected based on a documented progression of disease at a rate of no <-1 dB/year in mean deviation (MD) over the prior 3 years, even though IOP had been effectively controlled. Patients underwent four VF tests annually during the study period.

Despite maintaining IOP consistently under 18 mm Hg for a minimum of 3 years, the mean rate of VF decline at baseline still measured -1.1 (± 0.7) dB annually. At study initiation, the average IOP was calculated as 15.5 (± 2.6) mm Hg, while the most affected eye exhibited a MD of -9.2 (± 6.7) dB. After citicoline therapy commenced, the average rate of VF decline exhibited a marked reduction, reaching -0.15 (± 0.3) dB annually by study completion ($p=0.01$). The results imply that adding citicoline to the treatment regimen might play a substantial role in slowing down glaucomatous deterioration (21).

Lanza et al. (22) enrolled one eye per subject from a total of 60 individuals diagnosed with POAG, subsequently allo-

ating them randomly into two equal groups, labeled A and B. Computed tomography (CT) therapy was administered exclusively to Group A, with both groups being comparable in terms of age, sex, and duration of disease. Although IOP remained within controlled limits, all participants exhibited gradual disease progression over the preceding 3 years, as determined through standard automated white-on-white perimetry (SAP). Comprehensive ophthalmic evaluations – including IOP assessment, SAP, and OCT-derived measurements of RNFL and GCC thickness – were performed on all patients before CT initiation and at 6, 12, 18, and 24-month follow-ups.

By the 18-month mark, Group A demonstrated a significantly less negative mean MD value of -7.25 dB compared to -8.64 dB in Group B ($p=0.039$). In Group A, MD values remained relatively unchanged, whereas Group B exhibited a continued and statistically significant decline, reaching -9.28 dB over time ($p<0.001$). Following 12 months of CT treatment, Group A exhibited significantly greater mean RNFL and GCC thicknesses – $70.39 \mu\text{m}$ and $71.19 \mu\text{m}$, respectively – than those measured in Group B, which averaged $64.91 \mu\text{m}$ and $65.60 \mu\text{m}$ ($p<0.01$). These thicknesses remained stable in group A during subsequent visits, while they significantly thinned ($p<0.001$) in group B (22).

Researchers carried out a study to investigate how liposomal citicoline (CLF) eye drops influence retinal performance and neural signal transmission through the visual pathway in individuals diagnosed with OAG. The cohort consisted of 12 individuals diagnosed with OAG, averaging 52.58 ± 11.39 years in age, all exhibiting controlled IOP (<18 mmHg) through topical agents and a Humphrey MD value of -4.49 ± 2.46 dB. CLF eye drops (OMKI-LF[®], Omikron Italia) were administered to a single eye per participant at a dosage of three drops daily over a 4-month treatment period. Evaluations of retinal activity and neural signal transmission were conducted through PERG, VEP, and VF testing both before treatment initiation and following the 4-month intervention period. Treated eyes demonstrated notable functional enhancements, evidenced by elevated PERG P50-N95 amplitudes and shortened VEP P100 implicit times. Moreover, a significant correlation was found between the reduction in VEP P100 implicit time and the enhancement in PERG P50-N95 amplitude. This pilot study suggests that CLF eye drops enhance retinal bioelectrical responses (evidenced by increased PERG amplitude), leading to improved bioelectrical activity in the visual cortex (23).

The study conducted by Sahin et al. (24) focused on assessing early structural changes in RNFL and mGCIPL following a short duration of oral citicoline therapy in POAG patients. The study included 54 eyes of 54 patients, divided into two groups: 27 patients received 250 mg of oral citi-

coline in addition to topical hypotensive therapy, while the other 27 served as a CG. RNFL and mGCIPL thickness were measured using OCT 1 day before treatment, 3 months after starting treatment, and 1 month after discontinuing citicoline (washout period). In the citicoline group, the average RNFL thickness was significantly higher at the 3-month mark compared to baseline ($p=0.038$), although this improvement partially diminished after the washout period. RNFL measurements in the superior, nasal, temporal, and inferior sectors showed no meaningful variation at the 3- and 4-month timepoints ($p>0.05$). Nevertheless, at the 3-month mark, the citicoline group exhibited a significantly greater increase in both average RNFL thickness and inferior quadrant measurements compared to controls ($p=0.006$ and $p=0.014$, respectively). There were no statistically significant intergroup differences in mGCIPL thickness or in RNFL measurements across the superior, nasal, and temporal quadrants ($p>0.05$). The findings suggest that oral citicoline therapy may help preserve average RNFL thickness in the short term for POAG patients, potentially slowing glaucoma progression.

Another study explored the controversial role of nutraceuticals in glaucoma treatment, aiming to assess the effects of Vitamin C, citicoline, and docosahexaenoic acid (DHA) on glaucoma patients. This study included 73 participants who were divided into four groups: One receiving Vitamin C, another DHA, a third citicoline, and a fourth DHA and citicoline, all treated for 3 months. Participants underwent monthly comprehensive eye evaluations and VF testing, with subsequent analysis and comparison of VFI values and their progression slopes across the study groups. Patients receiving a combination of citicoline and DHA exhibited a marked enhancement in VF parameters, with MD improving from -9.52 ± 4.36 to -7.85 ± 4.36 dB ($p=0.001$), alongside a significant rise in mean VFI ($p=0.001$) over the course of the study. Among all groups, only the DHA and citicoline group demonstrated a statistically significant shift in MD slope, improving from -0.1041 ± 0.2471 to 0.1383 ± 0.2544 dB/month ($p=0.006$), along with a corresponding enhancement in the VFI slope (25).

Parisi et al. (26) studied 56 patients with OAG receiving topical β -blocker monotherapy and maintaining IOP below 18 mmHg. Forty-seven eyes completed follow-up. Of these, 24 eyes were assigned to receive topical citicoline (OMKI[®], Omikron Italia), 3 times daily for 4 months, followed by a 2-month washout (GC group), while 23 eyes continued β -blocker monotherapy alone (GP group). At baseline, PERG and VEP parameters did not differ between groups. After 4 months, the GC group showed clear functional improvement with increased VEP N75-P100 and PERG P50-N95 amplitudes and a significant shortening of P100 implicit time ($p<0.01$). The reduction in P100 implicit time correlated

with the increase in PERG P50-N95 amplitude. Following the washout period, electrophysiological values in the GC group returned to levels comparable to baseline, with no significant intergroup differences, whereas the GP group demonstrated stable PERG and VEP findings throughout the study.

While the results appeared comparable to those achieved with oral citicoline, the concept of topical citicoline delivery is less favorable. Due to its water solubility, citicoline demonstrates poor corneal penetration. Nonetheless, the authors propose – based on preclinical evidence – that citicoline may penetrate into the vitreous chamber when formulated with high molecular weight hyaluronic acid and benzalkonium chloride serving as absorption enhancers. Oral citicoline, which is typically devoid of significant side effects, presents a considerably more favorable alternative.

In their investigation, Rosetti et al. (27) focused on individuals diagnosed with mild to moderate OAG, all of whom demonstrated a VF deterioration exceeding -0.5 dB annually over the past 2 years, even though their IOP remained within controlled limits. In this trial, participants were randomly assigned to administer either citicoline ophthalmic solution or a placebo, with dosing scheduled 3 times/day over a period of 3 years. The evaluation parameters comprised alterations in the progression rates of VF loss – quantified via MD values from both 24-2 to 10-2 testing algorithms – as well as changes in RNFL thickness. The study cohort comprised 80 patients. Following 3 years of treatment, the citicoline group exhibited a mean 24-2 MD decline of -1.03 dB (± 2.14), while the placebo group showed a greater deterioration at -1.92 dB (± 2.23), with the difference approaching statistical significance ($p=0.07$). For 10-2 MD, the progression rate was significantly slower in the citicoline group (-0.41 dB ± 3.45) compared to the placebo group (-2.22 dB ± 3.63 , $p=0.02$). In addition, the citicoline group experienced less RNFL thinning, with an average loss of 1.86 μ m over 3 years, compared to 2.99 μ m in the placebo group ($p=0.02$).

Carnevale et al. (28) recently showed that citicoline eye drops, when applied topically, achieve high concentrations in the vitreous of the human eye.

In a study exploring parallels between glaucoma and senile dementia, the authors proposed that neuroenhancement could be pursued in both conditions using agents like citicoline (18).

In the study conducted by Rosetti et al., (29) participants were randomized into two treatment sequences: One group received 500 mg/day of oral citicoline before switching to placebo, while the other group followed the reverse sequence. After 3 months, the treatments were switched, and patients were monitored for an additional 6 months. The main endpoint was the average change from baseline in VFQ-25 composite scores at 6 months, comparing citicoline

oral solution to placebo within the same patients. This multicenter study, carried out in five European ophthalmology centers, enrolled OAG patients with bilateral field defects, a better-eye MD ranging from -5 to -13 dB, and stable IOP. The predefined primary analysis revealed a significant benefit favoring citicoline ($p=0.0413$), with the most notable improvement observed in patients initially assigned to placebo followed by citicoline ($p=0.0096$, 0.0007 , and 0.0006). Citicoline's impact was particularly evident in those with poorer baseline vision-related quality of life.

Arrico et al. (30) evaluate the neuroprotective effects of oral citicoline in patients with POAG. A total of 110 patients with Stage IV POAG and well-controlled IOP were included. The participants were randomly divided into two groups: The therapy group (TG), which received 500 mg of citicoline daily for 4 months, followed by a 2-month wash-out period before resuming the same treatment; and the CG, which continued their standard glaucoma therapy without citicoline. Both groups were also treated with pressure-lowering medications. The results showed that the TG experienced a statistically significant improvement in MD values at 12 months ($\Delta=21\%$) and in PSD at 24 months ($\Delta=35\%$). In addition, there was a gradual improvement in the glaucoma staging system (GSS2) stage, reaching the 3rd stage with localized defects after 36 months of therapy. In contrast, the CG continued to experience deterioration in both MD and PSD indices throughout the study (30).

A study involving 22 patients with glaucoma and progressive visual dysfunction assessed the effects of oral citicoline. VEP analysis revealed fluctuations in P100 wave amplitude, with a notable increase at 6 months. P2 wave amplitude exhibited minimal variation, while a statistically significant increase in P2 latency was observed at the 6-month mark. Negative correlations emerged between RGC layer thickness and P100 latency, as well as between the amplitude and latency of the P100 wave. Conversely, at 6 months, a positive correlation between RGC layer thickness and P100 amplitude was detected. Furthermore, RNFL thickness at the optic disc demonstrated a statistically significant increase at 6 months, accompanied by a slight rise in RGC layer thickness. However, these findings may reflect measurement artifacts rather than true clinical improvement. Notably, RNFL thickness correlated positively with the amplitudes of P100 and P2 waves (31).

Glaucoma is increasingly recognized as a neurological disorder, and evidence pointing to the limitations of exclusively relying on IOP-lowering therapies highlights the potential role of neuroprotection as an alternative or complementary approach in its management. However, current evidence is insufficient to confirm that citicoline effectively slows the progression of glaucoma.

Citicoline in Non-arteritic Ischemic Optic Neuropathy

Non-arteritic anterior ischemic optic neuropathy (NAION) is a sudden, typically painless ischemic event affecting the intraocular optic nerve. It results in irreversible damage, leading to a reduction in VA and VF. Multiple pharmacological strategies have been investigated in an effort to preserve or enhance visual function in individuals affected by NAION, among them systemic corticosteroids, diphenylhydantoin, anticoagulant therapies, and hyperbaric oxygen treatment. However, none have demonstrated proven efficacy. In 2008, Parisi et al. (32) assessed visual function in patients with NAION before and after treatment with citicoline. 26 patients, at least 6 months post-NAION onset, were randomly assigned to two age-matched groups. 14 patients received citicoline (Cebrolux-Tubilux, Italy) for 60 days, followed by a 120-day washout period (days 60–180) (T-NAION group). The remaining 12 patients received no treatment during the same period (NT-NAION group). In the T-NAION group, a second treatment phase was administered from days 181 to 240, followed by another washout period from days 241 to 360. Normative data were obtained from 14 age-matched healthy controls. PERG, VEPs, and VA were measured in all patients at baseline, day 60, and day 180. Additional measurements were conducted in the T-NAION group at days 240 and 360. Initial assessments revealed that patients with both NT-NAION and T-NAION had impaired PERG and VEP readings, as well as diminished VA, relative to healthy subjects. Following treatment (at days 60 and 240), the T-NAION group showed statistically significant gains ($p<0.01$) across all three measures compared to baseline. These functional improvements persisted even after the washout period, while no changes were observed in the NT-NAION group (32).

Parisi et al. (33) investigated the effects of a 6-month treatment with citicoline oral solution (500 mg/day) in 36 patients diagnosed with NAION. They evaluated various parameters, including VA, RNFL thickness, VEP, and Humphrey 24-2 VF, pERG results. The study revealed significant improvements across all measured parameters in the citicoline-treated group. Notably, these benefits persisted even after a 3-month washout period, reinforcing the neuroprotective role of citicoline in managing this condition (33).

Although the limited studies on the use of citicoline in NAION have reported beneficial findings, further research with a larger number of participants is necessary to establish definitive conclusions.

Application of Citicoline after Laser *in situ* Keratomileusis (LASIK)

There is only one study that meets the inclusion criteria for this topic. Çınar et al. (34) investigated the effect of topical citicoline drops on macular microcirculation in 45 patients after LASIK. They found no significant difference between

the CG and the treatment group in measurements of the superficial retinal vessel density, foveal avascular zone and deep retinal vessel density at pre-operative, 1-month post-operative, and 3-month post-operative evaluations ($p>0.05$) (34).

Strengths and Limitations

This article is a comprehensive evaluation of citicoline use in ophthalmology, incorporating studies on its application across various ophthalmic conditions. A broad range of articles from different years was reviewed.

However, several limitations should be acknowledged. Due to institutional access restrictions, the literature search was conducted using PubMed, Google Scholar, and CrossRef which together provide a broad coverage of clinical research articles, and only articles published in English were included. This language restriction may have led to omission of relevant data and introduces a potential selection bias. In addition, the available studies are heterogeneous with respect to patient characteristics (age, disease stage, and etiology), ophthalmic indication (amblyopia, glaucoma, NAION), and outcome measures (VA, contrast sensitivity, VF indices, electrophysiology, and OCT parameters), which makes direct comparison difficult. One of the key weaknesses of the current literature is the absence of a standardized citicoline regimen. Across published studies, dosing schemes vary considerably, from 250 to 500 mg/day in pediatric amblyopia to 1.0–1.6 g/day in adult glaucoma. Citicoline has been administered as short im cycles of 10–15 days, as intermittent oral courses lasting several months, and as long-term topical 2% eye drops. The duration of therapy likewise ranges from a few weeks to follow-up periods extending over several years, and treatment schedules are largely empirical rather than evidence-based. Moreover, few trials were specifically designed to compare different doses, routes of administration, or treatment intervals, so a reliable dose-response profile is still lacking. Consequently, an optimal citicoline regimen for ophthalmic indications cannot yet be defined, and its use should currently be considered an adjunctive, investigational neuroprotective option until more standardized randomized controlled studies become available. This lack of standardization in dosing, treatment schedules, and routes of administration has also been underscored in recent comprehensive reviews and systematic analyses of citicoline use in ophthalmology and glaucoma (35,36).

Conclusion

This systematic review highlights the broad spectrum of applications for citicoline in ophthalmologic conditions. Although its use as a supplement in glaucoma treatment is increasingly common today, larger, long-term, and more comprehensive studies are needed. Depending on its use, citicoline can be regarded both as a pharmaceutical agent and a dietary sup-

plement. Further studies are needed to explore its potential benefits in both ophthalmic and non-ophthalmic diseases.

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Corneal Structural Alterations Under Chronic Hyperglycemia: Biomechanical and Densitometric Insights in Type 2 Diabetes with and Without Retinopathy

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Abstract

Objectives: To evaluate and compare corneal biomechanical properties and densitometry in healthy individuals and type 2 diabetic patients, with and without non-proliferative diabetic retinopathy (NPDR), and to investigate potential associations with glycemic control.

Methods: This prospective, observational study included 61 diabetic patients (30 without DR and 31 with NPDR) and 76 healthy controls. Comprehensive ophthalmic examinations were performed for all participants, including Corvis ST for corneal biomechanical assessment and Scheimpflug-based densitometry. Glycated hemoglobin (HbA1c) and blood glucose levels were recorded in the diabetic group. Patients with proliferative DR were excluded to maintain more homogeneous cohorts.

Results: Diabetic patients demonstrated significantly higher stiffness parameters (stress-strain index) and corneal densitometry compared with healthy controls ($p < 0.001$). In subgroup analyses, the tomographic biomechanical index (TBI) was lower among diabetic patients with retinopathy than those without ($p = 0.036$), suggesting an additional impact of retinopathy on corneal biomechanics. Moderate correlations were identified between HbA1c and specific corneal deformation parameters, highlighting the influence of metabolic control on corneal properties. Blood glucose levels exhibited a moderate positive correlation with TBI ($p = 0.033$).

Conclusion: Corneal biomechanics and densitometry differ significantly between diabetic patients and healthy controls, with further alterations in those with non-proliferative retinopathy, and these changes may correlate with glycemic control.

Keywords: Corneal biomechanics, corneal densitometry, corvis ST, Type 2 diabetes mellitus

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Introduction

Diabetes mellitus (DM) is a systemic metabolic disorder characterized by chronic hyperglycemia due to impaired glucose regulation (1). It affects multiple organ systems and remains a leading cause of blindness in developed countries (2,3). While ophthalmologists primarily concentrate on diabetic retinopathy (DR), it is also important to recognize that diabetes can lead to significant structural and biomechanical alterations in the cornea (4). Previous research has indicated an increase in central corneal thickness in individuals with diabetes, potentially resulting from epithelial and endothelial cell dysfunction, which impairs corneal hydration regulation and leads to edema (4-6). Chronic hyperglycemia may also lead to oxidative stress and changes in the corneal extracellular matrix composition (7,8). These findings suggest that these factors may contribute to alterations in the biomechanical characteristics of the cornea in patients with DM.

The corvis ST (CST) (Oculus, Wetzlar, Germany) is a dynamic, non-contact device based on Scheimpflug imaging, designed to assess corneal biomechanical properties *in vivo* (9). It applies a controlled air puff to deform the cornea, while a high-speed Scheimpflug camera records 4300 images per second over a 100-ms duration (10,11). This high-resolution, real-time imaging allows for detailed analysis of the corneal deformation process, offering valuable biomechanical insights in diabetic patients. Moreover, corneal densitometry (CD), increasingly recognized as a reliable biomarker of corneal transparency, provides valuable insights into corneal tissue integrity (12,13). Scheimpflug-based anterior segment tomography enables a quantitative assessment of CD through the analysis of backscattered light, offering a detailed, layer-by-layer evaluation of corneal clarity (14).

Several studies have demonstrated corneal biomechanical differences between diabetic and non-diabetic individuals, with notable associations between biomechanical properties and systemic glycemic control markers such as glycated hemoglobin (HbA1c) (15-17). Poorly controlled diabetes has been linked to increased corneal stiffness and altered dynamic corneal response parameters, which may impact intraocular pressure (IOP) measurements and glaucoma risk assessment (18). However, there remains a gap in knowledge regarding the correlation between corneal biomechanics, glycemic control, and the presence of DR.

This study aims to evaluate and compare corneal biomechanical properties across three distinct groups: healthy individuals, diabetic patients without retinopathy (DM-no DR), and those with DR. Furthermore, the relationship between HbA1c levels and corneal biomechanical metrics will be explored to assess the potential impact of glycemic control on corneal behavior. The findings may offer valuable insight into

the utility of corneal biomechanics as a non-invasive marker for both ocular manifestations and systemic progression of diabetes.

Methods

This prospective, observational study was conducted at a tertiary hospital, following approval by the Institutional Review Board (193–2024-KAEK-11/July 15, 2025) and in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants before enrollment.

Inclusion criteria were IOP <21 mmHg by applanation tonometry and refractive error <5 diopters spherical equivalent and astigmatism <3 diopters in type 2 DM patients older than 18 years. Patients with DM with a history of corneal disorder or systemic collagen disease, contact lens wear within 2 weeks prior to enrollment, irregular astigmatism, previous refractive surgery or any ocular surgery, glaucoma, and/or chronic topical IOP-lowering medication use were excluded from the study. Another exclusion criterion was proliferative DR (PDR) because of difficulties in obtaining an adequate sample of untreated cases. By omitting these patients, more homogeneous cohorts were maintained, thereby helping to ensure the validity of the biomechanical and densitometric assessments. Sixty-one eyes of 61 DM patients were included in the study. Seventy-six age- and sex-matched individuals without a history of DM or ocular disease were defined as the control group. DM patients were divided into two subgroups: with (DM-DR) and without (DM-nonDR) DRP.

All patients had a thorough ophthalmologic examination of the anterior and posterior segments prior to the measurements. The diagnosis of non-PDR (NPDR) was based on dilated fundus examination and color fundus photography. Optical coherence tomography (OCT) and OCT angiography (OCTA) were used as supportive tools when clinically indicated. NPDR severity was classified according to international clinical DR/Early Treatment DR Study (ETDRS)-based criteria and categorized as mild, moderate, or severe NPDR. Mild NPDR was defined by the presence of microaneurysms only. Moderate NPDR included cases with microaneurysms accompanied by intraretinal hemorrhages, hard exudates, or cotton wool spots not meeting criteria for severe NPDR. Severe NPDR was defined according to the ETDRS 4-2-1 rule, including extensive intraretinal hemorrhages/microaneurysms in four quadrants, venous beading in two or more quadrants, or prominent intraretinal microvascular abnormalities in at least one quadrant. All NPDR gradings were performed by a single experienced retina specialist who was masked to corneal biomechanical and densitometry results. When both eyes of a participant were eligible for inclusion, one eye was randomly selected for analysis to ensure statistical independence and to avoid inter-eye correlation bias.

To rule out any corneal alterations, ocular biometry (IOL-Master; Carl Zeiss Meditec, Oberkochen, Germany) and corneal topography were conducted. Corneal biomechanical assessment was performed using the CST (Oculus, Wetzlar, Germany). All measurements were obtained by a single experienced examiner under standardized room conditions. Participants were instructed to blink immediately before acquisition, and the eye was aligned using the device's fixation target. Only measurements fulfilling the built-in quality specification (QS) criteria (e.g., "OK") were accepted. The device records the dynamic corneal response to an air puff using ultra-high-speed Scheimpflug imaging and provides deformation parameters (A1/A2 length and velocity, peak distance, highest concavity radius, and deformation amplitude) as well as derived indices, including the stress-strain index (SSI) and tomographic biomechanical index (TBI). For each participant, one eye was included in the analysis. CD was assessed using Scheimpflug tomography (Pentacam HR; Oculus, Wetzlar, Germany). Densitometry values were recorded in grayscale units (GSU), where higher values indicate increased backscatter (reduced transparency). We extracted densitometry parameters corresponding to the anterior, central, and posterior corneal layers, as well as the total densitometry value (CD ant, CD center, CD post, and CD total). Only scans meeting the device QS were included. HbA1c and blood glucose levels were recorded in diabetic patients. In addition, the duration of DM was assessed in the patients' anamneses.

During CST measurement, a two-dimensional image of the cross-section of the deforming cornea is created using a high-speed Scheimpflug camera to measure the apical displacement of the cornea and the IOP. During the deformation process, amplitude, duration, and velocity of the corneal appplanation are recorded (19). Measurements with the CST were only taken once in every eye because previous reports described reliable and good quality results even after a single measurement time point (20-22).

All data were analyzed with the Statistical Package for the Social Sciences (Version 25; IBM Statistics, NY). The test for normal distribution of the data in both groups was performed using the Kolmogorov-Smirnov test. Since the data were normally distributed, Student's *t*-test was applied. When we divided DM patients into subgroups and compared them with healthy controls, a one-way analysis of variance test was used, and a Bonferroni correction was made. The Pearson correlation test was used for the effect of HbA1c, blood glucose level, and duration of DM on CST measurement results. *P* values below 0.05 were accepted as statistically significant.

Results

Sixty-one eyes of 61 patients with DM and 76 eyes of 76 healthy controls were included in the study. Baseline data of

diabetic patients and healthy controls are summarized in Table 1. While BCVA was significantly higher in healthy controls ($p=0.001$), no significant difference was observed between the groups in terms of age, gender, IOP, and axial length ($p>0.05$). While non-proliferative DR findings were observed in 31 of the DM patients, DRP was not observed in 30 patients. All DM patients were using oral antidiabetic agents.

Dynamic corneal response results between DM patients and the control group are summarized in Table 2. BCVA and HcPeak Distance were found to be significantly higher in the control group ($p<0.001$). SSI and corneal opacity densitometry were found to be significantly higher in the DM group ($p<0.001$).

The results of the subgroup analysis are summarized in Table 3. The mean duration of diabetes was 8.06 ± 5.01 years in the DM-DR group and 7.06 ± 2.43 years in the DM-non-DR group, with no statistically significant difference between the two ($p=0.630$). SSI was significantly lower in the control group than in the DM-DR and DM-nonDR groups ($p=0.029$, 0.018 , respectively). TBI was significantly lower in the DM-DR group ($p=0.036$). Corneal opacity density was significantly lower in the control group than in both DM groups ($p<0.001$), whereas no significant difference was observed between the DM-DR and DM-nonDR groups ($p>0.05$).

In the correlation analysis, HbA1c showed a moderate positive correlation with SPA1 and A2V ($r=0.501$, $p=0.015$ and 0.539 , $p=0.008$, respectively); while it showed a moderate negative correlation with A1V, HC peak distance, and HC def ampl (-0.408 , $p=0.043$, $r=-0.583$, $p=0.003$, and $r=-0.523$, $p=0.010$, respectively). Blood sugar level and TBI value showed a moderate positive correlation ($r=0.412$, $p=0.033$).

Table 1. Baseline characteristics of the normal control and diabetes mellitus groups

	DM (n=61)	Control (n=76)	<i>p</i>
Age (year)	55.70±11.54	54.22±11.32	0.761
Sex (M/F)	16/45	28/48	0.273
BMI (kg/m ²)	28.58±3.89	N/A	
BCVA (logmar)	0.17±0.18	0±0	<0.001
IOP (mmHg)	15.87±4.43	15.76±2.46	0.356
HbA1c (%)	7.91±3.94	N/A	
Blood glucose (mg/dL)	168.62±61.74	N/A	
ECC (cells/mm ²)	2225±523	2364±632	0.274
Axial length (mm)	23.32±0.82	23.43±0.76	0.765
CCT (µm)	544±40.82	546.82±40.47	0.609

HbA1c: Glycated hemoglobin, BCVA: Best-corrected visual acuity, BMI: Body-mass index, CCT: Central corneal thickness, DM: Diabetes mellitus, ECC: Endothelial cell count, IOP: Intraocular pressure.

Table 2. Corvis ST corneal deformation and corneal curvatures measurements of participant groups

	DM (n=61)	Control (n=76)	p
A1L (mm)	2.19±0.33	2.20±0.33	0.857
A1V (m/s)	0.15±0.03	0.14±0.04	0.328
A2L (mm)	1.89±0.49	1.88±0.36	0.760
A2V (m/s)	-0.27±0.04	-0.28±0.03	0.971
Peak distance (mm)	4.73±0.44	4.92±0.26	0.039
HC radius (mm)	7.08±2.26	6.99±0.78	0.251
Hc deformation amplitude (mm)	1.09±0.14	1.07±0.10	0.640
K1 (D)	43.42±1.73	42.14±1.52	0.052
K2 (D)	44.13±1.71	43.22±1.78	0.063
Kmax (D)	45.45±1.76	44.82±2.14	0.253
CBIF	6.34±0.42	6.35±0.51	0.702
e-staging	0.36±0.43	0.43±0.62	0.944
DA ratio	4.27±0.71	4.31±3.55	0.455
IR (mm ⁻¹)	8.80±1.34	8.62±2.06	0.187
ARTh	530.94±116.09	544.61±155.87	0.797
SPA1 (mmHg/mm)	111.53±44.90	110.90±18.72	0.773
SS-I	1.10±0.24	0.95±0.14	<0.001
TBI	0.35±0.29	0.28±0.29	0.118
CD ant	35.85±5.50	27.34±3.43	<0.001
CD center	25.51±4.88	18.57±3.28	<0.001
CD post	24.83±4.81	18.05±3.41	<0.001
CD total	28.72±4.80	21.32±3.21	<0.001
biOP (mmHg)	15.87±4.43	15.76±2.46	0.410

ARTh: Ambrosio relational thickness, A1L: Cord length of the first applanation, A1V: Speed of the first applanation, A2L: Cord length of the second applanation, A2V: Speed of the second applanation, biOP: Biomechanically corrected intraocular pressure, CBIF: Corvis biomechanical factor, CCT: Central corneal thickness, CD ant: Anterior corneal optical density, CD center: Center corneal optical density, CD post: Posterior corneal optical density, CD total: Total corneal optical density, DA ratio: Ratio between the deformation amplitude at the apex. HC deformation amplitude; Corneal displacement at the highest concavity. HC Radius: Radius of curvature of the cornea at the highest concavity. IR: Integrated radius. Represents the amount of the corneal concave state. K1: Flat keratometry, K2: Steep keratometry. Kmax: Maximum keratometry. SP-A1: Stiffness parameter A1. The resulting pressure on the cornea is divided by the deflection amplitude at A1 over the time between A1 and A2. SSI: Stress strain index. Finite element modeling algorithm for the estimation of the non-linear *in vivo* biomechanical behaviour in corneal with normal topography TBI: Tomographic and biomechanical index.

Discussion

In this study, corneal biomechanical properties of DM patients and healthy subjects were evaluated using the CST device. In addition, the possible effects of the presence of reti-

nopathy on corneal biomechanical changes were analyzed by comparing diabetic patients with DR (DM-DR) and without DR (DM-nonDR). In our study, significant differences were found between healthy subjects and DM patients in corneal biomechanical parameters such as SSI and CD. In addition, TBI values were found to be significantly lower in the DM-DR group in subgroup analyses. Similarly, it has been reported in the literature that corneal biomechanical properties are different in diabetic patients compared to healthy subjects, and it has been suggested that corneal biomechanical parameters may be related to the severity of DR (15,16,23). In this context, our findings suggest that corneal biomechanical parameters can be used as a potential non-invasive biomarker to assess structural changes in diabetic eyes and provide valuable information about disease progression (4,8,16,18).

In our study, SSI and CD parameters were significantly higher in the DM group compared to the healthy group ($p < 0.001$). These results are consistent with the literature and support the biomechanical changes caused by diabetes in the cornea (16,23). Pérez-Rico *et al.* reported that corneal hardening increased in diabetic patients, and this hardening may be related to diabetes-induced hyperglycemia (8). Similarly, Ohn *et al.* emphasized that there are significant differences in diabetic patients compared to healthy controls and that especially high SSI values represent corneal stiffness (16). A meta-analysis by Wang *et al.* also showed that biomechanical parameters such as corneal hysteresis (CH) and corneal resistance factor (CRF) were significantly higher in diabetic patients compared to healthy controls (15). The findings of our study are consistent with the results of other studies in the literature and suggest that this increase in corneal stiffness reflects the chronic effect of diabetes on ocular tissues.

In our study, significant differences were found in corneal biomechanical parameters between diabetic patients with and without DRP. Especially, TBI values were found to be lower in the group with DRP. This suggests that DR may have an additional effect on corneal biomechanical properties. Similarly, Ramm *et al.* reported that patients with DR had significant differences in corneal deformation amplitude and maximum deflection amplitude and that the corneal deformation process was prolonged as the severity of DRP increased.^[23] Other studies in the literature also support that the presence of retinopathy is associated with corneal biomechanical parameters and that these biomechanical differences become more pronounced as the severity of retinopathy increases (15,16). In this regard, our results suggest that corneal biomechanical properties may be associated with DR and that corneal biomechanical parameters can be used as a potential indicator in the assessment of the severity of DR (15,16,23,24).

Table 3. Corvis ST measurements of subgroups of DM patients

	DM-DR (n=31)	DM-nonDR (n=30)	Control (n=76)	P1	P2	P3	P4
A1L (mm)	2.27±0.37	2.10±0.26	2.20±0.33	0.451			
A1V (m/s)	0.15±0.02	0.15±0.03	0.14±0.04	0.444			
A2L (mm)	1.92±0.42	1.86±0.57	1.88±0.36	0.566			
A2V (m/s)	-0.27±0.03	-0.26±0.05	-0.28±0.03	0.823			
Peak distance (mm)	4.76±0.28	4.71±0.57	4.92±0.26	0.116			
HC radius (mm)	6.79±1.22	7.38±3.03	6.99±0.78	0.403			
Hc deformation amplitude (mm)	1.11±0.12	1.06±0.16	1.07±0.10	0.588			
K1 (D)	43.63±1.53	43.19±1.95	42.14±1.52	0.082			
K2 (D)	44.40±1.59	43.84±1.85	43.22±1.78	0.112			
Kmax (D)	45.84±1.63	45.04±1.85	44.82±2.14	0.324			
CBIF	6.30±0.39	6.39±0.46	6.35±0.51	0.760			
e-staging	0.42±0.46	0.30±0.41	0.43±0.62	0.854			
DA ratio	4.20±0.86	4.34±0.51	4.31±3.55	0.742			
IR (mm ⁻¹)	8.80±1.35	8.80±1.38	8.62±2.06	0.390			
ARTh	542.35±94.23	518.78±138.05	544.61±155.87	0.956			
SPA1 (mmHg/mm)	107.11±23.00	116.26±33.60	110.90±18.72	0.756			
SS-I	1.10±0.27	1.11±0.20	0.95±0.14	0.001	0.03	0.007	1.00
TBI	0.22±0.18	0.48±0.32	0.28±0.29	0.036	0.97	0.042	0.14
CD ant	35.26±5.17	36.49±5.94	27.34±3.43	<0.001	<0.001	<0.001	0.818
CD center	24.22±3.88	26.88±5.57	18.57±3.28	<0.001	<0.001	<0.001	0.45
CD post	23.71±4.18	26.02±5.28	18.05±3.41	<0.001	<0.001	<0.001	0.42
CD total	27.73±4.21	29.78±5.31	21.32±3.21	<0.001	<0.001	<0.001	0.57
biOP (mmHg)	14.83±3.14	16.98±5.38	15.76±2.46	0.458			

ARTh: Ambrosio relational thickness, A1L: Cord length of the first applanation, A1V: Speed of the first applanation, A2L: Cord length of the second applanation, A2V: Speed of the second applanation, biOP: Biomechanically corrected intraocular pressure, CBIF: Corvis biomechanical factor, CCT: Central corneal thickness, CD ant: Anterior corneal optical density, CD center: Center corneal optical density, CD post: Posterior corneal optical density, CD total: Total corneal optical density, DA ratio: Ratio between the deformation amplitude at the apex, HC Deformation amplitude; Corneal displacement at highest concavity. HC Radius: Radius of curvature of the cornea at the highest concavity. IR: Integrated radius. Represents the amount of the corneal concave state. K1: Flat keratometry, K2: Steep keratometry. Kmax: Maximum keratometry, TBI: Tomographic and biomechanical index, SS1: Stress-strain index, SP-A1: Stiffness parameter A1. The resulting pressure on the cornea is divided by the deflection amplitude at A1 over the time between A1 and A2. Finite element modeling algorithm for the estimation of the non-linear biomechanical behaviour in corneal with normal topography. P1: Overall P-value from one-way analysis of variance, P2: DM-DR versus control (Bonferroni-adjusted), P3: DM-nonDR versus Control (Bonferroni-adjusted); P4: DM-DR versus DM-nonDR (Bonferroni-adjusted)

In this study, corneal biomechanical parameters of diabetic patients with (DM-DR) and without (DM-nonDR) DRP were compared. In our results, we observed that TBI values were significantly lower in patients with DR. This finding is consistent with the results previously reported in the literature that the presence of retinopathy may affect corneal biomechanical parameters (15,16,23). Ramm *et al.* reported that the duration of corneal deformation was prolonged and the maximum deflection amplitude changed significantly with increasing severity of DR (23).

In our study, we evaluated the relationship between diabetic parameters such as duration of diabetes, HbA1c, and blood

glucose with corneal biomechanical properties and analyzed the potential effects of these parameters on the development and progression of DRP. According to our findings, HbA1c level was moderately positive with SPA1 and A2V values; A1V, HC, peak distance, and HC deflection amplitude showed a moderate negative correlation. In addition, there was a moderate positive correlation between blood glucose levels and TBI, and a significant negative correlation between diabetes duration and A2 time. Similar results have been reported in the literature, and it is emphasized that high HbA1c levels and long duration of diabetes cause significant changes in corneal biomechanical parameters, and these changes may be associated with DR

(15,16,23,25). Sahin *et al.* reported that significant differences in CH and CRF occurred as the duration of diabetes and HbA1c levels increased, and these differences may be associated with the development of DR (25). In addition, a systematic review and meta-analysis by Wang *et al.* reported that HbA1c levels were associated with corneal biomechanical changes in diabetic patients and that these changes were associated with the severity of DR (15). In this perspective, monitoring the effects of metabolic control on corneal biomechanical properties may play an important role in the early identification and clinical follow-up of patients at risk for DR.

Most studies investigating CD in diabetic patients observe that diabetes is associated with higher backward light scattering (i.e., increased densitometry) than healthy individuals, particularly in the anterior corneal layers (26-29). In our study, CD was higher in DM patients compared to healthy volunteers, supporting the literature. Özyol and Özyol^[29] reported significantly higher densitometry values among diabetic patients, whereas Gao *et al.* (28) similarly reported increased corneal optical density associated with hyperglycemia-related changes in collagen and corneal nerve function. In a study conducted with children with type 1 DM, Tekin *et al.* (13) showed that the CD of healthy children and children with type 1 DM were similar. The difference in this study may be due to the inclusion of children with type 1 DM, well-controlled diabetes, and shorter duration of DM. In contrast, Ramm *et al.* (30) describe a cohort of diabetic patients with unexpectedly lower CD than controls.

Subgroup analysis according to the presence of DR and evaluation of the relationship between corneal biomechanical parameters and metabolic parameters are the aspects that contribute to the literature. However, our study has some limitations. These include cross-sectional design, relatively small sample size, and the fact that HbA1c and blood glucose levels were not measured in the healthy control group. In addition, possible time-dependent changes in corneal biomechanical parameters could not be evaluated because the measurements were performed at a single time point. Another limitation of this study is the absence of a PDR group. Including patients with PDR, ideally those who have not yet undergone treatment, could provide valuable insights into how advanced retinal pathology affects corneal biomechanics and densitometric parameters. Future investigations that incorporate this subgroup may help clarify disease progression and guide more targeted management strategies.

Conclusion

Corneal biomechanical parameters and densitometry are significantly altered in type 2 diabetes, especially among patients who have non-proliferative retinopathy. The correlations between glycemic control and corneal biomechanics

underscore the potential utility of these metrics as non-invasive indicators of disease-related ocular changes. These alterations may be significant in clinical practice for the accuracy of IOP measurements and the eligibility of individuals with diabetes for keratorefractive surgeries. In the future, the role of corneal biomechanical changes in the development of DR can be examined in more detail with larger sample sizes, prospective, and long-term follow-up studies.

Disclosures

Ethics Committee Approval: This study was approved by the Basaksehir Cam and Sakura City Hospital Ethics Committee (Date: 15.07.2025, Number:) and conducted in accordance with the tenets of the Declaration of Helsinki.

Informed Consent: Written informed consents were obtained from all patients.

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Impact of Prior Ahmed Glaucoma Valve Implantation on Surgical Success and Prognosis in Eyes Undergoing Keratoplasty

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Abstract

Objectives: This study aimed to evaluate the surgical outcomes and prognosis of patients who underwent Descemet membrane endothelial keratoplasty (DMEK) or penetrating keratoplasty (PK) following Ahmed glaucoma valve (AGV) implantation.

Methods: Patients who underwent keratoplasty at the cornea department of our hospital between April 2016 and April 2024 were retrospectively reviewed. Patients with a history of prior AGV implantation were included. Surgical success was defined as maintaining graft clarity for a minimum of 6 months post-keratoplasty.

Results: A total of 13 eyes of 13 patients (four women, nine men) with a mean age of 62.0 ± 16.0 years were included. Five patients had a history of multiple glaucoma surgeries prior to AGV implantation. Among the included patients, six had no history of corneal transplantation before AGV implantation, whereas four had previously undergone PK, and two had undergone DMEK. One patient had received two DMEK procedures followed by PK. No tube-related complications, including endothelial touch, were observed. Corneal decompensation developed at a mean of 12.7 ± 10.5 months after AGV implantation, prompting PK in four patients, repeat PK in five patients, and DMEK in four patients. The mean follow-up period after keratoplasty was 21.3 ± 17.3 months. Although the best-corrected visual acuity (BCVA) achieved postoperatively was 1.5 (0.4–2.3) LogMAR at a mean of 13.9 ± 12.3 months, there was no statistically significant difference between pre-operative BCVA (2.3 [1.0–2.3] LogMAR) and final post-operative BCVA (2.3 [0.4–2.7] LogMAR) ($p=0.735$). Similarly, no significant change was observed in intraocular pressure before and after keratoplasty ($p=0.283$). A second keratoplasty was recommended in five cases after the initial keratoplasty. At the final follow-up, graft rejection was observed in eight patients, two of whom developed keratitis. The overall surgical success rate was calculated as 23.1%.

Conclusion: In patients undergoing keratoplasty for corneal decompensation following AGV implantation, both graft survival and overall surgical outcomes were found to be unfavorable.

Keywords: Ahmed glaucoma valve, Descemet membrane endothelial keratoplasty, Glaucoma, Graft survival, Keratoplasty

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Introduction

Penetrating keratoplasty (PK) is commonly undertaken for visual rehabilitation in eyes that currently have, or are anticipated to need, one or more glaucoma drainage devices (GDDs). The presence of glaucoma alone predisposes to corneal graft failure (1,2), with the additional presence of a GDD further compounding the risk. While corneal graft survival in eyes with GDD is thought to be unfavorable in the long term, the 1-year incidence of graft failure has been reported to vary significantly between studies (3,4). In a study, graft failure was observed more frequently in keratoplasty-treated eyes with GDD compared to those whose intraocular pressure (IOP) was managed with medical therapy (3). Ahmed glaucoma valve (AGV) remains among the most frequently utilized drainage devices; nevertheless, it has been associated with corneal decompensation in the implanted eyes over the long term (5). Following AGV implantation, a progressive decline in corneal endothelial cell density has been documented (6). Corneal endothelial cell loss over time also appears to result from multiple contributing factors (7).

In addition, a study indicates that glaucoma can cause irreversible vision loss and may also compromise graft survival following endothelial keratoplasty (8). Another study reported that endothelial keratoplasty in eyes with a history of glaucoma surgery exhibited low survival rates and a similarly high incidence of rejection (9). However, another study found that Descemet's membrane endothelial keratoplasty (DMEK) did not elevate the risk of post-operative complications and achieved similar clinical outcomes in eyes with iridocorneal endothelial syndrome regardless of the presence of a GDD (10).

This study aimed to investigate corneal graft failure and surgical prognosis in eyes that had undergone AGV implantation followed by either PK or DMEK surgery.

Methods

Patients

A retrospective review was conducted of patients who underwent PK or DMEK surgery at the cornea unit of the ophthalmology department at our hospital between April 2016 and April 2024. Individuals with a documented history of AGV implantation prior to keratoplasty were identified and included in the study. Following approval by the hospital's clinical research ethics committee (Ref: 2025/010.99/15/20), the study was conducted in full alignment with the principles outlined in the Declaration of Helsinki. Before enrollment, all participants provided written informed consent.

Detailed ophthalmological examination findings were recorded, including pre- and post-operative autorefractometry measurements, best-corrected visual acuity (BCVA) using

the Snellen chart, anterior and posterior segment biomicroscopic examinations, and IOP measurements using Goldmann applanation tonometry. In addition, when available, findings from dilated fundus examinations – including the optic nerve head cup-to-disc (c/d) ratio – and parameters derived from optical coherence tomography (OCT; Triton DRI, Topcon, Tokyo, Japan), such as global peripapillary retinal nerve fiber layer thickness, as well as central corneal thickness (CCT) values obtained by anterior segment (AS) OCT, were documented.

Retrospective data of the patients were reviewed, and only those with complete examination and test records were included in the study. The types of keratoplasty previously performed were documented. Furthermore, any additional ocular surgeries undergone by the patients were recorded alongside the pre- and post-operative clinical data. Surgical success was defined as the preservation of graft transparency for a minimum duration of 6 months following the procedure.

Primary outcome data

Data such as age at the time of keratoplasty, sex, the affected eye, type of corneal disease, the number of prior keratoplasty surgeries, glaucoma type, previous glaucoma surgeries, location and site of AGV insertion, IOP control post-keratoplasty, and graft clarity status were retrospectively collected from medical records. Effective glaucoma control was defined as an IOP ranging from 5 to 22 mm Hg, with or without the use of antiglaucoma medications. Patients who developed tube-related complications, including endothelial touch or any other complication during or after AGV implantation, were excluded from the study. Eyes that developed corneal decompensation following AGV implantation and subsequently underwent keratoplasty were evaluated. Graft rejection was considered present in cases of stromal thickening, opacification, irreversible corneal edema, or the development of keratitis.

Surgery procedures

DMEK

Donor tissue preparation and marking

The corneoscleral button was mounted on a Barron suction trephine. The peripheral endothelium was marked with a Y-shaped hook or 9.0–9.5 mm trephine and stained with 0.06% trypan blue. The Descemet-endothelium complex was partially peeled centripetally with forceps and trephined to 8.0–8.50 mm. A single triangular mark was created on the endothelial surface using a 45° ophthalmic knife. The graft was stained and loaded into a lens cartridge.

Surgical technique

Retrolbulbar anesthesia was administered, followed by ocular massage and Honan balloon to lower IOP. The epithelium

was debrided. Side ports were created at 10 and 1 o'clock, the anterior chamber filled with air, and Descemetorhexis was performed. The graft was injected through a 3.0 mm tunnel at 12 o'clock. Miosis was induced with carbachol, and a peripheral iridectomy was performed at 6 o'clock. The graft was positioned and secured with an air fill. For post-operative management, eyes received 0.5% moxifloxacin and 0.1% dexamethasone 5 times/day. Sutures were removed at 2 weeks. The antibiotic was stopped on day 10; steroids were tapered to 0.5% loteprednol at 3 months and gradually reduced to a maintenance dose. Rebubbling was performed for large or central graft detachments within the 1st month.

PK

Recipient corneas were trephined with a Barron vacuum trephine (7.00–8.25 mm), and donor corneas were cut 0.25 mm larger (7.25–8.50 mm) using a matching punch trephine. Donor tissue was secured with either 16 interrupted 10-0 nylon sutures or 8 interrupted plus 16 continuous sutures. Patients were examined preoperatively and postoperatively at 1 day, 1 week, 1, 3, 6, 12, 24, and 36 months. All patients received topical 0.5% moxifloxacin and 0.1% dexamethasone 5 times daily after surgery. Antibiotics were stopped at 10 days, and dexamethasone was tapered to 0.5% loteprednol by 3–6 months. Topical steroid therapy continued for 18–24 months, gradually reducing to once daily based on clinical findings.

AGV implantation

All cases received sub-Tenon's anesthesia. A silicone AGV model FP7 was implanted. A fornix-based conjunctival incision was made, followed by a 4 × 5 mm partial-thickness scleral flap. Balanced salt solution was injected into the tube to prime the valve. The reservoir was advanced under the conjunctiva to the equator and fixed to the sclera 9 mm from the limbus with 6/0 Vicryl. A 22-gauge needle created an anterior chamber track under the flap. The tube was trimmed to 2–3 mm inside the anterior chamber and secured with a 10/0 nylon U-suture. The scleral flap was closed with 10/0 nylon, and the conjunctiva and Tenon's capsule were closed with 8/0 Vicryl. Post-operative treatment included topical 0.5% moxifloxacin for 2 weeks and 0.1% dexamethasone 5 times a day for 4 weeks.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Due to the retrospective design of the study, no formal a priori sample size or power calculation was performed. Age, sex, post-operative follow-up duration, type of keratoplasty, and post-operative surgical success status were analyzed using standard statistical methods. Time-related surgical success was assessed using the Kaplan–Meier survival analysis.

To assess the changes in eye conditions before and after keratoplasty, the Wilcoxon signed-rank test, a non-parametric method for paired data, was applied.

Results

The demographic characteristics of the patients are presented in Table 1. The study included 13 eyes (seven right and six left) of 13 patients (four females and nine males) with a mean age of 62.0±16.0 years.

Clinical diagnoses related to glaucoma prompting AGV implantation were noted. Of the 13 patients included in the study, six had no prior history of corneal transplantation before AGV implantation; four had previously undergone PK, and two had undergone DMEK. One patient had received two DMEK surgeries followed by a PK. Among the 13 eyes that underwent AGV implantation, five had a history of trabeculectomy. Of these five eyes, two had previously undergone unsuccessful XEN implantation. The glaucoma types included primary open-angle glaucoma (*n*=2), pseudoexfoliative glaucoma (*n*=1), keratoplasty-induced glaucoma following PK (*n*=5) and DMEK (*n*=2), traumatic glaucoma (*n*=1), aphakic glaucoma (*n*=1), and ICE syndrome (*n*=1). All AGVs were located in the superior temporal quadrant, with the tube tip placed in the anterior chamber. Due to corneal decompensation observed at a mean of 12.7±10.5 months post-AGV implantation, four patients underwent PK, five underwent repeat PK, and four underwent DMEK surgery (Table 2).

The mean follow-up period after keratoplasty was 21.3±17.3 months. Although the BCVA reached a maximum of 1.5 (0.4–2.3) LogMAR at an average of 13.9±12.3 months post-keratoplasty, there was no statistically significant difference between pre-operative and the final post-operative BCVA (respectively, 2.3 [1.0–2.3] LogMAR vs. 2.3 [0.4–2.7] LogMAR, *p*=0.735). Although a decrease in CCT was observed when comparing pre-operative and post-operative values, the difference was not statistically significant (respec-

Table 1. Demographic and clinical characteristics of study eyes

	<i>n</i>
Age (years)*	62.0±16.0
Patients (female/male)	13 (4/9)
Eyes (right/left)	13 (7/6)
Cup/disk ratio*	0.8±0.1
Lens status	
Pseudophakic	12
Aphakic	1
AGV plate/tube location	
Superotemporal/anterior chamber	13/13

*Mean±standard deviation. *n*: Number, AGV: Ahmed glaucoma valve.

Table 2. Summary of glaucoma diagnosis and keratoplasty procedures in relation to AGV implantation

	13 patients, 13 eyes
Glaucoma diagnosis	
Primary open-angle glaucoma	2
Pseudoexfoliative glaucoma	1
Keratoplasty-induced glaucoma	
PK	5
DMEK	2
Traumatic glaucoma	1
Aphakic glaucoma	1
ICE Syndrome	1
Corneal transplantation history before AGV	
No prior history	6
PK history	4
DMEK history	2
Two DMEK surgeries followed by one PK	1
Glaucoma surgery history before AGV	
no prior history	8
Trabeculectomy*	5
AGV plate/tube location	
Superotemporal/anterior chamber	13/13
Duration between AGV implantation and subsequent keratoplasty†	12.7±10.5
Indications for keratoplasty after AGV	
Corneal endothelial decompensation	6
Graft failure	7
Type of keratoplasty after AGV	
PK	4
Re-PK	5
DMEK	4
Number of antiglaucomatous drugs	2 (0–4)
Mean follow-up duration after keratoplasty‡	21.3±17.3

*Two had previously undergone XEN implantation, †(months, mean±standard deviation).AGV:Ahmed glaucoma valve, DMEK:Descemet membrane endothelial keratoplasty, ICE: Iridocorneal endothelial syndrome, PK: Penetrating keratoplasty.

Table 3. Clinical measurements of eyes before and after keratoplasty‡

	Pre-operative	Post-operative	P*
BCVA (LogMAR)	2.3 (1.0–2.3)	2.3 (0.4–2.7)	0.735
IOP (mmHg)†	13 (7–20)	14 (7–19)	0.283
CCT (µm)	816 (700–1053)	613 (570–670)	0.109

*Wilcoxon test, ‡Median (minimum-maximum). BCVA: Best-corrected visual acuity, IOP: Intraocular pressure, CCT: Central corneal thickness.

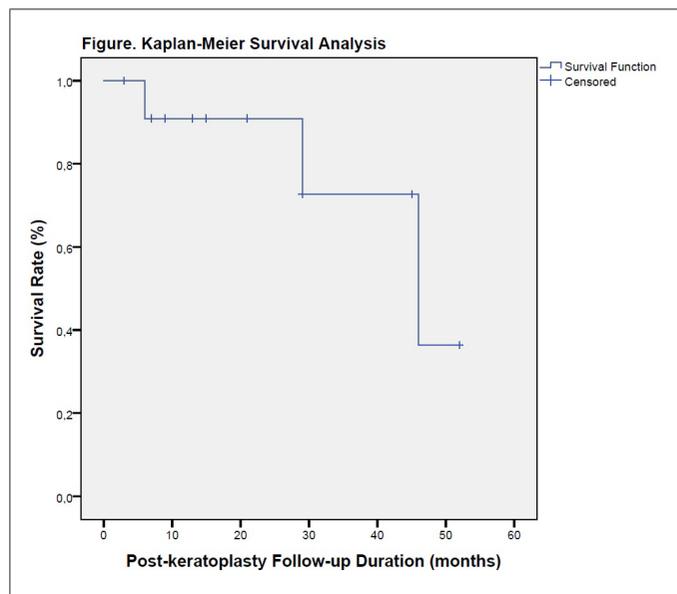


Figure 1. Kaplan–Meier survival analysis reported a surgical success rate of 23.1%.

tively, 816 [700–1053] µm vs. 613 [570–670] µm; $p=0.109$). Similarly, there was no significant difference in IOP values before and after keratoplasty (respectively, 13 [7–20] mm Hg vs. 14 [7–19] mm HG, $p=0.283$) (Table 3). By the final follow-up, graft failure was identified in eight patients, including two cases associated with keratitis. Among these patients who had keratoplasty following AGV implantation, five needed repeat keratoplasty due to graft rejection. The overall surgical success rate was reported as 23.1% based on Kaplan–Meier survival analysis (Figure 1), corresponding to three successful cases. Of the three patients with successful grafts, two had received DMEK after AGV implantation, and one had received PK after AGV implantation in a patient with a previous history of DMEK. Even though the graft was clear, one patient was not considered successful as they were still in the 3rd post-operative month (Table 4). Based on the Cox regression analysis, pre-operative IOP, BCVA, glaucoma diagnosis, prior history of keratoplasty, and subsequent DMEK or PK after AGV were not found to be significantly associated with surgical success (all $p=0.87$).

Discussion

GDD implantation is an effective surgical approach for controlling glaucoma when medical therapy fails. However, the presence of such devices, including the AGV, has been associated with poorer long-term outcomes of corneal grafts in eyes undergoing PK. In these studies, GDD implantation was performed either simultaneously with PK or subsequently after PK (11-13).

In our study, among patients who already had an AGV and underwent keratoplasty (either DMEK or PK), the graft

Table 4. Patient's summary

Patient	Age	Keratoplasty history	Glaucoma diagnosis	Glaucoma surgery history before AGV	Keratoplasty type	Second keratoplasty after AGV	GF after AGV	Surgical success
1	65	No	Traumatic	No	PK	Yes	GF	No
2	58	No	ICE	No	DMEK	No	No (3 rd month)	No
3	26	PK	PK-induced	No	Re-PK	No	GF	No
4	83	No	POAG	No	DMEK	No	No	Yes
5	84	No	PEXG	Trab	DMEK	No	No	Yes
6	57	PK	PK-induced	No	Re-PK	Yes	GF+Keratitis	No
7	39	DMEK	Post-DMEK	No	PK	No	No	Yes
8	60	No	POAG	Trab	DMEK	Yes	GF	No
9	65	DMEK	Post-DMEK	No	PK	No	GF	No
10	63	PK	PK-induced	Trab	Re-PK	No	GF+Keratitis	No
11	75	No	Aphakic	Trab	PK	Yes	No	No
12	60	PK	PK-induced	No	Re-PK	No	GF	No
13	72	2 DMEK+1 PK	PK-induced	Trab	Re-PK	Yes	GF	No

AGV: Ahmed glaucoma valve, DMEK: Descemet membrane endothelial keratoplasty, GF: Graft failure, ICE: Iridocorneal endothelial syndrome, PEXG: Pseudoexfoliative glaucoma, PK: Penetrating keratoplasty, Trab: Trabeculectomy.

survival rate was found to be 23.1% at a mean follow-up of 21.3 ± 17.3 months, which is considered poor and consistent with the literature. A retrospective study of 40 grafts with GDD involving 33 patients who underwent PK reported graft clarity rates of 58.5% and 25.8% at 1 and 2 years, respectively. Graft survival was significantly influenced by the presence of a GDD. However, in that study, not all GDDs were implanted before PK, and only 11 eyes with pre-existing GDDs were included (3). In eyes that underwent PK, glaucoma was reported in approximately 34% of cases within an average of 24 weeks (14). Similarly, the literature reports increased rates of graft failure in eyes with pre-existing glaucoma or a history of glaucoma surgery (15,16).

A retrospective analysis was conducted on 85 eyes of 83 patients who underwent descemet stripping endothelial keratoplasty (DSEK) and had either prior or concurrent GDD implantation. The graft survival rate was found to be 50% at 3 years (17). A study reported that in eyes with glaucoma undergoing DSEK, the 5-year graft survival rate was 25% in those with a GDD and 59% in those with trabeculectomy alone, highlighting prior glaucoma surgery as a significant and independent predictor of graft failure (16). Another study was conducted to investigate whether DMEK or descemet-stripping automated endothelial keratoplasty (DSAEK) offers superior long-term outcomes in eyes with a history of glaucoma surgery, given the previously reported reduced graft durability in such cases. The analysis demonstrated similarly low graft survival at 4 years, with rates of 28% for

DMEK and 33% for DSAEK, as well as 28% and 29% at 5 years, respectively, with no significant difference between the groups ($p=0.899$) (9). A recent study demonstrated that eyes that previously received a GDD ($n=27$) had a higher risk of requiring repeat DMEK due to secondary graft failure, with an average graft survival of approximately 2 years, compared to eyes that underwent trabeculectomy ($n=39$) (18). In addition, the study mentioned that performing keratoplasty in glaucomatous eyes with a history of previous glaucoma surgery is generally challenging. The main reasons for this difficulty include advanced corneal edema and anatomical changes in the anterior chamber, such as peripheral anterior synechiae, tube tips of GDD, or large iridectomies resulting from trabeculectomy.

Following the initial post-operative phase, the longevity of grafts in eyes with a history of glaucoma surgery may be continually compromised due to progressive endothelial cell loss, which can stem from the presence of a GDD or from chronic endothelial damage associated with sustained disruption of the blood-aqueous barrier following glaucoma procedures (19). In addition, several mechanisms have been proposed to explain endothelial cell loss and the increased risk of corneal graft rejection, including inflammation related to multiple prior surgeries, retrograde migration of inflammatory cells into the anterior chamber despite the unidirectional valve mechanism, mechanical trauma from transient tube-endothelial contact during blinking or eye rubbing, and immune-mediated damage secondary to alterations in the

immunologic environment of the anterior chamber (20). Furthermore, eyes with a history of glaucoma surgery undergoing endothelial keratoplasty present a post-operative management challenge for rejection prophylaxis, as they may have an increased risk of graft rejection due to chronic sub-clinical inflammation and disruption of the blood–aqueous barrier, yet their susceptibility to steroid-induced IOP elevation and limited optic nerve reserve may restrict the safe use of intensive corticosteroid therapy (21).

The absence of significant improvement in BCVA and CCT following keratoplasty should be interpreted in the context of the advanced and complex nature of the study population. Although post-operative IOP levels at the final follow-up were comparable to post-keratoplasty values, the limited visual improvement may be largely attributable to the advanced glaucomatous optic neuropathy present in the included eyes. The mean cup-to-disc ratio of approximately 0.8 in the eyes included in our study indicates markedly reduced optic nerve reserve, which inherently limits the potential for functional visual recovery despite successful corneal transplantation.

In addition, a substantial proportion of patients had undergone multiple prior intraocular surgeries, including glaucoma and corneal procedures. Such repeated surgical interventions are known to adversely affect graft survival, compromise ocular surface and AS integrity, and limit post-operative visual potential, even in cases where corneal clarity is restored. Furthermore, repeated keratoplasty, episodes of graft rejection, and prolonged corneal edema may have contributed to persistent corneal thickening and the lack of measurable anatomical improvement in CCT. Collectively, these factors reflect the advanced disease stage and cumulative surgical burden of the study population and likely account for the limited functional and anatomical gains observed after keratoplasty.

In pseudophakic eyes, AGV tube placement in the ciliary sulcus has been suggested to reduce endothelial cell loss and the risk of corneal decompensation (22). However, in the present study, the majority of eyes had open-angle configuration, and anterior chamber tube placement was therefore preferred to ensure adequate tube positioning and post-operative IOP control. Notably, a subset of patients had a prior history of keratoplasty, in whom sulcus placement could have been considered to potentially improve graft survival. Anterior chamber tube location, particularly in eyes with compromised corneal endothelium and prior grafts, may have contributed to increased endothelial stress and adversely affected graft survival. Surgical decision-making in these complex eyes was influenced by anatomical considerations, prior surgeries, and the need for reliable IOP control.

Our study indicates that keratoplasty outcomes in eyes with AGV implantation are not satisfactory. Larger-scale

studies may offer deeper insights into expected outcomes following transplantation in eyes with different histories of glaucoma surgery. Such data could also assist glaucoma surgeons in selecting the most appropriate surgical approach for patients with uncontrolled glaucoma and coexisting endothelial dysfunction.

This study has several limitations, the foremost being its retrospective design and limited sample size. In addition, accurate endothelial cell counts could not be obtained both preoperatively and postoperatively in all patients. Furthermore, the study cohort was highly heterogeneous, including eyes with different glaucoma etiologies, variable histories of prior glaucoma and corneal surgeries, and different types of keratoplasty (primary PK, repeat PK, and DMEK). This heterogeneity limits the interpretability of the outcomes and precludes meaningful subgroup analyses. Given the limited number of cases within each subgroup, the study was not designed to allow meaningful comparisons between different keratoplasty types, including PK and DMEK. Accordingly, this study is primarily descriptive in nature and was not designed to draw definitive comparative conclusions between keratoplasty types or glaucoma subgroups. Although two of the three successful cases occurred in the DMEK group, the small sample size and cohort heterogeneity preclude any comparative conclusions between DMEK and PK. Moreover, DMEK and PK cases were not analyzed separately, and in some patients, a history of keratoplasty ($n=7$) or trabeculectomy ($n=5$) prior to AGV implantation may have negatively influenced graft survival. Finally, the absence of a control group represents an additional limitation of the study.

Conclusion

This study offers valuable insights due to several strengths: post-operative IOP was well controlled, only eyes with AGV implantation were included, the number of similar studies in the literature is limited, and the follow-up period of approximately 2 years provides meaningful long-term data. In conclusion, in eyes with prior AGV implantation, keratoplasty (both DMEK and PK) was associated with low graft survival and high rejection rates.

Disclosures

Ethics Committee Approval: This study was approved by the Kartal Dr. Lutfi Kırdar City Hospital Scientific Research Ethics Committee (Date: 30.04.2025, Number: 2025/010.99/15/20) and conducted in accordance with the tenets of the Declaration of Helsinki.

Informed Consent: Written informed consents were obtained from all patients.

Conflict of Interest: None declared.

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Comparison of Swept-Source Optical Biometry and Contact A-Scan Ultrasonography for Axial Length Measurement in Eyes with Mature Cataract

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Abstract

Objectives: The objectives are to compare axial length (AL) measurements obtained using swept-source optical biometers and contact A-scan ultrasonography (USG) in eyes with mature cataract, and to evaluate inter-device agreement and acquisition success rates.

Methods: This retrospective cross-sectional study included eyes with clinically defined mature cataract. AL measurements were obtained using two swept-source optical devices (Tomey - OA and Heidelberg Anterior) and contact A-scan USG (Tomey UD-800), all performed on the same day by a single examiner. Inter-device comparisons, Bland-Altman agreement analyses, and intraclass correlation coefficients (ICC) were calculated. Optical measurement failure rates were recorded.

Results: AL measurements were successfully obtained with both optical biometers in 50 eyes. AL values showed strong agreement between the Tomey - OA OA-2000 and Anterior, with no significant inter-device difference. In contrast, contact A-scan USG yielded significantly shorter AL measurements compared with both optical devices (mean difference approximately 0.26–0.30 mm). Optical biometry failed to obtain AL measurements in approximately one-third of eyes with mature cataract. Inter-method reliability for AL was high (ICC >0.90).

Conclusion: Swept-source optical biometers provide consistent and interchangeable AL measurements in eyes with mature cataract when measurements are obtainable. However, optical acquisition failure remains common in advanced cataracts, highlighting the continued clinical relevance of A-scan USG. The systematic tendency of contact ultrasound to produce shorter AL measurements should be considered during intraocular lens power calculation.

Keywords: A-scan ultrasonography, axial length, intraocular lens power calculation, mature cataract, swept-source optical biometry

Introduction

A mature cataract represents an advanced stage of lens opacification in which all cortical fibers become opaque, resulting in severe visual impairment and increased complexity of surgical management (1). Accurate ocular biometry is therefore particularly critical in patients with mature cata-

tracts to achieve optimal refractive outcomes following cataract surgery.

Intraocular lens (IOL) power calculation relies on several key biometric parameters, including keratometry, axial length (AL), anterior chamber depth (ACD), and lens thickness (LT) (2-4). Among these parameters, AL is the most influential de-

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terminant of post-operative refractive accuracy. As IOL calculation formulas continue to evolve and incorporate an increasing number of biometric inputs, the need for precise and reliable ocular biometry has become even more pronounced (5-7).

Optical biometry based on partial coherence interferometry (PCI) and, more recently, swept-source optical coherence tomography (SS-OCT) has become the standard method for AL measurement because of its high accuracy, reproducibility, and non-contact nature (8). SS-OCT-based devices, utilizing longer wavelengths and advanced signal-processing algorithms, have demonstrated superior AL acquisition success compared with PCI-based systems (9). Nevertheless, in eyes with mature or very dense cataracts, severe lens opacification can significantly limit optical signal penetration, and reliable AL measurements may still not be obtainable even with advanced swept-source technology (10).

Despite the widespread adoption of optical biometry in routine clinical practice, A-scan ultrasonography (USG) continues to play an essential role in the evaluation of dense and mature cataracts. When optical biometry fails, AL measurement must necessarily be performed using ultrasound. Moreover, ultrasound biometry remains widely used in many developing countries due to its cost-effectiveness and the higher prevalence of advanced cataracts in these settings (11,12). Although newer SS-OCT-based optical devices offer improved accuracy, their performance may still be constrained by patient-related factors such as severe lens opacity, underscoring the continued clinical relevance of ultrasound-based biometry (13).

The primary aim of this study was to compare AL measurements obtained using three different modalities in eyes with mature cataracts: the Tomey-OA swept-source optical biometer, the Heidelberg Anterior swept-source OCT device, and contact A-scan USG. Secondary objectives included evaluating inter-device agreement, measurement reliability, and AL acquisition success rates under real-world clinical conditions.

Methods

This retrospective cross-sectional observational study evaluated AL measurements obtained using three different biometric devices in consecutive patients with mature cataract who underwent preoperative cataract assessment at the Ophthalmology Clinic of Cam and Sakura City Hospital a tertiary referral center.

Mature cataract was clinically defined as complete lens opacification precluding visualization of the posterior segment on dilated fundus examination.

All included patients underwent AL measurements using three different biometry techniques. Optical biometry was performed with the Tomey OA-2000 (Tomey Corporation, Japan), a SS-OCT-based device providing AL, keratometry, ACD, and LT measurements, and with the Anterior® (Hei-

delberg Engineering, Germany), a high-resolution anterior segment SS-OCT platform capable of acquiring AL and additional biometric parameters.

Ultrasonic AL measurements were obtained using the Tomey UD-800 contact A-scan USG device. Contact A-scan measurements were performed by an experienced examiner using the applanation technique with careful perpendicular alignment to the visual axis. Topical anesthesia was instilled prior to measurement, and minimal corneal contact was ensured to reduce the potential effect of corneal indentation.

All measurements were obtained on the same day by the same examiner to minimize inter-operator variability. For each device, three consecutive measurements were acquired, and the mean AL value was used for statistical analysis. Measurement failure due to dense media opacity was recorded for the optical biometers. Comparisons of AL values between devices were performed only in eyes in which measurements were successfully obtained with the respective modality. To avoid possible corneal compression affecting optical measurements, contact ultrasound biometry was deliberately performed after completion of measurements with the two non-contact optical devices.

Patients with coexisting corneal pathology, extreme ALs (<20 mm or >28 mm), retinal detachment, previous intraocular surgery, or any condition preventing adequate posterior segment assessment even with USG were excluded. Demographic and clinical data collected included age, sex, laterality, keratometry, ACD, LT, and AL measurements. The primary outcome measure was the comparison of AL values obtained with the three biometry techniques, while secondary outcomes included measurement success rates and inter-device agreement.

The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the local Institutional Ethics Committee (2023-252).

Statistical Analysis

All statistical analyses were performed using Statistical Package for Social Sciences (version 22.0; IBM Corp., Armonk, NY, USA). Normality of distributions was assessed using the Shapiro-Wilk test. For AL, comparisons across USG, Tomey-OA, and Anterior were performed using the Friedman test. If significant, *post hoc* pairwise comparisons were conducted using the Wilcoxon signed-rank test with Bonferroni correction. For Tomey-OA versus Anterior comparisons of other parameters, paired *t*-tests or Wilcoxon signed-rank tests were used as appropriate. Agreement was assessed using Bland-Altman statistics (bias and 95% limits of agreement). Bland-Altman plots were provided for AL only; agreement for other parameters was reported numerically. Inter-device reliability was assessed using intraclass correlation coefficients (ICC). A two-sided $p < 0.05$ was considered statistically significant.

Results

AL measurements were attempted in 79 eyes with mature cataract using both devices. AL could not be measured in 24 eyes with the Tomey - OA device and in 26 eyes with the Anterion device ($p=0.875$). A total of 50 eyes in which AL measurements were successfully obtained with both devices were included in the final analysis. The mean age was 69.1 ± 10.2 years, and 27 (54.0%) were male. Paired comparisons of Tomey - OA and Anterion measurements for biometric parameters are summarized in Table 1. Overall, Tomey - OA produced slightly higher anterior keratometry readings, lower LT and deeper ACD than Anterion, while the remaining parameters showed no statistically significant differences.

AL differed significantly across the three measurement methods (USG, Tomey - OA, and Anterion). *Post hoc* analyses indicated that USG tended to yield shorter AL measurements than both optical biometers, whereas no statistically significant difference was observed between Tomey - OA and Anterion (Table 2).

Table 1. Comparison of biometric measurements among devices

Parameter	USG	Tomey - OA	Anterion	P
AL (mm)	23.05±0.85	23.17±0.90	23.15±0.89	<0.001
K1 (D)		42.87±2.28	42.67±1.85	0.013
K2 (D)		44.35±1.80	44.13±1.61	0.025
Avg K (D)		43.61±1.92	43.40±1.58	0.011
Corneal astigmatism (D)		1.48±1.46	1.46±1.43	0.489
ACD (mm)		3.51±0.53	3.26±0.50	0.017
WTW		11.99±0.48	11.59±0.44	0.099
Pupil diameter (mm)		5.28±1.50	4.95±1.30	0.394
LT (mm)		4.27±0.43	4.51±0.42	<0.001

AL: Axial length, ACD: Anterior chamber depth, LT: Lens thickness, WTW: White-to-white, USG: Ultrasonography, K1: Flat keratometry, K2: Steep keratometry, Avg K: Mean keratometry, D: Diopter. Values are presented as mean±standard deviation. P-values are from paired comparisons between devices.

Table 2. Pairwise comparisons of axial length measurements among USG, Tomey - OA, and Anterion

Item	Mean difference	P	95% LoA (min/max)
USG versus Tomey - OA	-0.261±0.367	<0.0001	-0.980-0.458
USG versus Anterion	-0.298±0.428	0.0001	-1.137-0.541
Tomey - OA versus Anterion	0.005±0.075	0.8857	—

LoA: Limits of agreement, USG: Ultrasonography.

A summary of AL measurements across methods, including pairwise comparisons and Bland-Altman agreement statistics, is provided in Table 2. Bland-Altman plots are presented for AL to visualize pairwise agreement. Compared with Anterion, USG tended to produce shorter AL measurements, indicating a systematic negative bias (Fig. 1). A similar negative bias was observed when comparing USG with Tomey - OA (Fig. 2). In contrast, Anterion and Tomey - OA showed minimal mean bias with relatively narrow limits of agreement, supporting close agreement between the two optical biometers (Fig. 3).

Inter-method reliability for AL was high in complete cases measured by all three methods, with strong absolute agreement ($ICC(2,1)=0.919$) and similarly high consistency ($ICC(3,1)=0.940$). For non-AL parameters, agreement between Tomey - OA and Anterion is summarized using Bland-Altman bias and 95% limits of agreement in Table 3. Inter-device reliability for these parameters, assessed using $ICC(2,1)$ absolute agreement, is presented in Table 4.

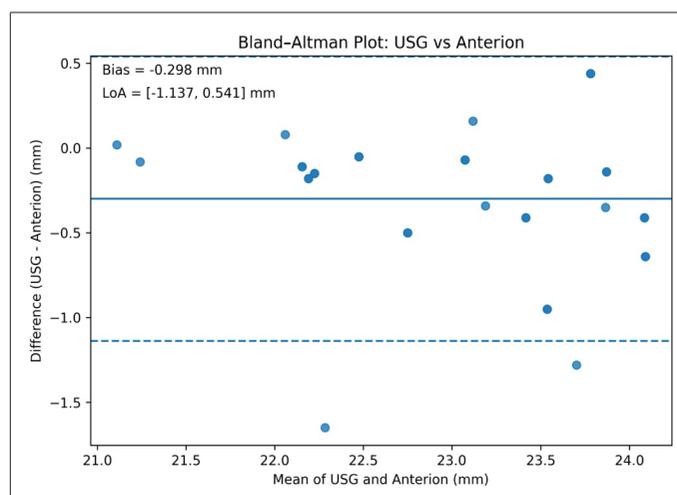


Figure 1. Bland-Altman plot for axial length: Ultrasonography versus Anterion.

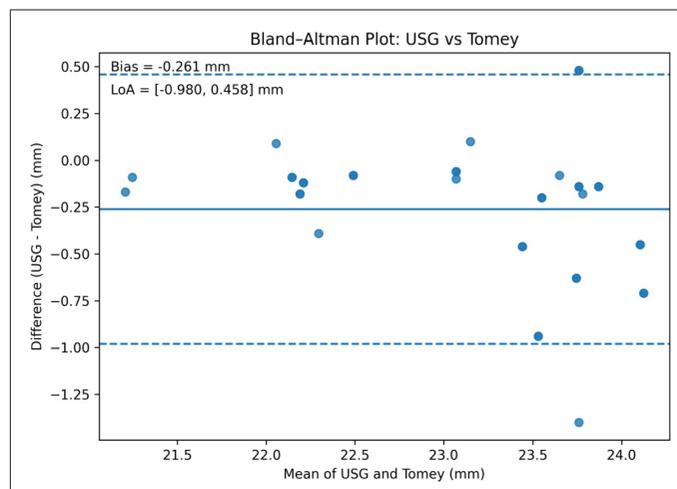


Figure 2. Bland-Altman plot for axial length: Ultrasonography versus Tomey - OA.

Table 3. Agreement between Tomey - OA and anterior for biometric parameters

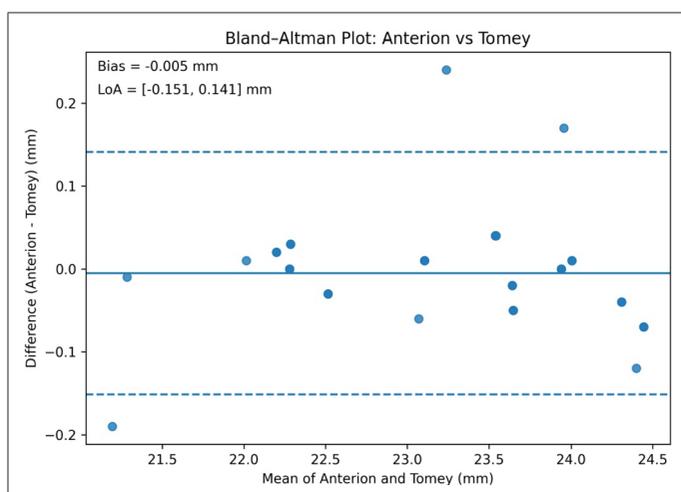
Parameter	Mean	LoA min	LoA max
ACD (mm)	0.224	-0.403	0.852
LT (mm)	-0.196	-0.756	0.363
WTW (mm)	0.243	-0.525	1.012
Pupil diameter	0.347	-2.498	3.191
Corneal astigmatism (D)	-0.016	-1.898	1.866
K1 (D)	0.188	-1.955	2.331
K2 (D)	0.203	-0.747	1.154
Avg K (D)	0.222	-1.147	1.590

AL: Axial length, ACD: Anterior chamber depth, LT: Lens thickness, WTW: White-to-white, K1: Flat keratometry, K2: Steep keratometry, Avg K: Mean keratometry, D: Diopter. Agreement is summarized numerically using Bland-Altman bias and 95% limits of agreement (LoA).

Table 4. Inter-device reliability between Tomey - OA and anterior for biometric parameters (ICC)

Parameter	ICC(2,1) absolute agreement
ACD	0.731
LT	0.694
WTW	0.462
Pupil diameter	0.370
Corneal astigmatism	0.734
K1	0.858
K2	0.953
Avg K	0.916

AL: Axial length, ACD: Anterior chamber depth, LT: Lens thickness, WTW: White-to-white, K1: Flat keratometry, K2: Steep keratometry, Avg K: Mean keratometry, D: Diopter. ICC(2,1) was calculated using a two-way random effects model with absolute agreement

**Figure 3.** Bland-Altman plot for axial length:Anterior versus Tomey – OA.

Discussion

Accurate AL measurement is fundamental to achieving optimal refractive outcomes after cataract surgery, particularly in eyes with mature cataract where dense media opacity poses significant challenges to biometric assessment. In this study, AL measurements obtained using two swept-source optical biometers, the Tomey - OA and Heidelberg Anterior, were compared with contact A-scan USG in eyes with mature cataract. The findings demonstrated a high level of agreement between the two swept-source optical devices when measurements were successfully acquired, while contact A-scan USG yielded significantly shorter AL values compared with both optical biometers. Moreover, AL acquisition with swept-source optical biometry was not achievable in a substantial proportion of eyes, highlighting the persistent clinical relevance of ultrasound biometry in the evaluation of mature cataracts.

Numerous studies have compared optical biometric devices in eyes with mature or dense cataracts (6,7,10,11,13-16). However, studies evaluating SS-OCT-based biometers in comparison with earlier biometric technologies in dense cataracts remain limited (8-10,13,14,16-18). Moreover, direct comparisons among SS-OCT devices themselves are scarce. To the best of our knowledge, this is among the first studies to directly compare the Heidelberg Anterior and Tomey - OA swept-source biometers specifically in eyes with mature cataract. Our findings indicate that even in mature cataracts, AL measurements obtained with the Tomey - OA and Heidelberg Anterior remain highly comparable, with no significant inter-device difference when measurements are successfully acquired.

Ocular biometry devices based on SS-OCT principles are known to have a superior ability to successfully measure AL compared with PCI-based systems (9,14,15). Nevertheless, even advanced swept-source OCT-based devices may fail to obtain reliable measurements in eyes with mature or very dense cataracts (10,13). In such cases, AL assessment necessarily relies on A-scan USG. Although optical and ultrasound biometry devices are both widely used in clinical practice, ultrasound biometry remains particularly important in developing countries owing to its cost-effectiveness and the higher prevalence of advanced cataracts. Previous studies have demonstrated a high correlation between swept-source OCT-based optical biometers and ultrasound AL measurements in dense cataract cohorts; however, systematic differences between these techniques have also been consistently reported (10,11). In the present study, AL measurements obtained using contact A-scan USG were consistently shorter than those obtained with swept-source optical biometers, with a mean difference of approximately 0.26–0.30 mm. This

finding is in agreement with earlier studies comparing optical and ultrasound biometry, which have similarly reported shorter AL values with contact ultrasound measurements (3,10,11). These discrepancies have primarily been attributed to corneal indentation associated with the applanation technique, as well as differences in the anatomical reference points used by ultrasound- and optical-based devices, and have been observed in both PCI- and swept-source OCT-based comparative studies.

The close agreement observed between the Tomey - OA and the Heidelberg Anterior devices in the present study is another important finding. Bland-Altman analysis demonstrated minimal mean bias and relatively narrow limits of agreement between the two swept-source optical biometers, indicating that AL measurements obtained with these devices are largely interchangeable when successful acquisition is achieved. This finding is consistent with previous reports showing high agreement among swept-source optical biometers, including comparisons between devices such as the IOL Master 700, OA-2000, Heidelberg Anterior and other SS-OCT-based platforms (17-20). Although the Anterior device was originally designed as an anterior segment imaging platform, its AL measurement capability demonstrated good agreement with a dedicated optical biometer in the present study, supporting its potential utility in selected cases. Therefore, while good agreement was observed between swept-source optical biometers in measurable cases, these results should be interpreted in the context of the relatively high optical acquisition failure rate in eyes with mature cataract.

Despite these favorable agreement results, it is noteworthy that AL measurements could not be obtained with swept-source optical biometers in approximately one-third of the eyes included in this study. Severe lens opacification in mature cataract remains a major limitation for optical biometry, even with the longer wavelengths and improved signal penetration of swept-source technology. Similar acquisition failure rates in dense or mature cataracts have been reported in previous studies, emphasizing that optical biometry cannot yet fully replace ultrasound in all clinical scenarios (21,22).

From a clinical perspective, these findings underscore the importance of being aware of systematic differences between measurement modalities. When ultrasound biometry is used as a fallback method due to optical measurement failure, surgeons should recognize the tendency toward shorter AL values and consider this potential bias during IOL power calculation. While swept-source optical biometry should remain the preferred method when measurements are obtainable, contact A-scan USG continues to play an indispensable role in the pre-operative evaluation of eyes with mature cataract.

Recent advances in IOL power calculation formulas have shifted emphasis toward multivariable models that incorporate several biometric parameters beyond AL alone. Contemporary formulas, such as the Barrett Universal II, Olsen, Kane, and Holladay 2, integrate AL, ACD, LT, and keratometric values, with some also including white-to-white (WTW) distance, to improve effective lens position prediction (23,24). Consequently, the accuracy and inter-device agreement of these parameters have become increasingly important, particularly in eyes with mature cataract where biometric reliability may be compromised.

In the present study, AL and keratometric parameters showed strong agreement between the Tomey - OA and Anterior devices, whereas differences were observed in ACD and LT measurements, and WTW measurements demonstrated relatively lower inter-device agreement. Similar findings have been reported in previous studies, suggesting that ACD, LT, and WTW may be more sensitive to variations in measurement principles and segmentation algorithms among swept-source optical biometers (25,26). Although WTW plays a secondary role in most IOL power calculation formulas, variations in ACD and LT may be more clinically relevant, as both parameters directly influence effective lens position estimation in contemporary multivariable formulas (27). However, the present study did not evaluate the impact of these inter-device differences on postoperative refractive outcomes or IOL power prediction error, which represents an important limitation. Future studies correlating device-specific biometric differences with refractive outcomes in eyes with mature cataract are warranted.

This study has several limitations. First, its retrospective design may have introduced inherent selection bias. Second, immersion A-scan USG was not used, which might have affected AL measurements obtained with contact ultrasound. In addition, eyes with unsuccessful optical biometry measurements were excluded from the final analysis, which may have resulted in underrepresentation of the most advanced mature cataracts. Finally, the single-center design and measurements performed by a single examiner may limit the generalizability of the findings.

Conclusion

Swept-source optical biometry provides consistent AL measurements in eyes with mature cataract when acquisition is successful, with strong agreement between the Tomey - OA and Heidelberg Anterior devices. However, optical measurement failure remains common in advanced cataracts, emphasizing the continued clinical relevance of A-scan USG. The tendency of contact ultrasound to yield shorter AL values should be considered during IOL power calculation when optical biometry is not feasible.

Disclosures

Ethics Committee Approval: This study was approved by the Basaksehir Cam Sakura City Hospital Ethics Committee (Date: 07.06.2023, Number: 2023-252) and conducted in accordance with the tenets of the Declaration of Helsinki.

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The Influence of Intraocular Monofocal Lens Position During Phacoemulsification Cataract Surgery on the Occurrence of Dysphotopsia

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Abstract

Objectives: The study aimed to evaluate the occurrence and intensity of positive and negative dysphotopsias in patients with different intraocular lens (IOL) positions – vertical, horizontal, superonasal, and inferonasal – and to determine whether IOL position correlates positive or negative dysphotopsias.

Methods: This prospective cohort study included 80 patients, divided into four equal groups based on IOL positioning. Each group received a monofocal hydrophobic acrylic IOL during ultrasound phacoemulsification cataract surgery. Patients with horizontally placed IOL served as the control group. In each group, there were twenty participants. Clinical assessments, including visual acuity and biometry measurements, were recorded preoperatively and 1 month postoperatively. Post-surgery, patients completed a questionnaire evaluating the presence and severity of dysphotopsias.

Results: Positive dysphotopsia was reported by 26.3% of patients, with no significant difference among the groups (Fisher's exact test, $p=0.63$). Negative dysphotopsia appeared in 11.3% of patients, significantly more frequent in those with superonasal and inferonasal IOL positions (Fisher's exact test, $p=0.01$). Regarding the IOL location, there was no discernible difference in the severity of positive (Kruskal–Wallis test, $p=0.33$) and negative (Kruskal–Wallis test, $p=0.23$) dysphotopsias among patients who were experiencing them. Postoperatively, all patients demonstrated improved visual acuity, anterior chamber depth, and axial length measurements.

Conclusion: The study found a significant association between IOL position and the incidence of negative dysphotopsia, especially with inferonasal and superonasal placements. However, the IOL position did not influence the intensity of either positive or negative dysphotopsia. This implies that post-surgery negative dysphotopsia perception is influenced by lens location. Patient satisfaction remained high, though negative dysphotopsia intensity negatively correlated with satisfaction scores.

Keywords: Cataract surgery, negative dysphotopsia, positive dysphotopsia

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Introduction

Even though cataract surgery generally leads to improved vision, higher quality of life, and excellent overall success rates, post-operative dysphotopsias may occur, potentially compromising visual quality and patient satisfaction (1). Tester *et al.* (2) were the first to define dysphotopsia as “any light-related visual phenomenon experienced by phakic and pseudophakic patients.” Today, the term is commonly used to describe the subjective visual phenomena experienced by pseudophakic patients following cataract surgery (3).

Dysphotopsias remain an insufficiently studied complication of cataract surgery, yet they are of considerable importance because they can cause patient frustration and represent a key source of dissatisfaction despite an otherwise successful surgical outcome (4) research by Tester *et al.* (2) indicated that dysphotopsia can develop in up to 49% of patients postoperatively, whereas Bournas *et al.* (5) reported that 19.5% of patients experienced it on the 1st post-operative day. Although symptoms often resolve spontaneously over time, approximately one-fifth of patients suffer from severe and persistent dysphotopsia (6). Post-operative dysphotopsia can be categorized into two types: Positive and negative, based on symptomatology and etiology (7).

Positive dysphotopsias are perceived as light phenomena, typically described as streaks, rays, arcs, flashes, or an aura in the peripheral visual field, usually induced by an external light source (8,9) (Fig. 1).

Davison originally described negative dysphotopsia as a dark shadow appearing in the peripheral visual field, resembling a temporal scotoma (10). Patients typically perceive this shadow as an arc- or crescent-shaped area of darkness in the periphery of vision (11) (Fig. 2).

Positive dysphotopsias are believed to result from glare caused by internal reflections along the edge of the intraocular lens (IOL). Light entering the eye from one side of the visual field – or even from outside the field of view – may be reflected off the opposite edge of the IOL. These reflected rays are detected on the retina and perceived as peripheral flashes or arcs of light that appear to originate from no identifiable external source (12,13) (Fig. 3a).

The most widely accepted explanation for the occurrence of negative dysphotopsia is the illumination gap theory. According to this theory, an illumination gap forms on the nasal retina due to a discontinuity between light rays reflected from the nasal edge of the implanted IOL and those that bypass the IOL and directly reach the retina. As a result, the gap is bounded posteriorly by rays refracted through the lens and anteriorly by rays that pass outside the optic without refraction, creating a shadow perceived in the temporal visual field (14) (Fig. 3b).

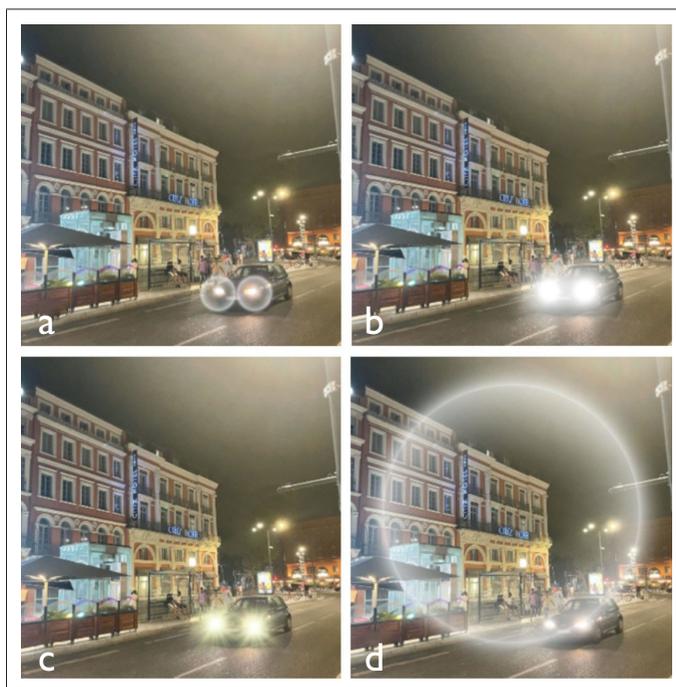


Figure 1. Illustrations of glare, aura, flash of light and ring-shaped dysphotopsia. (a) Aura; (b) Glare; (c) Flashes of light; (d) Ring-shaped dysphotopsia. Source: created by the author of the paper.

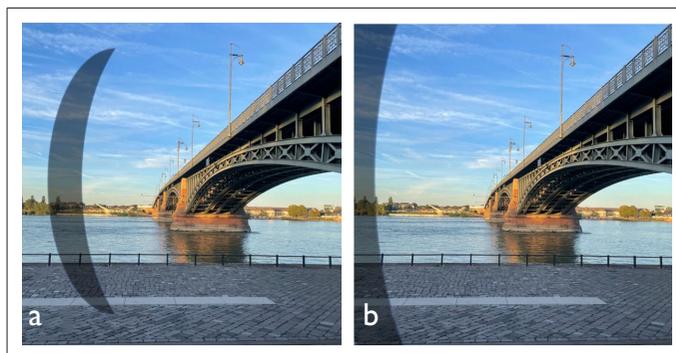


Figure 2. Crescent-shaped negative dysphotopsia (a), Arc-shaped negative dysphotopsia (b).

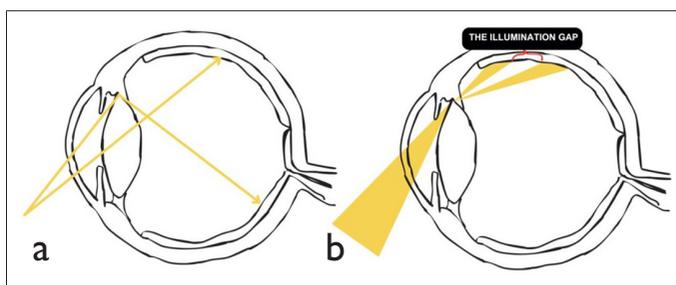


Figure 3. (a) Light falling on the edge of the intraocular lens (IOL) can be reflected elsewhere on the retina, leading to unwanted dysphotopsia. (b) Illumination gap theory – the gap created by the different refractions of rays hitting the periphery of the IOL and rays missing the IOL.

We hypothesized that the occurrence of dysphotopsias is associated with the position of the IOL. The objectives of this study were to evaluate the incidence and intensity of positive and negative dysphotopsias in four groups of patients with different IOL orientations (vertical, horizontal, superonasal, and inferonasal), and to determine whether a correlation exists between the type and intensity of dysphotopsia and the IOL position.

Methods

In collaboration with the Faculty of Medicine in Osijek this prospective cohort study was conducted at the Department Ophthalmology. Patients underwent cataract surgery between April and June of 2024.

Participants

Participants were randomized in a 1:1:1:1 ratio to one of four IOL orientation groups – horizontal (control), vertical, superonasal, or inferonasal – using computer-generated permuted block randomization with variable block sizes (4 and 8). The random sequence was prepared by an investigator not involved in recruitment or surgery, and allocation concealment was ensured using sequentially numbered, opaque, sealed envelopes. After confirming eligibility and obtaining consent, the next envelope in sequence was opened to reveal the assignment, which was masked to the operating surgeon until that moment. Deviations from the sequence, if any, were recorded. The IOL was implanted vertically in the vertical group, horizontally in the control group, superonasally (right eye 135°, left eye 45°) in the superonasal group, and inferonasally (right eye 45°, left eye 135°) in the inferonasal group.

Exclusion criteria included irregular pre-operative astigmatism, a history of corneal transplantation or refractive eye surgery, corneal diseases such as keratoconus, long-term topical therapy, dry eye syndrome, central vision impairment due to any pathology affecting the visual center, previous ocular surgery or laser procedures of any cause, and a history of blunt or penetrating ocular trauma. All participants provided written informed consent for anonymous post-operative data collection and analysis, after being informed of the potential risks associated with cataract surgery. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of the Faculty of Medicine Osijek at Josip Juraj Strossmayer University of Osijek (Approval No. 2158-61-46-24-08, February 02, 2024) and from the Ethics Committee of Osijek University Hospital Centre (Approval No. R1-4642/2024, April 23, 2024).

Pre-operative Clinical Assessment

Patient age, gender, operated eye, and keratorefractometry values were recorded using the Nidek device (Japan,

2023) on the day of surgery and 1 month postoperatively. Best-corrected visual acuity (BCVA) was evaluated using Snellen charts at both time points. Optical biometry parameters, including axial length (AL) and anterior chamber depth (ACD), were measured with the IOLMaster 700 device (Zeiss, 2020).

Surgical Technique

All phacoemulsification surgeries were performed using the Centurion system (Alcon, 2019) by the same surgeon. All patients received a monofocal, hydrophobic acrylic, single-piece IOL from Johnson and Johnson, model AAB00 (Limerick, Ireland), with an optical diameter of 6 mm and a total length of 13 mm. During phacoemulsification, a 2.75 mm clear corneal incision was made, and a viscoelastic material was applied to the anterior chamber. A continuous curvilinear capsulorhexis of the desired size was then performed, followed by phacoemulsification and aspiration of the lens nucleus using an ultrasound probe inserted through the main incision. The remaining cortical material was removed from the capsular bag, and a foldable IOL was implanted.

Post-operative Evaluation

One month after surgery, each patient completed a questionnaire based on previously published studies⁽¹⁵⁾. The questionnaire contained five items assessing visual symptoms and overall satisfaction with post-operative vision.

The first question asked about the presence of unwanted visual phenomena such as flashes of light, arcs, halos, or partial circles, with response options “Yes” or “No.” If patients reported such symptoms, they were asked to rate their severity on a scale from 0 to 10, where 0 indicated no problem, and 10 represented debilitating symptoms.

The third question addressed the presence of a dark or gray shadow in the peripheral visual field, with “Yes” or “No” response options. If present, patients rated its severity using the same 0–10 scale.

The final question evaluated overall satisfaction with vision after surgery, rated on a 0–10 scale, where 0 indicated complete dissatisfaction, and 10 indicated complete satisfaction.

Statistical Analysis

Statistical analysis was performed to evaluate differences among study groups and to assess correlations between clinical parameters. Categorical data were presented as absolute and relative frequencies, and differences between categories were tested using Fisher’s exact test. The normality of distribution for numerical variables was assessed with the Shapiro–Wilk test. As most data were not normally distributed, results are expressed as medians with interquartile range (IQR) boundaries. Differences between pre-operative and post-operative values were analyzed using the Wilcox-

on signed-rank test, while differences among three or more independent groups were evaluated using the Kruskal–Wallis test with *post hoc* Conover comparisons. Correlations were assessed using Spearman's rank correlation coefficient (ρ).

In addition to *P*-values, effect sizes were reported to estimate the magnitude of differences: Cramér's *V* for associations between categorical variables, rank-biserial correlation (*r*) for Mann–Whitney tests, and Spearman's ρ for correlations. Odds ratios with 95% confidence intervals (CIs) were calculated for pairwise comparisons of dysphotopsia incidence, and Wilson 95% CIs were reported for proportions. All *P*-values were two-tailed, and statistical significance was set at $\alpha=0.05$.

Statistical analysis was performed using MedCalc® Statistical Software, version 22.018 (MedCalc Software Ltd., Ostend, Belgium; <https://www.medcalc.org>; 2024).

Results

Eighty patients were included in the study, and they were split into four groups according to the position of the IOL: Vertical in one group, horizontal in another (control group), superonasal in a third group (right eye's optic-haptic junction was at 135°, left eye at 45°), and inferonasal in a fourth (right eye's optic-haptic junction was at 45°, left eye at 135°). Twenty patients made up each group, making up 25% of the total patients.

Regarding gender distribution, there were 37 (46.3%) male patients and 43 (53.8%) female patients. The patients' median age was 76 years, with a minimum age of 45 and a maximum age of 97. Right eye surgery was performed on 41 (51.3%) patients.

Significantly, the longest time for phacoemulsification aspiration time (AST) was observed in the superonasal position of IOL compared to the inferonasal and horizontal positions (Kruskal–Wallis test, $p=0.04$). However, no significant difference was observed compared to the vertical position. Fur-

thermore, compared to the superonasal and vertical placements of the IOL, the total amount of fluid required during the procedure was considerably lower in the inferonasal position (Kruskal–Wallis test, $p=0.03$). There was no significant difference compared to the horizontal position (Table 1).

Analysis revealed that the estimated fluid used during phacoemulsification was significantly higher among patients who developed positive dysphotopsia ($p=0.008$). Moreover, a weak but significant positive correlation was observed between the total amount of fluid used and the intensity of positive dysphotopsia ($\rho=0.25$, $p=0.025$). No significant associations were found between AST and either the presence or intensity of positive or negative dysphotopsia.

Significant improvements were observed after surgery compared to pre-operative values in BCVA (Wilcoxon test, $p<0.001$), ACD (Wilcoxon test, $p<0.001$), and AL (Wilcoxon test, $p=0.02$) across all patients. Among patients with a horizontal IOL position, there were significant increases in BCVA (Wilcoxon test, $p<0.001$) and AL (Wilcoxon test, $p=0.02$) postoperatively, while no significant difference was observed in ACD values. For those with an inferonasal IOL position, post-operative BCVA and ACD values showed significant improvements (Wilcoxon test, $p<0.001$), whereas there was no significant change in AL compared to pre-operative measures. Similar significant improvements were noted in patients with a superonasal IOL position, where both BCVA and ACD values were significantly higher after surgery (Wilcoxon test, $p<0.001$), with no significant change in AL. In patients with a vertical IOL position, all measured parameters BCVA, ACD, and AL, showed significant increases after surgery compared to pre-operative values (Table 2).

Positive dysphotopsia was present in 21 patients (26.3%), with no significant difference across IOL positions. Negative dysphotopsia was observed in 9 patients (11.3%), significantly more prevalent in patients with inferonasal and superonasal IOL positions (Fisher's exact test, $p=0.01$) (Table 3).

Table 1. Values of power of IOL, cumulative dissipated energy during procedure, aspiration time, and estimated fluid used during procedure in relation to the position of the IOL

	Median (interquartile range) by IOL position					<i>P</i>
	Horizontal	Inferonasal	Superonasal	Vertical	Total	
Lens power	23 (21–24.8)	22.5 (20–24.7)	23.5 (20.1–24.8)	24.0 (22–25.9)	23.0 (21–25)	0.29
Cumulative dissipated energy	9.05 (6.8–15.3)	7.85 (3.5–13.1)	4.82 (3.9–8.5)	11.3 (3.9–14.8)	7.3 (4.0–13.4)	0.12
Aspiration time	1.74 (1.3–2.3)	2.06 (1.0–2.5)	2.38 (2–3.5)	2.22 (1.6–3.1)	2.14 (1.4–2.9)	0.04 [†]
Estimated fluid used	40.5 (32–56.5)	33.5 (21.3–51.3)	51.5 (33.8–62.0)	51.5 (34.8–68)	45 (33–58)	0.03 [‡]

IOL: Intraocular lens. *Kruskal–Wallis test (*post hoc* Conover). [†]At the $p<0.05$ level, the longest time of aspiration of lens masses is significant in the case of superonasal intraocular lens position compared to horizontal and inferonasal. [‡]At the $p<0.05$ level, the smallest amount of liquid is significantly lower in the inferonasal position compared to the superonasal and vertical.

The overall clinical meaning of these findings is summarized as follows. Positive dysphotopsia occurred in 26.3% of patients (95% CI: 17.5–37.2%), while negative dysphotopsia was observed in 11.3% (95% CI: 5.7–20.8%). The association between IOL position and negative dysphotopsia showed a

Table 2. Values of BCVA, ACD and AL in all patients and in relation to the position of the IOL

	Median (interquartile range)		p*
	Before surgery	After surgery	
All patients			
BCVA	0.20 (0.10–0.40)	1.0 (0.90–1.0)	<0.001
ACD	3.33 (2.86–3.60)	3.41 (3.00–3.88)	<0.001
AL	23.0 (22.05–24)	23.2 (22.18–24.08)	0.02
Horizontal position			
BCVA	0.25 (0.09–0.50)	1.0 (0.73–1.0)	<0.001
ACD	3.37 (3.24–3.49)	3.43 (3.24–3.56)	0.07
AL	22.62 (22.05–23.51)	22.90 (22.25–23.85)	0.02
Inferonasal position			
BCVA	0.20 (0.10–0.35)	1.0 (0.90–1.0)	<0.001
ACD	3.05 (2.7–3.49)	3.15 (2.8–3.58)	<0.001
AL	23.0 (22.0–23.61)	23.0 (22.0–23.55)	0.21
Superonasal position			
BCVA	0.30 (0.20–0.45)	1.0 (0.80–1.0)	<0.001
ACD	2.87 (2.68–3.97)	3.33 (2.97–4.80)	<0.001
AL	22.64 (21.96–23.59)	22.85 (22.06–23.69)	0.21
Vertical position			
BCVA	0.20 (0.13–0.35)	1.0 (0.90–1.0)	<0.001
ACD	3.85 (3.25–4.41)	3.85 (3.25–4.50)	<0.001
AL	24.0 (22.73–25.0)	24.05 (22.8–25.0)	0.03

BCV: Best corrected visual acuity, ACD: Anterior chamber depth, AL: Axial length, IOL: Intraocular lens. *Wilcoxon test. Significant increases after surgery are shown in bold.

small-to-moderate effect size (Cramér's $V \approx 0.34$), with cases occurring almost exclusively in inferonasal and superonasal IOL positions. In contrast, the link between IOL position and positive dysphotopsia was weak (Cramér's $V \approx 0.16$). Patients with positive dysphotopsia had higher intraoperative fluid use (rank-biserial $r \approx 0.34$, $p = 0.008$), suggesting that greater fluid turbulence may contribute to post-operative light phenomena. However, the overall effect sizes were small, indicating that these differences, while statistically significant, are likely of limited clinical relevance.

There is no significant difference in the intensity of positive and negative dysphotopsia among patients where dysphotopsias are present, relative to the IOL position (Table 4).

Patient satisfaction with the surgery was rated with a median score of 10 (IQR 9–10), ranging from 5 to a maximum of 10. Spearman's correlation coefficient was applied to evaluate the association between satisfaction scores, patient age, and the severity of positive and negative dysphotopsia. It was observed that there is no significant correlation between the intensity of positive dysphotopsia and patient satisfaction scores. However, the intensity of negative dysphotopsia showed a significant negative correlation with satisfaction scores. In other words, higher satisfaction scores were associated with lower intensity of negative dysphotopsia ($\rho = -0.717$). Patient age did not show a significant relationship with satisfaction scores (Table 5).

Discussion

The results of this study provide insight into the influence of IOL position on the occurrence of dysphotopsia following ultrasonic cataract surgery with phacoemulsification. Based on the hypothesis that dysphotopsias are related to IOL position, we analyzed the incidence and intensity of positive and negative dysphotopsias in four patient groups and investigated their association with IOL orientation.

The overall incidence of dysphotopsia was relatively low, with 26.3% of patients reporting positive dysphotopsia and

Table 3. Distribution of patients according to the presence of positive and negative dysphotopsia in relation to IOLs position

	Number (%) of patients regarding the position of the IOL					p*
	Horizontal	Inferonasal	Superonasal	Vertical	Total	
Positive dysphotopsia						
Not present	16 (80)	16 (80)	14 (70)	13 (65)	59 (73.8)	0.63
Present	4 (20)	4 (20)	6 (30)	7 (35)	21 (26.3)	
Negative dysphotopsia						
Not present	20 (100)	16 (80)	15 (75)	20 (100)	71 (88.8)	0.01†
Present	0	4 (20)	5 (25)	0	9 (11.3)	

*Fisher's exact test; Cramér's $V = 0.16$ for positive dysphotopsia and 0.34 for negative dysphotopsia (small-to-moderate effect size). 95% confidence intervals for incidence: positive dysphotopsia 17.5–37.2%, negative dysphotopsia 5.7–20.8%. IOL: Intraocular lens.

Table 4. Positive and negative dysphotopsia intensity values with respect to position IOLs

	Median (interquartile range) s regarding the position of the IOL				p*
	Horizontal	Inferonasal	Superonasal	Vertical	
Intensity of positive dysphotopsia	4.0 (3.25–4.0)	1 (0–3.5)	2 (1.75–4.50)	3 (1–7)	0.33
Intensity of negative dysphotopsia	-	4 (3.25–4)	3 (2–6)	-	0.20

*Kruskal–Wallis test. IOL: Intraocular lens.

Table 5. Evaluation of the relationship between satisfaction with the surgery and the intensity of positive and negative dysphotopsia, as well as the age of patients

	Spearman’s rank correlation coefficient (p)
	Assessment of satisfaction with the operation
Intensity of positive dysphotopsia	–0.295 (0.19)
Intensity of negative dysphotopsia	–0.717 (0.03)†
Age of the patient	–0.012 (0.92)

†Significant at p<0.05.

11.3% experiencing negative dysphotopsia. Negative dysphotopsia was significantly more prevalent in the inferonasal and superonasal IOL positions, suggesting that lens orientation may influence the perception of dysphotopsia after surgery. However, no significant difference was observed in the incidence of positive dysphotopsia among the various IOL positions.

In this study, the incidence of negative dysphotopsia was 11.3%, which may be considered relatively low compared with the rates reported in the literature, where incidences commonly range between 15% and 20% in the early post-operative period. Several factors could account for the lower incidence observed in our sample.

First, patient selection may have influenced the results. The exclusion of individuals with pre-existing ocular conditions – such as irregular astigmatism, corneal disease, or prior ocular surgery – could have reduced the likelihood of post-operative visual disturbances. Second, the IOL model used – a monofocal hydrophobic acrylic single-piece IOL (AAB00, Johnson and Johnson) – is known for its favorable optical design and square-edge profile, which minimize internal reflections and edge-related light scatter, potentially lowering dysphotopsia occurrence.

Third, optical and surgical parameters, including consistent capsulorhexis size, centralized IOL positioning, and the experience of a single operating surgeon, likely contributed to uniform post-operative optical outcomes. Finally, the relatively short 1-month post-operative follow-up period may

also have contributed to the lower observed incidence, as neuroadaptation and capsular changes that can exacerbate ND may not yet be fully apparent during this time.

Post-operative analysis of ocular morphological parameters revealed significant improvements in AL, ACD, and BCVA across all groups. Specific changes depended on IOL orientation, as different positions were associated with improvements in certain parameters.

The longest AST for lens material was recorded in the superonasal IOL group, whereas the total amount of fluid used was significantly lower in the inferonasal group. These findings suggest that IOL orientation may influence technical aspects of surgery, potentially affecting the overall surgical experience.

Patient satisfaction was high, with a median score of 10, indicating a positive experience for most patients. Importantly, negative dysphotopsia showed a significant negative correlation with satisfaction, confirming that patients with less severe negative dysphotopsia tend to be more satisfied with surgical outcomes. Patient age did not significantly correlate with post-operative satisfaction, suggesting that age is not a major determinant of subjective surgical success.

Over the past decade, several studies have investigated the relationship between IOL orientation and dysphotopsia, contributing to a better understanding of this phenomenon.

Henderson *et al.* reported a 2.3-fold reduction in the incidence of negative dysphotopsia 1 day after cataract surgery when one of the two optic–haptic junctions of the IOL was placed inferotemporally compared to a vertically oriented control group. However, this difference was no longer statistically significant 1 month postoperatively (11).

Similarly, Manasseh *et al.* (6) conducted a randomized controlled study that demonstrated a reduction in the incidence of pseudophakic negative dysphotopsia from 16% to 8% when the optic–haptic junction was positioned horizontally.

Furthermore, Pamulapati *et al.* (15) performed a randomized controlled trial involving 163 patients implanted with bilateral Tecnis monofocal IOLs (ZCB00, Johnson and Johnson Vision). Participants were randomized to four IOL orientations (vertical, horizontal, superonasal, and inferonasal). Their findings showed that the horizontal group had the most favorable results 4–6 weeks after surgery, while the

superonasal group showed the lowest outcomes at both 1 week and 4–6 weeks postoperatively. No significant differences were observed in the frequency or intensity of positive dysphotopsia.

Taken together, these studies reinforce the importance of considering IOL orientation in the context of dysphotopsia. Their findings support and complement the results of our study, emphasizing the multifactorial nature of dysphotopsia and providing valuable guidance for future research and clinical practice aimed at optimizing patient outcomes following cataract surgery.

This study has several limitations. A formal power analysis was not conducted before data collection because of the exploratory nature of the study and limited patient availability. Consequently, with 20 patients per group, the statistical power was sufficient to detect only large differences between groups, while smaller or moderate effects may have gone undetected.

All surgeries were performed by a single experienced surgeon using the same technique and IOL model, which ensured procedural consistency but may limit the generalizability of the findings to other surgeons or IOL designs.

The follow-up period was limited to 1 month after surgery, which may not fully capture late-onset or transient dysphotopsia symptoms that can resolve or develop over a longer period.

Additionally, only monofocal hydrophobic acrylic lenses of a single model (AAB00, Johnson and Johnson) were used; therefore, the findings may not apply to other lens materials or optical designs.

Finally, the study did not include an analysis of other potential factors that might influence dysphotopsia, such as pupil size, capsulorhexis diameter, or individual anatomic differences, which could be addressed in future research.

Conclusion

Based on the conducted study and its findings, the following conclusions can be drawn.

Negative dysphotopsia is significantly more prevalent in inferonasal and superonasal IOL positions. However, there is no significant difference in the incidence of positive dysphotopsia across different IOL positions. AST and the volume of fluid used vary depending on IOL orientation: the superonasal position is associated with the longest AST for lens material, while the inferonasal position is associated with a significantly smaller volume of fluid used.

After surgery, all patients showed significant improvements in BCVA, as well as increases in ACD and AL. The presence of dysphotopsias was not correlated with the intensity of either positive or negative dysphotopsia. Moreover, the severity of dysphotopsias did not significantly differ according to IOL orientation.

Patient satisfaction after surgery was high, with a median score of 10. Satisfaction was not significantly correlated with the intensity of positive dysphotopsia. However, the intensity of negative dysphotopsia showed a significant negative correlation with satisfaction, indicating that greater satisfaction corresponds to lower intensity of negative dysphotopsia. Patient age was not significantly associated with post-operative satisfaction.

Disclosures

The Original Article has been published in the repository as a master's thesis.

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Ethics Committee Approval: This study was approved by the Faculty of Medicine Osijek at Josip Juraj Strossmayer University of Osijek Ethics Committee (Date: 02.02.2024, Number: 2158-61-46-24-08) and the Ethics Committee of Osijek University Hospital Centre. (Date: 23.04.2024, Number: R1-4642/2024) and conducted in accordance with the tenets of the Declaration of Helsinki.

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Evaluation of the Association of Senile Macular Degeneration in Patients with Glaucoma

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Abstract

Objectives: The aim of the study was to evaluate the incidence of senile macular degeneration (SMD) in patients with primary open-angle glaucoma (POAG) and pseudoexfoliation glaucoma (PEG).

Methods: The medical files of 2600 patients with glaucoma were analyzed. In this study, 168 patients (90 females and 78 males) with POAG and PEG were included. Patients diagnosed with POAG and PEG with SMD were also recorded. SMD was classified in two categories: Wet type and dry type. Lens status was classified as pseudophakic and phakic. Glaucoma severity was classified according to the Hodapp-Parrish-Anderson criteria. All patients underwent complete ophthalmologic examinations.

Results: Ninety (53.57%) patients were female, and 78 (46.43%) were male. The mean age was 63 ± 8.4 years for women and 66.5 ± 7.8 years for men. Sixty-six (73.3%) of women and 60 (76.9%) of men had POAG, 24 (26.7%) of women and 18 (23.1%) of men had PEG. 18 (20.0%) right and 25 (27.8%) left eyes of women and 30 (38.5%) right and 24 (30.8%) left eyes of men were pseudophakic, 72 (80.0%) right and 65 (72.2%) left eyes of women and 48 (61.5%) right and 54 (69.2%) left eyes of men were phakic. SMD was observed in 10 patients (5.95%); four women and five men had dry-type SMD, while one man had wet-type SMD.

Conclusion: In our study, when gender, age, severity of glaucoma, pseudophakic and phakic status of the lens were evaluated in patients with the association of glaucoma and SMD, these variables had no statistically significant effect on the association of glaucoma and SMD.

Keywords: Cataract, primary open-angle glaucoma, pseudoexfoliation glaucoma, senile macular degeneration

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Introduction

Glaucoma is a chronic optic neuropathy characterised by progressive degeneration of retinal ganglion cells, leading to visual field loss. Primary open-angle glaucoma (POAG) is the most common type of glaucoma. The etiology of POAG is multifactorial, and the exact cause is unknown. Vascular changes leading to perfusion disorders in the peripapillary region and optic nerve head are thought to be responsible for the pathogenesis of POAG. Risk factors for glaucoma include family history, ethnicity, advanced age, high intraocular pressure, thin cornea, high myopia, Type 2 diabetes, hypertension, oxidative stress, apoptosis, inflammation, and autoimmunity (1-8).

Pseudoexfoliation syndrome (PES) is a critical cause of glaucoma worldwide. It is an age-related systemic disorder caused by the production and accumulation of an abnormal fibrillar extracellular substance. It is characterised by the deposition of small grey-white deposits in the eye, most commonly at the pupillary margin and on the anterior capsule of the lens and trabecular meshwork. It often leads to the development of pseudoexfoliation glaucoma (PEG), which causes progressive and irreversible visual loss (2,6,7,9).

Senile macular degeneration (SMD) is a progressive degenerative eye disease that causes severe and irreversible vision loss involving the central part of the retina where the macula is located. It is a critical cause of blindness worldwide, affecting 196 million people. By 2040, it is expected to affect 288 million people. SMD is a complex, multifactorial disease. Risk factors include genetic predisposition, advanced age (≥ 65 years), family history, smoking, hyperlipidemia, hypertension, oxidative stress, environmental factors, and diet (1,10-13). Retinal pigment epithelium, photoreceptor cells, choriocapillaris, and Bruch's membrane are affected. Clinically, it is divided into two forms. The atrophic form accounts for 85% of the patients and the exudative form accounts for 15% (2). As the eye ages, cellular debris from the retinal pigment epithelium accumulates between Bruch's membrane and the neurosensory layer. These deposits, known as drusen, are the first ophthalmoscopic findings seen in SMD. Drusen are structures composed of lipids, proteins, and carbohydrates. Dry SMD is characterised by progressive loss of visual function due to deterioration of the choriocapillaris, atrophic loss of the outer retina, and deterioration and eventual death of the photoreceptor layer. Geographic atrophy is the most advanced form of dry-type SMD. In wet-type SMD, subretinal or intraretinal neovascularization occurs, and when these new blood vessels infiltrate, it may cause fluid accumulation, hemorrhages, and fibrosis (10,12,14). According to the clinical classification by Ferris et al., (15) if there are no drusen or pigment abnormalities in the fundus, there is no SMD. In late SMD, neovascular SMD and/or geographic atrophy are observed.

Both glaucoma and SMD cause progressive and irreversible vision loss in older patients. These are complex, multifactorial diseases that can significantly impact patients' daily activities and quality of life. Understanding the relationship between glaucoma and SMD is important for identifying the underlying pathological mechanisms and improving prognosis. This study aims to evaluate the incidence of SMD association in patients with POAG and PEG.

Methods

The files of 2600 glaucoma patients who were followed and treated at Inonu University Faculty of Medicine, Department of Ophthalmology, between January 2019 and December 2024 were retrospectively analyzed, and 168 patients with POAG and PEG were included in this study. Patients diagnosed with POAG and PEG with SMD were also recorded. Approval protocol number: 2024/6601 was obtained on December 17, 2024, from the Ethics Committee of Inonu University Faculty of Medicine. This study was conducted in accordance with the Declaration of Helsinki.

In this study, 90 female and 78 male patients with POAG and PEG were included in the study. The mean age of female patients was 63 ± 8.4 years, and the mean age of male patients was 66.5 ± 7.8 years. SMD was classified as a wet type and a dry type. Lens status was classified as pseudophakic and phakic. The severity of glaucoma was classified as early stage (mean deviation [MD] ≤ 6 dB), intermediate stage (MD -6 dB— 12 dB), and advanced stage (MD ≥ 12 dB) according to MD values and glaucomatous visual field defect according to Hodapp-Parrish-Anderson criteria (16).

All patients underwent complete ophthalmological examinations, including best-corrected visual acuity, slit-lamp biomicroscopy, fundus examination with a +90D lens after pharmacological dilatation, intraocular pressure measurement with Goldmann applanation tonometry, gonioscopy, optical coherence tomography (OCT) (DRI OCT Triton; Topcon Inc., Tokyo, Japan), color fundus photography, fundus fluorescein angiography (TRC-50DX; Topcon Inc., Tokyo, Japan), and Humphrey (Humphrey-Zeiss Systems, Dublin, CA, USA) 30-2 static threshold perimetry. Patients under 50 years of age, patients with retinal disease, diabetic retinopathy, hypertensive retinopathy, hyperlipidemia, vascular occlusions, infection, uveitis, nonglaucomatous optic neuropathy, neurological or other neuro-ophthalmic diseases, history of chronic drug use, eye surgery other than cataract surgery, ocular trauma, degenerative myopia and ocular laser history within the last 3 months were excluded from this study.

Glaucomatous optic nerves were defined as a cup-to-disc ratio ≥ 0.6 and/or asymmetry of the optic nerve cup-to-disc ratio between both eyes >0.2 (17). Typical glaucomatous visual field defects detected by the Humphrey automated

perimetry 30-2 program, according to the Anderson criteria, were recorded. For Humphrey visual fields, false positive, false negative, and loss-of-fixation rates of fewer than 33% were considered.

Statistical Analysis

Gender, age, type of glaucoma, type of SMD, the severity of glaucoma, lens status, and differences of all variables according to gender were analyzed by chi-square analysis. The correlations between glaucoma type and gender, age, and SMD; between glaucoma severity and gender, age, and SMD; and between lens condition and gender, age, and SMD were analyzed using Pearson correlation. The effect of gender, age, type of SMD, the severity of glaucoma, lens condition (dependent variables) on the type of glaucoma (independent variable) was analyzed by regression analysis. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 27.0 software (IBM SPSS Corporation, Chicago, USA). Statistical significance was accepted as $p \leq 0.05$.

Results

Ninety (53.57%) patients were female, and 78 (46.43%) were male. The mean age of the women was 63 ± 8.4 years, and the mean age of the men was 66.5 ± 7.8 years. When the type of glaucoma was analyzed, 66 (73.3%) of the women and 60 (76.9%) of the men had POAG, 24 (26.7%) of the women and 18 (23.1%) of the men had PEG. 18 (20.0%) right and 25 (27.8%) left eyes of women and 30 (38.5%) right and 24 (30.8%) left eyes of men were pseudophakic, 72 (80.0%) right and 65 (72.2%) left eyes of women and 48 (61.5%) right and 54 (69.2%) left eyes of men were phakic. In patients diagnosed with SMD, only dry type was observed in four women, while dry-type SMD was observed in five men, and wet-type SMD was observed in one man. According to the severity of glaucoma, 65 (72.7%) women and 43 (55.1%) men were diagnosed with early-stage glaucoma, 13 (14.4%) women and 13 (16.7%) men with intermediate stage, and 12 (13.3%) women and 22 (28.2%) men with advanced stage in the right eye. In the left eye, there were 61 (67.8%) women and 49 (62.8%) men diagnosed with early stage, 8 (8.9%) women and 11 (14.1%) men diagnosed with intermediate stage, and 21 (23.3%) women and 18 (23.1%) men diagnosed with advanced stage (Table 1).

Age, type of glaucoma, lens status in the left eye, type of SMD in patients with SMD, and severity of glaucoma in the left eye were not statistically significantly different according to gender ($p > 0.05$). However, lens status in the right eye ($p = 0.008$) and severity of glaucoma ($p = 0.037$) were statistically significant according to gender ($p \leq 0.05$). The number of women who were diagnosed with early-stage glaucoma in the right eye and who were phakic was higher (Table 1). There was a statistically significant difference in the severity of glau-

Table 1. Demographic and clinical characteristics of the patients

Variables	n	%	P
Gender			
Woman	90	53.57	-
Male	78	46.43	
Age \pm standard deviation			
Woman	63 ± 8.4	-	0.085
Male	66.5 ± 7.8		
Type of glaucoma			
Woman			0.592
POAG	66	73.3	
PEG	24	26.7	
Male			
POAG	60	76.9	
PEG	18	23.1	
Lens status of right eye			
Woman			0.008*
Pseudophakic	18	20.0	
Phakic	72	80.0	
Male			
Pseudophakic	30	38.5	
Phakic	48	61.5	
Lens status of left eye			
Woman			0.671
Pseudophakic	25	27.8	
Phakic	65	72.2	
Male			
Pseudophakic	24	30.8	
Phakic	54	69.2	
Patients diagnosed with SMD			
Woman			1.000
Dry type	4	100.0	
Wet type	0	0.0	
Male			
Dry type	5	83.3	
Wet type	1	16.7	
Glaucoma severity of right eye			
Woman			0.037*
Early stage	65	72.2	
Middle stage	13	14.4	
Advanced stage	12	13.3	
Male			
Early stage	43	55.1	
Middle stage	13	16.7	
Advanced stage	22	28.2	

Table 1. Continue

Variables	n	%	P
Glaucoma severity of left eye			
Woman			0.559
Early stage	61	67.8	
Middle stage	8	8.9	
Advanced stage	21	23.3	
Male			
Early stage	49	62.8	
Middle stage	11	14.1	
Advanced stage	18	23.1	

P<0.05. SMD: Senile macular degeneration, POAG: Primary open-angle glaucoma, PEG: Pseudoexfoliation glaucoma.

coma in the right eye. For this difference between the right and left eye, it is thought that other factors that could affect the right and left eyes, such as differences in blood flow at the optic nerve head, should be investigated in new studies.

In our study, there were 10 patients, six males (60.0%) and four females (40.0%), who had SMD with glaucoma type. The mean age of the patients was 72.70 ± 11.02 years. There were six patients (60.0%) with POAG and four patients (40.0%) with PEG, nine patients (90.0%) with dry-type SMD, and one patient (10.0%) with wet-type SMD. There was no correlation between age, gender, glaucoma type, and SMD type ($p > 0.05$) (Table 2).

Table 2. Correlation between type of glaucoma and type of concomitant SMD disease, gender and age variables

Variables	Gender	Age	Type of glaucoma	SMD type
Gender				
r	1			
P				
Age				
r	0.336	1		
P	0.343			
Type of glaucoma				
r	0.167	0.433	1	
P	0.645	0.211		
SMD type				
r	-0.272	0.488	-0.272	1
P	0.447	0.153	0.447	

Pearson correlation method was used to analyze the correlation between gender and age variables in patients with SMD with glaucoma. SMD: Senile macular degeneration.

When the severity of glaucoma, type of SMD, gender, and age characteristics of the patients with glaucoma and SMD were analyzed, there were four (40.0%) patients with early-stage glaucoma, two (20.0%) with intermediate stage, and four (40.0%) with advanced stage in the right eye. In the left eye, there were two (20.0%), 5 (50.0%), and three (30.0%) patients with early, intermediate, and advanced glaucoma, respectively. There was no correlation between the severity of glaucoma in the right and left eye, the type of concomitant SMD, gender, and age variables ($p > 0.05$) (Table 3).

When the lens status in the right and left eye, SMD type, gender, and age characteristics of the patients diagnosed with glaucoma. SMD were analyzed; there were seven (70.0%) patients diagnosed with pseudophakia in the right eye and three (30.0%) with phakia. In the left eye, 7 (70.0%) patients were diagnosed as pseudophakic and 3 (30.0%) as phakic. A statistically significant high-level positive correlation was found between age and lens status (Pseudophakic/Phakic) in the right eye ($p \leq 0.05$). No correlation was found between other variables ($p > 0.05$) (Table 4).

In our study, multiple linear regression analysis was performed to examine the effect of gender, age, severity of glaucoma and lens status on the diagnosis of glaucoma and SMD.

Table 3. Correlation between the severity of glaucoma in the right and left eye, type of SMD, gender and age variables

Variables	Gender	Age	Severity of glaucoma right eye	Severity of glaucoma left eye	SMD type
Gender					
r	1				
P					
Age					
r	0.336	1			
P	0.343				
Severity of glaucoma right eye					
r	-0.228	0.395	1		
P	0.526	0.258			
Severity of glaucoma left eye					
r	0.055	0.455	0.299	1	
P	0.881	0.187	0.402		
SMD type					
r	-0.272	0.488	0.373	0.356	1
P	0.447	0.153	0.289	0.312	

Pearson's correlation method was used to analyze the correlation between the severity of glaucoma in the right and left eye, the type of concomitant SMD, gender and age variables. SMD: Senile macular degeneration.

Table 4. Correlation between lens status in the right and left eye, concomitant SMD type, gender and age variables

	Gender	Age	Lens condition right eye	Lens condition left eye	SMD type
Gender					
r	1				
P					
Age					
r	0.336	1			
P	0.343				
Lens status right eye					
r	-0.167	0.660*	1		
P	0.645	0.038			
Lens status left eye					
r	0.250	0.562	0.583	1	
P	0.486	0.091	0.077		
SMD type					
r	-0.272	0.488	0.272	0.272	1
P	0.447	0.153	0.447	0.447	

Pearson correlation method was used to look at the correlation relationship between the variables of lens status in the right and left eye, type of SMD seen together, gender and age. SMD: Senile macular degeneration.

When variance inflation factor values were analyzed, it was seen that they were <10, and there was no multi-connection problem. The regression model was found to be statistically significant ($p=0.043z0.05$). This model examines the factors (fixed variables) that influence the diagnosis of glaucoma and SMD (dependent variable). These fixed variables were determined to be gender, age, right eye glaucoma severity,

left eye glaucoma severity, right eye lens status, and left eye lens status. 7.7% of the variation in the glaucoma and SMD diagnosis variable can be explained by these fixed variables. In the established model, except for the constant coefficient, other variables did not have a statistically significant effect on the diagnosis of glaucoma and SMD ($p>0.05$) (Table 5).

Discussion

Glaucoma and SMD are prevalent vision-threatening diseases whose incidence increases with advancing age. There are many common underlying mechanisms in the development of glaucoma and SMD. Mitochondrial dysfunction, inflammation, oxidative stress, and the accumulation of damaged molecules are reported as key mechanisms. The pathogenesis of SMD is not fully understood, but the currently accepted hypothesis is that metabolic and mitochondrial dysfunction are the main triggers of the disease. The pathogenesis of glaucoma is much better understood than that of SMD. It is caused by a disturbed balance between the aqueous humor production in the ciliary body and its outflow (4,7,8,14,18-20). PES is an age-related systemic disease characterized by the deposition of fibrillar protein aggregates called pseudoexfoliation fibrils on the tissue surfaces of the anterior and posterior segments of the eye. The early stage of the disease is called PES, and the more severe stage is called PEG.^[21] There was no difference in age according to gender in the glaucoma patients included in our study ($p=0.085$). About 74.99% of the patients had POAG, and 24.99% were PEG. There was no difference in the type of glaucoma and severity of glaucoma in the left eye according to gender ($p>0.05$). However, there was a statistically significant difference in the severity of glaucoma in the right eye ($p=0.037$) ($p\leq 0.05$). The number of women diagnosed with early-stage glaucoma in the right eye was higher.

SMD has emerged as a globally significant and increasingly prevalent eye disease. The prevalence of SMD steadily

Table 5. Regression analysis results

	Unstandardized coefficients		Standardised coefficients		t	Sig.	Collinearity statistics	
	B	Std. error	Beta				Tolerance	VIF
Fixed	-0.330	0.164			-2.016	0.045*		
Gender	-0.013	0.037	-0.028		-0.362	0.718	0.930	1.076
Age	0.004	0.002	0.148		1.735	0.085	0.788	1.270
Glaucoma severity right	0.010	0.025	0.033		0.389	0.698	0.774	1.293
Glaucoma severity left	0.027	0.024	0.096		1.124	0.263	0.780	1.283
Lens status right	0.023	0.051	0.044		0.444	0.658	0.593	1.685
Lens status left	0.034	0.048	0.066		0.706	0.481	0.665	1.503

Dependent variable: Diagnosis of glaucoma and SMD. $R=0.277$ $R^2=0.077$ $F=2.232$ $P=0.043$. r: Correlation coefficient, R: Multiple correlation coefficient, R^2 : Multiple coefficient of determination, Beta: Standardised B coefficient, B: Regression coefficient, Std Error: Standard error, t: Value determining the statistical significance of the relationship, Sig: Significance value, VIF: Variance inflation factor, F: F value, S: Fixed (point where it crosses the Y-axis).

increases with age, showing no significant gender differences (15,22). Glaucoma affects contrast discrimination and light/dark adaptation. SMD causes loss of contrast sensitivity, metamorphopsia and blurred vision (12). SMD affects activities requiring central vision, such as reading, writing and recognizing faces, whereas glaucoma affects activities requiring peripheral vision, such as walking and driving. As many patients have both conditions, they have a combined effect on their daily lives. Both glaucoma and SMD can cause significant limitations in the daily activities of patients and have a profound effect on their quality of life (4,14,18,23). In our study, 10 (5.95%) of 168 glaucoma patients had SMD. Of the patients with SMD, six (60%) were male and four (40%) were female. Nine (90%) had dry-type, and 1 (10%) had wet-type SMD. The mean age of the patients was 72.70 ± 11.02 years. There was no correlation between glaucoma type, SMD type, gender and age variables ($p > 0.05$). In the right eye, four (40.0%), two (20.0%) and four (40.0%) patients were diagnosed with early, intermediate and advanced glaucoma, respectively. In the left eye, two (20.0%), five (50.0%) and three (30.0%) patients were diagnosed with early, intermediate and advanced glaucoma, respectively. There was no correlation between the severity of glaucoma in the right and left eye, SMD type, gender and age variables ($p > 0.05$).

In a study by Hirvela *et al.*, (22) no association was found between SMD and glaucoma. In a study by Mergen *et al.*, (17) glaucoma was diagnosed or suspected at a significantly lower rate in patients with exudative SMD compared to non-exudative patients. Ganglion cell loss leads to retinal nerve fiber loss, causing thinning of the retinal nerve fiber layer and changes at the optic disc head (24). Aritürk *et al.* (25) found no significant difference in the neural rim, mean cup/disc ratio and peripapillary retinal nerve fiber layer thickness in the optic disc in the presence of macular degeneration compared to the control group in their studies. They stated that the coexistence of both diseases is rare, and although both diseases are independent of each other, vascular insufficiency is partially involved in their etiology. Vascular factors are important in the development of neovascular SMD. It has been reported that choroidal and retinal blood flow is decreased in patients with neovascular SMD. Ischemia and hypoxia resulting from inadequate perfusion of the choroid are thought to activate the development of angiogenesis. Angiogenesis usually causes visual loss by disrupting normal macular function (3). Zengin *et al.* (26) reported that the accumulation of pseudoexfoliative material in the walls of ophthalmic vessels affects the development of SMD, and there is a low prevalence relationship between PES and wet-type SMD. In their study, Gunes *et al.* (27) reported that PES was associated with SMD. In our study, no correlation was observed between PEG and SMD disease. In patients with

coexisting glaucoma and SMD, when gender, age, severity of glaucoma in the right and left eye, and pseudophakic and phakic status were evaluated, no statistically significant effect of these variables on the coexistence of glaucoma and SMD was observed ($p > 0.05$).

Cataracts cause blurred vision, monocular diplopia, contrast sensitivity and color vision impairment, reducing visual quality. Cataracts, glaucoma and SMD incidence increases with age (23,28). Wang *et al.*, (29) in a study of 6019 patients, reported that age-related maculopathy developed in 6.0–7.7% of aphakic patients and 0.7% of phakic patients. Klein *et al.* (30) reported that cataract surgery increased the risk of late-type age-related maculopathy. It has been reported that late SMD has an increased prevalence in patients with cataract diagnosis and cataract surgery, although the cause is unknown (31). In our study, there were 7 (70.0%) patients with pseudophakic and 3 (30.0%) with phakic diagnoses in the right and left eyes. A statistically significant high-level positive correlation was found between the status of the lens in the right eye and the age variable ($p \leq 0.05$).

This study has limitations due to its retrospective nature. The small number of patients and the information about the patients are limited to the information recorded during the patient's examination. The contribution of the study is that there are very few studies on this subject, which has remained under-researched, and the findings are consistent with previous studies.

Conclusion

Limited research has investigated the relationship between glaucoma and retinal diseases. Understanding the association between glaucoma and SMD is crucial for uncovering underlying pathological mechanisms, improving prognosis, guiding follow-up, and optimizing treatment strategies. Further studies could play a pivotal role in preventing visual loss, enhancing patients' quality of life, and decreasing the prevalence of glaucoma and SMD.

Disclosures

Ethics Committee Approval: This study was approved by the Inonu University Ethics Committee (Date: 17.12.2024, Number: 41) and conducted in accordance with the tenets of the Declaration of Helsinki.

Informed Consent: Written informed consents were obtained from all patients.

Conflict of Interest: None declared.

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The Comparison of Intracystic Hyperreflectivity in Different Macular Edema Etiologies. Is It a New Optical Coherence Tomography Biomarker?

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Abstract

Objectives: To detect the difference in internal hyperreflectivity of macular cystoid spaces in diabetic retinopathy (DR), exudative (wet) age-related macular degeneration (wet AMD), branch retinal vein occlusion (BRVO).

Methods: The medical records of the consecutive patients who were followed up from Prof. Dr. Cemil Taşcıoğlu City Hospital, from 01 April 2023 to 01 June 2023, in the retina department, have been included in this study. The mean gray value (GV) and max-min GV parameters of the cystoid spaces which were detected in the spectral domain optical coherence tomography (OCT) scans, were measured by using the ImageJ program (National Institutes of Health, Bethesda, Maryland, USA). The established diagnosis, baseline best corrected visual acuities (BCVA), OCT biomarkers such as serous macular detachment, hard exudate, hyperreflective foci and central macular thicknesses were also noted. The parameters were compared to each other regarding the different pathologies.

Results: The mean-max GV of cystoid spaces and the mean-max GV of cystoid/vitreous ratio were found to be highest in the DR, followed by BRVO, and lowest in wet AMD ($p<0.001$ and $p<0.001$; respectively). Correlation analyses revealed a positive correlation between OCT biomarkers and intracystic hyperreflectivity (ICH) ($p<0.001$, respectively). Besides, the max GV cystoid/vitreous ratio is positively correlated with the BCVA ($p<0.046$; $p=0.04$, respectively).

Conclusion: This pilot study investigates ICH in macular edema of various etiologies. The ICH was highest in the DR group, followed by the BRVO group, and lowest in the AMD group. It has been observed that there is a high correlation between ICH and OCT biomarkers. Findings support the hypothesis that ICH may reflect underlying inflammatory processes and contribute to individualized treatment approaches in retinal vascular pathologies.

Keywords: Branch retinal vein occlusion, diabetic maculopathy, diabetic retinopathy, intracystic hyperreflectivity, optical coherence tomography

Introduction

Macular edema accompanies various pathologies and is characterized by complaints of decreased vision. The main reason for the deterioration of vision in patients with DR, BRVO, and wet AMD is fluid accumulation in the macular region, which is very important in making treatment decisions (1-3).

Intraretinal fluid-containing cavities which are called cystoid spaces, pseudocysts, or at times inappropriate cysts, can arise from impairment of the inner blood-retina barrier (BRB), associated with an insufficiency in the metabolism of the Muller cells (4). Trauma, vascular, or inflammatory ocular diseases can cause disruption of the BRB and enable the fluid

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to pass to the retinal interstitium. Besides that, the localization of the cysts varies depending on whether the source is the inner BRB or the outer BRB because of the diffusion barrier function of the inner and outer plexiform layers (2).

Increased vascular hyperpermeability, disruption of BRB, and imbalance between osmotic-hydrostatic pressure in retinal vasculature caused by various underlying diseases such as DR and BRVO are the leading causes of this formation (2,5). Additionally, emerging hypoxia, oxidative stress, increased vascular leukostasis, and loss of pericytes contribute to the worsening of this situation simultaneously. One of the most prominent theories regarding the pathophysiology is the theory of increased inflammation, which holds that elevated levels of proinflammatory cytokines cause damage to BRB, vascular endothelial dysfunction, and increased vascular permeability. It has been shown in many studies that systemic and local proinflammatory cytokines such as VEGF, TNF- α , MCP-1, IL-6, and IL-8 are significantly increased in macular edema due to DR and BRVO (6,7). In addition to this, intraretinal fluids may arise from the choroidal vasculature due to the disruption of Bruch's membrane in wet AMD (8).

With the introduction of OCT in clinical practice, ophthalmologists can recognize the structural features of macular edema. By courtesy of this, several OCT biomarkers have been identified for many diseases, particularly for DR, such as intraretinal cyst (IRC), disorganization of retinal inner layers (DRIL), external limiting membrane (ELM)/ellipsoid zone (EZ) integrity, retinal hyperreflective foci (HRF), and serous macular detachment (SMD) (9). It has been shown in various studies that these biomarkers, detected by macula OCT, can be used to determine the type of intravitreal injection and that some of these biomarkers regress with an intravitreal steroid injection due to their anti-inflammatory effect (7,10,11).

The presence of intracystic hyperreflectivity is another finding detected by OCT in patients with CME. The contents of some cysts were found to be more hyperreflective compared to other cysts on OCT, and this condition was previously named a solid cyst (12). Various theories have been put forward regarding the content of cysts with this reflectivity, and it has been suggested that they may be blood, inflammatory end products or macrophages, and these theories have been tried to be confirmed by multi-modal imaging (13,14). However, none of these possible theories has yet been proven conclusive.

There are a few reports about intracystic hyperreflectivity in the literature but they all define the hyperreflective cyst with the help of trained individuals and compared with other findings, accompanied by the presence or absence of intracystic hyperreflectivity in a selected single disease, such as DME or BRVO. However, there are no reports regarding

the distribution and measurement of cystic hyperreflectivity in different macular edema etiologies. The aim of the current study was to investigate whether intracystic hyperreflectivity varies in different cystic edema etiologies, in order to highlight the pathogenesis of this clinical entity. With this purpose, we measure the intracystic hyperreflectiveness in DR, BRVO, and wet AMD patients to define the association between this value and the grade of inflammation; also find out the benefit of the cyst internal hyperreflectivity in predicting prognosis in such macular edema and to introduce intracystic hyperreflectivity as a new OCT biomarker.

Methods

The study was carried out in accordance with the tenets of the Declaration of Helsinki and ethical approval was obtained from the Institutional Ethical Board of Prof. Dr. Cemil Taşcıoğlu City Hospital in İstanbul (date: 19.02.2024, no: 24). Written informed consent was taken from all individual participants.

In our study, we studied the medical records of 172 eyes of 152 patients who were followed up from 01 April 2023 to 01 June 2023 in the retina department of Prof. Dr. Cemil Taşcıoğlu City Hospital. All consecutive patients admitted to our clinic between 01 April 2023 and 01 June 2023, who have been suffering from macular edema due to one of the following diseases: DR, BRVO, wet AMD, were included. All patients with these features within the specified date ranges were considered to have passed the preliminary criteria for the study. After that, diagnosis, age, and BCVA were noted from patients' files and macula OCT images captured by using SD-OCT (HRA-Spectralis, Heidelberg Engineering-Germany) were collected. Phacic patients, patients with files containing inadequate data, previous vitrectomy history, low-quality OCT images (Q score lower than 20) due to corneal opacity or vitreous opacity, macular edema without cyst formation in OCT images, patients with macular ischemia detected by FFA, and patients with two different etiologies simultaneously causing macular edema were excluded from the study.

Initially, OCT biomarkers such as SMD, hard exudate, number of HRF in macular OCT sections were evaluated and noted by two independent specialists before hyperreflectivity measurements. The presence of HRF was graded according to the range of the number of HRF detected in OCT sections (1-10; 11-20, ≥ 21). Central macular thickness (CMT) of each patient was also recorded. Subsequently, 128-bit images, which were selected so that the cyst appearance was in the 3x3 mm area of the central macula, were obtained (Shown in Fig. 1). For quantitative measurement of hyperreflectivity in cysts, images of the foveal median section -obtained in raster scan mode- were imported to Image J

software. After that, the largest cysts' borders were manually selected with the help of the tools integrated into Image J by two separate ophthalmology specialists independently

(Shown in Fig. 2a and Fig. 2b). Interobserver variability was evaluated by comparing the two observers' measurements statistically ($p=0.287$, $p=0.361$, respectively, Student's t-test).

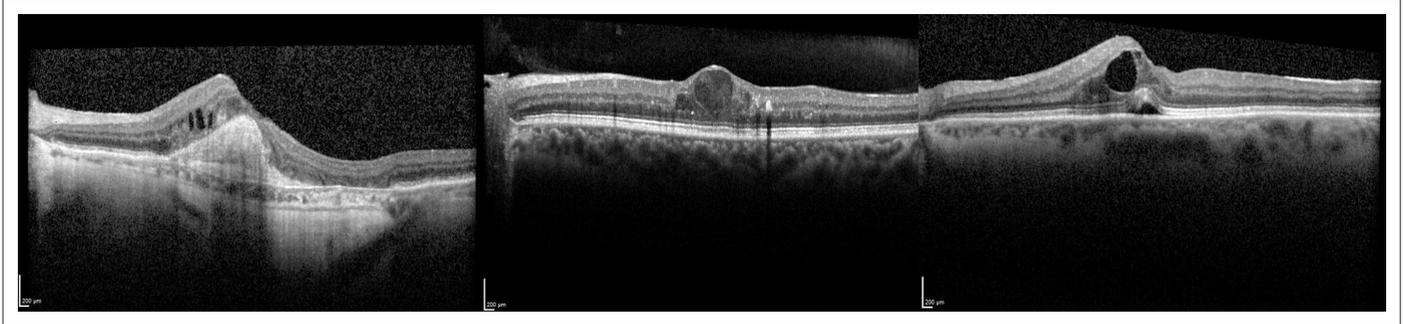


Figure 1. Example of cystoid spaces in macula without intracystic hyperreflective material in wet age-related macular degeneration (left side), cyst with intracystic hyperreflective material in diabetic macular edema (middle) and cystoid space appearance in branch retinal vein occlusion.

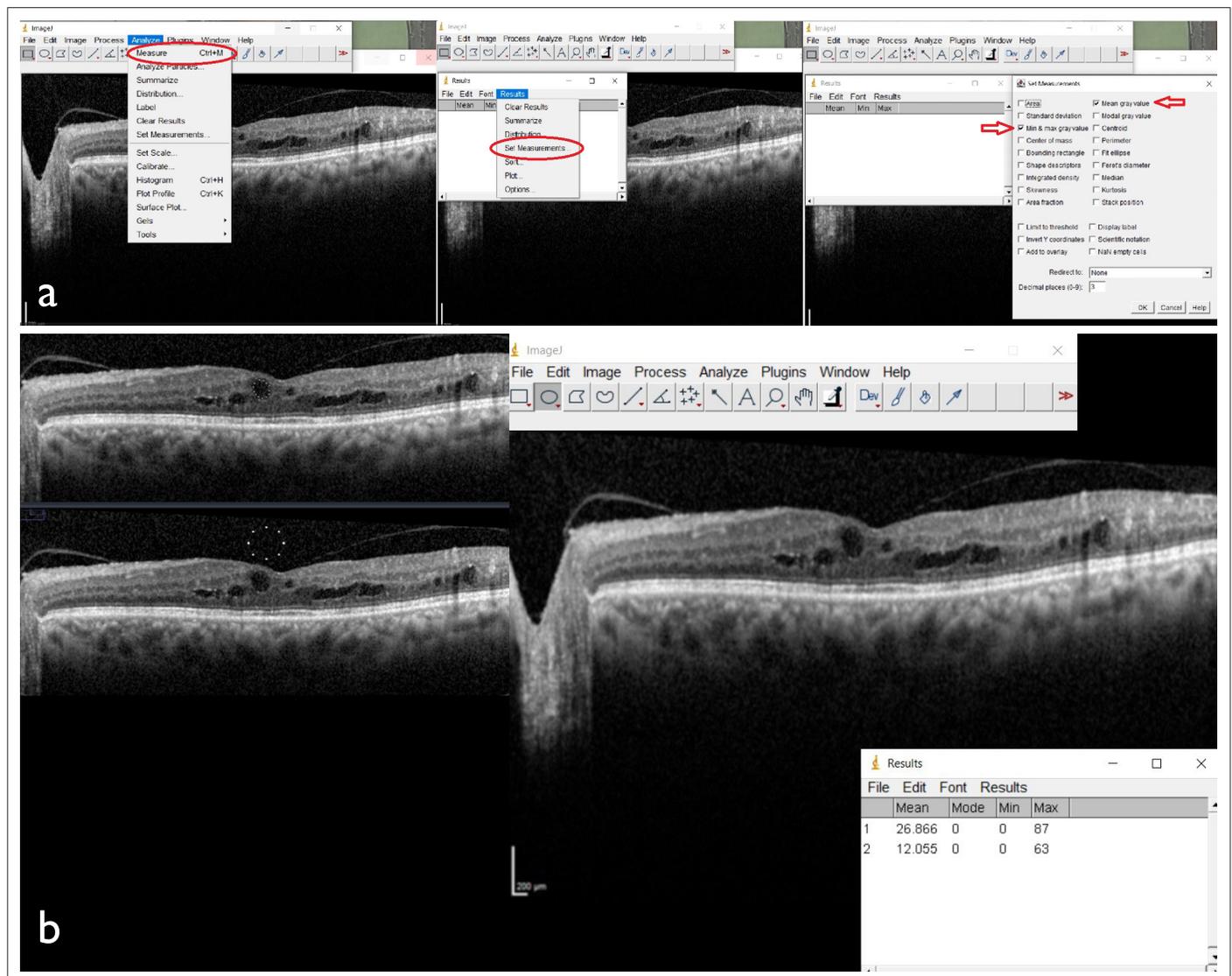


Figure 2. (a) Parameter selection settings before the measurements, (b) Example of cyst border and randomly chosen vitreous area manually selection and gray value measurements with the help of the tools integrated into Image J software.

Intraobserver variability was assessed by looking at the coefficient of variance (% CV). CV was calculated by using the following formula: $CV = SD / \text{mean} * 100$. The first observer's CV was 14%-15%, and the second observer's CV was 12%-14%.

The mean level of gray value, mode level of gray value, maximum level of gray value, and minimum level of gray value were measured inside the cysts. For each pixel, the program assigns a nominal gray value from its own scale in bit type, and as this value increases, the color of the pixel approaches white, and as this value decreases, it approaches black.

Considering that it will be a reference point against contrast and brightness differences that occur at the time of examination, all of these measurements were performed for the prefoveal vitreous area adjacent to the selected cyst which was identified in each patient's OCT images. The results of two different measurements that the specialists made were averaged for all values and noted. Afterward, intracystic values were compared to values of the selected vitreous region, and "Ratio mean gray value (RATmeanGV)", "Ratio maximum gray value (RATmaxGV)", "Ratio minimum gray value (RATminGV)" were calculated, and comparisons were made for each of these calculations.

These calculations and measurements were recorded by using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 23.0, IBM Corp., Armonk, NY, USA) program for statistical analysis. The variables were investigated using histograms and probability plots, and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Descriptive analyses were presented using means and standard deviations for normally distributed variables. One-way ANOVA was used to compare these parameters. Kruskal-Wallis tests were conducted for those variables that were not normally distributed. The Levene test was used to assess the homogeneity of the variances. An overall p-value of less than $p < 0.05$ was considered to show a statistically significant result. When an overall significance was observed, pairwise post-hoc tests were performed using Tukey's test. We performed Spearman and Pearson tests for the correlation analysis, depending on whether it was normally distributed or not.

Results

In this study, 172 eyes of 152 patients meeting these criteria were classified according to diagnoses: 40 eyes in the wet AMD group, 88 eyes in the DR group, and 44 eyes in the BRVO group. There were 83 (%48) male and 89 (%52) female patients. The mean age was 66.0 ± 8.0 for the DR group, 78.4 ± 8.4 for the wet AMD group, and 64.9 ± 10.6 for the BRVO group. The CMT was measured as 376.1 ± 96 for the DR

group, 430.6 ± 270.8 for the BRVO group, and 408.5 ± 179.4 for the wet AMD group. All the demographic findings, in addition to the central macular thickness, are summarized in Table 1. Mean durations of macular edema were 10.43 ± 8.07 months for the wet AMD group, 8.87 ± 6.50 months for the DR group and 7.85 ± 5.56 months for the BRVO group. The average of previous injection numbers was 5.95 ± 3.78 for the wet AMD group, 4.26 ± 2.66 for the DR group and 3.56 ± 1.70 for the BRVO group. The mean time since the last intravitreal intraocular injection was 1.80 ± 0.79 months for the AMD group, 2.05 ± 0.91 months for the DM group, and 2.36 ± 1.33 months for the BRVO group.

As expected, it was determined that there was no statistically significant difference between the groups in the maximum gray value (IVmaxGV), minimum gray value (IVminGV), or mean gray value (IVmeanGV) measurements of the selected vitreous area, which was taken as the reference point in each OCT section (Table 2).

As a result of the measurements, the mean gray value of intracystic space (ICmeanGV) was significantly higher in the DR group (57.43 ± 28.97) than in the other groups and followed by the BRVO group (45.98 ± 34.57), at the very least in the wet AMD group (36.28 ± 19.19 , $p < 0.001$). The DR group (112.68 ± 36.61) had the highest maximum gray value of intracystic space (ICmaxGV), followed by the BRVO group (100.73 ± 38.79) and finally the wet AMD (82.55 ± 31.72) group ($p < 0.001$). Similarly, RATmaxGV was found to be highest in the DR group (1.59 ± 0.73), second highest in

Table 1. All demographic findings and central macular thickness

Diagnosis	Age	BCVA (logMAR)	CMT
DR	66.0 ± 8.0	0.5 ± 0.5	376.1 ± 96
BRVO	64.9 ± 10.6	1.0 ± 0.7	430.6 ± 207.8
wet AMD	78.4 ± 8.4	1.1 ± 0.5	408.5 ± 179.4
p	< 0.001	0.23	< 0.001

DR: Diabetic Retinopathy; BRVO: Branch Retinal Vein Occlusion; AMD: Age-Related Macular Degeneration; BCVA: Best corrected visual acuity; CMT: Central macular thickness.

Table 2. Gray value measurements of selected vitreal areas as a reference point

Measurement	DR	BRVO	wet AMD	p
IVmeanGV	20.9 ± 10.1	20.4 ± 6.6	22.6 ± 12.28	0.85
IVmaxGV	77.2 ± 25.5	77.3 ± 19.3	79.4 ± 29	0.98
IVminGV	0	0	0	

IVmeanGV: Intravitreal mean gray value; IVmaxGV: Intravitreal maximum gray value; IVminGV: Intravitreal minimum gray value; DR: Diabetic Retinopathy; BRVO: Branch Retinal Vein Occlusion; AMD: Age-Related Macular Degeneration.

the BRVO group (1.39 ± 0.78), and lowest in the wet AMD group (1.08 ± 0.35) and these findings are statistically significant ($p < 0.001$). Likewise, the RATmeanGV value was again found to be highest in the DR group (3.26 ± 2.16), followed by the BRVO (2.66 ± 2.75) and the wet AMD (1.85 ± 1.33) groups, respectively. Afterward, statistical analyses show, in the DR group, a significant positive correlation between the BCVA and RATmeanGV-RATmaxGV. (RATmeanGV $p < 0.001$ CC: 0.3, RATmaxGV $p: 0.046$ CC: 0.2) For the BRVO group; RATmaxGV has to be found significantly positively correlated with BCVA. ($p = 0.04$, CC: 0.5) In all measurements, IC-

minGV, IVminGV, and RATminGV were not significant between groups (Table 3).

Correlation analyses between gray value measurements and OCT biomarkers have shown that ICmeanGV, ICmaxGV, ICminGV value was statistically significantly correlated in a positive manner with the presence of SMD, hard exudate and the number of HRF. On the contrary, it was observed that there was no statistically significant correlation between threshold measurements, IVmeanGV and IVmaxGV, and biomarkers. Correlation coefficients and p-value between these groups have been summarized in Table 4.

Discussion

The current study is a pilot study that measured intracystic hyperreflectivity in cystoid spaces in different pathologies and found that the intracystic hyperreflectivity was highest in DR, followed by BRVO, and lowest in wet AMD. Additionally, our study first to assess a high positive correlation between defined OCT biomarkers and elevated intracystic reflectivity. Therefore, we hypothesize that intracystic hyperreflectivity correlates with and indicates the inflammatory status.

In OCT images, fluid accumulations within the retina are generally defined as cystoid spaces located between different layers of the retina. The imbalance between fluid mechanisms can be explained by increased transudation and exudate in terms of inflow and by the deterioration in Müller cells and retina pigment epithelium (RPE) functions at the cellular level in terms of outflow. When the diseases we examined in our study are compared, the edema pathogenesis that comes to the fore in DME and BRVO is mostly cytotoxic edema (intracellular swelling) and vasogenic edema, but on the other hand, in wet AMD, the main mechanism is vasogenic edema due to increased vascular permeability in neovascularization (2,4,6,7). Berlin et al. (15) stated that hyperreflective cystoid spaces in OCT images of AMD patients can contain higher amounts of exudative materials such as lipids, proteins, and blood components, suggesting that increased reflectivity is caused by surface lipids, high-molecular-weight cellular components, and transport lipoproteins. In our study, although the intracystic reflectivity parameters (ICmeanGV, ICmaxGV, RATmaxGV) were lowest in AMD eyes, this can be attributed to the degenerative and serous nature of the cystoid spaces typically seen in AMD, which are less protein-rich and contain fewer cellular residues. Conversely, in DME and BRVO, the breakdown of the blood-retina barrier and cytotoxic edema can result in an acute vascular leakage and the accumulation of proteinaceous, lipid-rich, and cellular material, explaining the higher reflectivity measured in these groups. We believe that, although this hyperreflective pattern may also be observed in certain AMD cases, its overall prevalence is much lower compared to DME and BRVO, and this difference in frequency likely accounts for

Table 3. Intracystic gray values and comparison results of intracystic measurements to values of the selected vitreous region

Measurement	DR group	BRVO group	wet AMD	p
ICmeanGV	57.4±29	46±34.6	36.3±19.2	<0.001*
ICmaxGV	112.7±36.6	100.7±38.8	82.5±31.7	<0.001*
ICminGV	0	0	0	
RATmeanGV	3.3±2.1	2.7±2.7	1.8±1.3	<0.001*
RATmaxGV	1.6±0.7	1.4±0.8	1.08±0.3	<0.001*
RATminGV	0	0	0	

ICmeanGV: Intracystic mean gray value; ICmaxGV: Intracystic maximum gray value; ICminGV: Intracystic minimal gray value; RATmeanGV: Ratio mean gray value; RATmaxGV: Ratio maximum gray value; DR: Diabetic Retinopathy; BRVO: Branch Retinal Vein Occlusion; AMD: Age-Related Macular Degeneration.

Table 4. Results of correlation analysis between gray value measurements and OCT biomarkers

	SMD	Hard exudate	HRF
ICmeanGV	p<0.001 r: 0.320	p<0.001 r: 0.442	p<0.001 r: 0.641
ICmaxGV	p<0.001 r: 0.335	p<0.001 r: 0.407	p<0.001 r: 0.550
ICminGV	p<0.001 r: 0.287	p<0.001 r: 0.427	p<0.001 r: 0.554
RATmeanGV	p<0.001 r: 0.289	p<0.001 r: 0.421	p<0.001 r: 0.591
RATmaxGV	p<0.001 r: 0.364	p<0.001 r: 0.471	p<0.001 r: 0.601
IVmeanGV	p: 0.691 r: -0.031	p: 0.776 r: -0.022	p: 0.824 r: -0.017
IVmaxGV	p: 0.395 r: -0.065	p: 0.381 r: -0.067	p: 0.464 r: -0.061

SMD: Serous Macular Detachment; HRF: Hyperreflective foci; ICmeanGV: Intracystic mean gray value; ICmaxGV: Intracystic maximum gray value; ICminGV: Intracystic minimal gray value; RATmeanGV: Ratio mean gray value; RATmaxGV: Ratio maximum gray value; IVmeanGV: Intravitreal mean gray value; IVmaxGV: Intravitreal max gray value.

the higher mean reflectivity values detected in DR and BRVO groups. Therefore, we believe that the mechanism proposed by Berlin et al. (15) should not be restricted solely to AMD but may also apply to the DR and RVO groups, where similar exudative and inflammatory mechanisms are more dominant. We advocate the idea that the sources of these materials are the acute extravasation of large molecules from compromised vessels in early disease stages, and the cytoplasmic remnants of degenerated retinal cells subjected to chronic mechanical stretching from recurrent cytotoxic edema during later stages.

Quan-Yong Yi et al. (16) indicated that by comparing diseases caused by macular edema, such as central retinal vein occlusion (CRVO), BRVO, wet AMD, and DR with each other based on inflammatory cytokine levels in aqueous humor, DME patients had the highest level of inflammation, after CRVO patients. According to our study, hyperreflectivity values of inner cystoid spaces were higher in DR patients among the other etiologies included in this comparison. To our knowledge, our study is the first in the literature to detect nominally and compare the hyperreflectivity of the cystoid spaces in various diseases caused by macular edema. These findings strongly suggest that internal hyperreflectivity of cystoid spaces was correlated with disease inflammation levels.

Optical coherence tomography is indispensable for distinguishing the basis of structure in macular edema and also for detecting the evaluation of edema after treatment (3,17,18). Thanks to these opportunities, relationships between the disease courses and the treatment modality could be determined; in this way, several biomarkers associated with inflammation were identified (10,19). Several studies show that in these biomarkers' presence, there is an increased necessity for a repeated intravitreal anti-vascular endothelial growth factor (Anti-VEGF) and steroid injection. Moreover, for diabetic macular edema (DME) patients intracystic hyperreflective material emerged in approximately in 7. month of evaluation of macular edema appearance in their OCT and the patients who had this indication has more persistent DME appearance in their follow-up. Additionally, patients who had ICHRM had received an increased number of intravitreal injections and in these patients, findings such as EZ-ELM defects and inner segment-outer segment junction layer disruption were more common than in patients without intracystic hyperreflective material (ICHRM). Because of this interrelation, after hyperreflective material resolution, final visual acuity has been found to decrease further than in patients with low-reflective cysts (15). According to this study, we hypothesize that the ICHM is a new OCT biomarker that appears in the early stages of DME pathogenesis. In chronic stages, cysts transform into cystoid degeneration and this may explain the correlation between ICHRM and BCVA in our study.

Possible theories run about the cyst's containing material and pathophysiology which causes a hyperreflective appearance in OCT (13,20-21). Most prominent ones defend the idea that cysts containing blood, inflammation end products, or fibrinoid material increase the reflectivity of cysts; however, the definitive answer is still unclear. Besides, Kashani et al. (22) have mentioned in their study that fibrin or exudative material located within and around the cysts can cause a high level of reflectance in OCT and optic coherence tomography angiography (OCTA) images. Our study demonstrates that the diseases have the same order in the level of Aqueous inflammation and reflectivity measurements such as ICmeanGV, ICmaxGV, RATmaxGV, and RATmeanGV. In addition, our study has shown that there is a statistically positive correlation between the ICmeanGV, ICmaxGV, ICminGV, RATmeanGV and RATmaxGV values, which indicate an increase in intracystic reflectivity and OCT biomarkers that have been determined to be correlated with increased inflammation by other studies. Hence, these findings strongly suggest that the contents located within the cystoid spaces are more likely to be inflammation-related, such as inflammation and product or fibrinoid material, rather than red blood cell (RBC) or low-weighted serum proteins.

It is important to note that our study has limitations. Initially, these findings obtained one cyst of each section which was manually selected, and in the future, automatic selection of all cysts in macular OCT images by artificial intelligence improves the validity of measurements. Secondly, our study may have been a low level of evidence base. The hyperreflective material inside cysts can be RBCs or lipids. Also, our study shows the correlation between baseline BCVA and ICHRM hence, it would be more accurate to evaluate the changes during long-term follow-up in order to predict the prognosis of the ICHRM sign. Our results should be supported by studies with higher evidence investigating the relationship between cytokines in the anterior chamber and intracystic hyperreflectivity. In the future, exact materials can be identified in histopathological *in vitro* studies with animal models.

Nowadays, multiple treatment modalities have been used against macular edema. These include, most prominently, intravitreal anti-VEGF injection, intravitreal steroid implants, and laser photocoagulation. There are a variety of different strategies and methods to bring patients and these treatments together. However, some patients with macular edema do not respond well and persist with these first-line treatments. In DME patients, refractory or persistent macular edema prevalence estimates up to %50 and patients are referred to a different therapeutic option (23). As the time between choosing the right agent and non-response to the given treatments increases, irreversible damage occurs to

the macula and vision decreases permanently. Therefore, we believe that it is important to identify new generation OCT biomarkers, such as ICHRM, to show their response to the agents used in treatment and their effects on prognosis; to ensure that the right patient is administered the appropriate treatment agent earlier.

Conclusion

Our study reveals that intracystic hyperreflectivity was highest in the DR group, followed by BRVO patients and lastly wet AMD patients. As has been determined, this ranking appears to be correlated with the degree of inflammation of the diseases. Furthermore, this study has shown a high positive correlation between intracystic reflectivity and OCT biomarkers. Considering this, in a disease with high inflammation levels, the intracystic hyperreflectivity value increases and from our perspective, intracystic hyperreflectivity should be positioned as a new inflammatory OCT biomarker. Overall, considering that inflammation is one of the main factors in the formation of DME. Patients with OCT biomarkers like ICHRM, because of the effect due to the high inflammation burden, can respond favorably to intravitreal steroid therapy with anti-VEGF treatment. Hence, earlier and more effective results can be obtained at macular edema resolution.

Disclosures

Ethics Committee Approval: This study was approved by the Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committee (Date: 19.02.2024, Number: 24) and conducted in accordance with the tenets of the Declaration of Helsinki.

Informed Consent: Written informed consents were obtained from all patients.

Conflict of Interest: None declared.

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Consecutive Esotropia Following Exotropia Surgery: Possible Risk Factors, Changes in the Angle of Deviation, and Esotropia Rates

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Abstract

Objectives: To evaluate the risk factors associated with consecutive esotropia, as well as the changes in deviation angle and the prevalence of esotropia in patients who underwent surgery for exotropia.

Methods: The records of patients with basic-type exotropia who underwent either bilateral lateral rectus recession (symmetric surgery) or unilateral lateral rectus recession combined with medial rectus resection (asymmetric surgery), and who were followed for at least one year, were retrospectively reviewed. Preoperative, early postoperative, and late postoperative findings were analyzed for both groups: symmetric surgery (Group 1) and asymmetric surgery (Group 2). Consecutive esotropia was defined as ≥ 5 prism diopters of esotropia at either distance or near fixation.

Results: Of the 114 patients included, 52 (46%) were female and 62 (54%) were male. The mean age at surgery was 20.42 years in Group 1 and 15.59 years in Group 2 ($p>0.05$). Group 2 had significantly lower visual acuity, stereopsis, and fusion rates, and higher rates of amblyopia and anisometropia compared to Group 1. At the final follow-up examination, the deviation angles decreased significantly in both groups ($p<0.001$), and the prevalence of consecutive esotropia reduced from 17% to 7% in Group 1 and from 30% to 19% in Group 2 ($p=0.031$). While stereopsis did not significantly improve postoperatively in Group 1, increased significantly in Group 2 ($p=0.031$). Fusion improved significantly in both groups ($p<0.001$). Refractive error, anisometropia, preoperative and early postoperative deviation angles, and the extent of surgery were identified as significant risk factors for consecutive esotropia ($p<0.05$).

Conclusion: Although initial overcorrection following exotropia surgery tends to decrease over time, patients with high preoperative and early postoperative deviation angles, high refractive errors, anisometropia, and greater surgical amounts should be carefully monitored for the development of consecutive esotropia.

Keywords: Asymmetric surgery, consecutive esotropia, diplopia, exotropia, symmetric surgery

Introduction

Consecutive esotropia (ET) is a well-known form of strabismus that develops after surgical correction of exotropia (XT), although it is less common than consecutive XT observed after ET surgery (1). In most cases, consecutive ET arises following surgery for XT, but in rare instances, a spon-

aneous conversion from an initially fixed XT to consecutive ET may occur (2,3).

The incidence of consecutive ET after XT surgery varies between 2% and 25%, depending on diagnostic criteria such as 5 prism diopters (PD) or 10 PD, study population characteristics, and differences in follow-up duration (4-10). Several risk factors for the development of consecu-

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tive ET have been identified, including large preoperative deviation angles, amblyopia, high myopia, poor stereopsis, high accommodative convergence to accommodation ratio, younger age at surgery, excessive correction, and increased tonic convergence (4,5,7-10). Recognition of these factors is essential for proper surgical planning and achieving optimal outcomes.

Beyond these risk factors, even if consecutive ET develops after XT surgery, cases generally exhibit a gradual shift in the deviation angle with a tendency toward XT and a reduction in ET. Therefore, a slight initial overcorrection is often considered desirable to counteract this exodrift (11,12).

This study aimed to evaluate possible risk factors for the development of consecutive ET and to assess postoperative changes in deviation angles, as well as the incidence of ET following XT surgery.

Methods

This study adhered to the principles of the Declaration of Helsinki. As this was a retrospective study, ethics committee approval was waived. Written informed consent was obtained from the patients or their guardians before surgery.

The medical records of patients with basic-type XT who underwent either bilateral lateral rectus recession (BLR, symmetric surgery) or unilateral lateral rectus recession combined with medial rectus resection on the same eye (RR, asymmetric surgery) between July 2001 and December 2023 were reviewed retrospectively. Only patients with basic-type XT and a minimum follow-up of one year were included. Basic-type XT was defined as a distance deviation within 10 PD of the near deviation.

Patients with XT secondary to organic pathologies, those who had surgery on more than two muscles, strabismus surgery for consecutive ET, and who had botulinum toxin injection, vertical deviation, or inferior oblique overaction, history of any neurologic diseases, more than 10 PD distance-near disparity, and inadequate cooperation for examination were excluded from the study.

All patients underwent comprehensive ophthalmologic evaluations, including visual acuity, stereopsis and fusion, eye movements and ocular alignment assessments, cycloplegic refraction, slit-lamp biomicroscopy, and fundus examination with a +90 diopter (D) indirect lens. The examination findings of symmetric (Group 1) and asymmetric (Group 2) surgery cases operated for XT were investigated and compared before and after surgery.

Manifest refraction was assessed using the autorefractometer (Topcon KR-8100, Japan). The spherical equivalents (SE, spherical error plus half the cylindrical component) of the refractive errors of both eyes were used. Myopia was recorded as negative, hypermetropia as positive values.

Amblyopia was diagnosed as a difference of two lines or more in Snellen visual acuity between two eyes or best corrected visual acuity lower than 0.80. Anisometropia was defined when the two eyes had a difference of SE of 1.0 D or more. Spectacles were prescribed for refractive errors greater than 1.0 D, and occlusion therapy was initiated when indicated, based on patient age and amblyopia severity.

Deviation angles were measured by the alternate prism cover test using an accommodative target with refractive correction for near and distance fixation in the primary position. Stereopsis and fusion were tested with the Titmus fly (Stereo Optical, Chicago, IL, USA) and Worth 4-dot tests at distance, respectively. Stereopsis of ≤ 100 arc/seconds was considered positive; fusion was recorded as present if 4 dots were perceived.

Surgery was indicated for patients with a manifest XT of ≥ 18 PD at maximum deviation. Surgical planning was based on the presence of alternation, amblyopia, and the maximum deviation angle. The amount of surgery was determined using Wright's (13) and Parks's (14) surgical tables, in conjunction with the surgeon's experience. General or local anesthesia was administered based on the patients' cooperation. All procedures were performed by a single surgeon. The conjunctiva was opened at the limbus, and the muscles were operated on using standard surgical steps.

Patients were examined postoperatively on the first day, one week, one month, and at subsequent intervals until at least 12 months. Evaluations included measurement of deviation angles, diplopia assessment, sensory testing, and potential risk factors contributing to the development of ET. Consecutive ET was defined as ≥ 5 PD of ET (-) at either near or distance fixation.

Patients with diplopia and consecutive ET were managed initially with alternate or monocular occlusion therapy, either part-time or full-time, until diplopia resolved. Residual hyperopia, when present, was fully corrected. For patients with consecutive ET > 15 PD or persistent diplopia beyond one month, base-out prism glasses were prescribed. Surgical correction for ET was considered only in cases with > 10 PD of ET persisting for at least six months.

All data were analyzed using the Statistical Package for Social Sciences (SPSS) version 25.0 (IBM Corp., Armonk, NY, USA). Categorical variables were summarized as frequencies and percentages, while numerical variables were presented as mean \pm standard deviation (SD). Statistical tests included Pearson Chi-square, Mann-Whitney U, McNemar, Wilcoxon Signed-Rank, and Fisher's exact tests. A comparative analysis of both groups was conducted regarding their findings during preoperative assessments and early postoperative evaluations, performed at one week and at the final follow-up. Variables were examined at a 95% confidence interval, and p -values < 0.05 were considered statistically significant.

Results

A total of 114 patients were included in the study. In Group 1, 26 patients (43%) were female and 34 (57%) were male, while Group 2 consisted of 26 females (48%) and 28 males (52%), with no statistically significant difference between the groups ($p=0.606$ and $p=0.510$, respectively).

The mean age at surgery was 20.42 ± 15.11 years (range: 5-41) in Group 1 and 15.59 ± 6.99 years (range: 5-35) in Group 2 ($p=0.510$). The mean postoperative follow-up period was 38.27 ± 40.27 months (range: 12-156) in Group 1 and 34.48 ± 33.61 months (range: 12-167) in Group 2, showing no significant difference ($p=0.973$).

The mean preoperative near deviation was significantly lower in Group 1 (28.87 ± 8.23 PD, range: 18-45) compared to Group 2 (37.85 ± 7.86 PD, range: 20-53) ($p<0.001$). Similarly, the preoperative distance deviation was 33.60 ± 6.93 PD (range: 20-53) in Group 1 and 41.15 ± 6.94 PD (range: 30-50) in Group 2 ($p<0.001$). Group 2 also had significantly higher rates of amblyopia, anisometropia, and preoperative diplopia, while Group 1 demonstrated better baseline visual acuity, stereopsis, and fusion rates ($p<0.05$).

Early postoperative consecutive ET was observed in 10 patients (17%) in Group 1 and 16 patients (30%) in Group 2 ($p=0.100$). At the final follow-up, the prevalence of consecutive ET decreased to 4 patients (7%) in Group 1 and 10 patients (19%) in Group 2 ($p=0.054$). Although not statistically significant, both early and late postoperative consecutive ET rates were consistently higher in Group 2 than in Group 1 ($p>0.05$).

The mean initial and final postoperative near deviation angles in Group 1 were -0.87 PD and 3.47 PD, respectively, while in Group 2 they were -4.04 PD and -0.81 PD. For distance deviation, Group 1 demonstrated -0.93 PD initially and 5.23 PD at the last follow-up, whereas Group 2 showed -2.44 PD initially and 0.44 PD at the last follow-up. Both groups exhibited a significant reduction in deviation angles over time ($p<0.001$).

Compared to before surgery, in Group 1, there was no significant improvement in stereopsis rates postoperatively ($p=0.500$). Conversely, Group 2 demonstrated a significant postoperative increase in stereopsis ($p=0.031$). Fusion rates improved significantly in both groups ($p<0.001$).

The preoperative frequency of diplopia was higher in Group 1 (17%) compared to Group 2 (4%) ($p=0.024$). At the final follow-up, the diplopia rate in Group 1 decreased, but not significantly to 7% ($p=0.180$). In contrast, Group 2 experienced a significant increase in diplopia from 4% preoperatively to 19% postoperatively, which was strongly associated with the development of consecutive ET ($p=0.039$).

When the possible risk factors for the development of consecutive ET after XT surgery were examined, refractive

Table 1. Demographic characteristics and preoperative findings of patients who underwent symmetric (Group 1) and asymmetric (Group 2) surgery for exotropia

	Group 1 (n=60)	Group 2 (n=54)	P
Sex			
Female	26 (43%)	26 (48%)	0.606*
Male	34 (57%)	28 (52%)	
Age at surgery (years)	20.42 ± 15.11 (5-41)	15.59 ± 6.99 (5-35)	0.510**
Follow-up (months)	38.27 ± 40.27 (12-156)	34.48 ± 33.61 (12-167)	0.973**
Refraction (diopter)	0.50 ± 1.62 (-5.25/+4.25)	-0.28 ± 1.78 (-5.50/+2.63)	0.014**
Visual acuity (Snellen)	0.97 ± 0.09 (0.65-1.00)	0.89 ± 0.16 (0.45-1.00)	0.008**
Near deviation angle (PD)	28.87 ± 8.23 (18-45)	37.85 ± 7.86 (20-53)	<0.001**
Distance deviation angle (PD)	33.60 ± 6.93 (20-53)	41.15 ± 6.94 (30-50)	<0.001**
Amblyopia	6 (10%)	18 (33%)	0.002*
Anisometropia	8 (13%)	20 (37%)	0.003*
Diplopia	10 (17%)	2 (4%)	0.024*
Stereopsis	50 (83%)	20 (37%)	<0.001*
Fusion	22 (37%)	10 (16%)	0.031*

PD: Prism diopter, *Pearson Chi-Square Test, **Mann-Whitney U Test

error, anisometropia, preoperative and early postoperative deviation angles, and surgical amounts were found to be significant ($p<0.05$).

Demographic characteristics, preoperative and postoperative findings, sensorial situation, and the possible risk factors for the development of ET are shown in Tables 1, 2, 3, 4, and 5.

Discussion

The optimal degree of initial overcorrection required to achieve long-term stability after XT surgery remains a matter of debate. It is generally accepted that a mild early postoperative overcorrection may be beneficial because of the natural tendency toward postoperative exodrift. Recommended levels of early overcorrection vary in the literature, ranging from 6 PD to 20 PD (11,12,15,16). However, overcorrection of 20 PD or more on the first postoperative day has been associated with a substantially increased risk of developing consecutive ET (4). Recent studies also suggest that initial overcorrection may not always have long-term benefits, particularly with respect to motor and sensory outcomes in visually immature children (1,8,17). In this study, both groups demonstrated a significant decrease in deviation angles and in the rates of

Table 2. Postoperative findings of patients who underwent symmetric (Group 1) and asymmetric (Group 2) surgery for exotropia

	Group 1 (n=60)	Group 2 (n=54)	P
Near deviation angle (PD)			
Early	-0.87±3.85 (-16/6)	-4.04±7.29 (-25/4)	0.024*
Final	3.47±5.21 (-6/10)	-0.81±6.98 (-18/6)	0.002*
Distance deviation angle (PD)			
Early	-0.93±4.59 (-18/8)	-2.44±6.67 (-25/10)	0.207*
Final	5.23±6.47 (-8/25)	0.44±5.72 (-16/10)	0.001*
Consecutive esotropia			
Early	10 (17%)	16 (30%)	0.100**
Final	4 (7%)	10 (19%)	0.054**
Stereopsis	52 (87%)	26 (48%)	<0.001**
Fusion	48 (80%)	24 (44%)	<0.001**

PD: Prism Diopter; *Mann-Whitney U test; **Pearson Chi-Square Test.

consecutive ET between the early and final postoperative evaluations. Despite nonsurgical interventions and occasional spontaneous resolution, persistent ET was observed in 7% of patients in the BLR group and 19% of patients in the RR group at the final follow-up. These findings indicate that initial over-

Table 5. Possible risk factors for the development of consecutive esotropia following exotropia surgery

	P
Age at surgery (years)	0.510*
Refraction (diopter)	0.014*
Amblyopia	0.489**
Anisometropia	0.020**
Preoperative deviation angle (PD)	
Near	<0.001*
Distance	<0.001*
Surgery type	0.054***
Symetric	
Asymmetric	
Amount of surgery (mm)	<0.001*
Preoperative binocular vision	
Stereopsis	0.128***
Fusion	0.343**
Postoperative first deviation angle (PD)	
Near	<0.001*
Distance	<0.001*

PD; Prism Diopter; *Mann-Whitney U Test; **Fisher Exact Probability Test; ***Pearson Chi-Square Test.

correction does not consistently predict long-term outcomes, a conclusion supported by Choi et al. (18).

Table 3. Early and Final consecutive esotropia rates and deviation angles of patients who underwent symmetric (Group 1) and asymmetric (Group 2) surgery for exotropia

	Group 1 (n=60)		P	Group 2 (n=54)		P
	Early	Final		Early	Final	
Esotropia rates	10 (%17)	4 (7%)	0.031*	16 (%30)	10 (%19)	0.031*
Near deviation angle (PD)	-0.87±3.85 (-16/6)	3.47±5.21 (-6/10)	<0.001**	-4.04±7.29 (-25/4)	-0.81±6.98 (-18/6)	<0.001**
Distance deviation angle (PD)	-0.93±4.59 (-18/8)	5.23±6.47 (-8/25)	<0.001**	-2.44±6.67 (-25/10)	0.44±5.72 (-16/10)	<0.001**

PD: Prism Diopter; *Mc-Nemar Test for Two Matched Samples; **Wilcoxon Signed Rank Test for Two Paired Samples.

Table 4. Stereopsis, fusion, and diplopia rates of patients who underwent symmetric (Group 1) and asymmetric (Group 2) surgery for exotropia

	Group 1 (n=60)		p*	Group 2 (n=54)		P
	Preoperative	Postoperative		Preoperative	Postoperative	
Stereopsis	50 (83%)	52 (87%)	0.500	20 (37%)	26 (48%)	0.031
Fusion	22 (37%)	48 (80%)	<0.001	10 (17%)	24 (44%)	<0.001
Diplopia	10 (17%)	4 (7%)	0.180	2 (4%)	10 (19%)	0.039

Mc-Nemar Test for Two Matched Samples.

The influence of preoperative deviation angle on the development of consecutive ET has been investigated in previous studies with conflicting results. Jang et al. (8) reported that patients with larger preoperative angles had a significantly higher incidence of consecutive ET, whereas Kim and Choi (4) found no such association. The findings of this study are consistent with those of Jeon and Choi (15), demonstrating that higher preoperative deviation angles are a significant risk factor for consecutive ET. Nevertheless, multiple other factors may also play an important role in its development.

Both symmetric and asymmetric surgical approaches have been linked to the development of consecutive ET. Kim and Choi (4) and Baik et al. (7) reported a higher incidence of consecutive ET following BLR surgery. This may be related to strong tonic convergence and increased medial rectus muscle tone or tightness, which can contribute to postoperative overcorrection (19). In contrast, Jang et al. (8) and Lee and Hwang (9) found a stronger association with RR surgery. Other studies, including those by Lee et al. (20) and Kim et al. (5), reported no significant difference between the two surgical approaches. In this current study, consecutive ET was more frequent following RR surgery, which is consistent with several reports in the literature (8,9). Furthermore, it was also found that the total amount of surgery performed was significantly associated with the development of consecutive ET.

The role of age at the time of surgery is another area of controversy. Several authors (4,10,21) have reported that younger age at the time of surgery increases the risk of consecutive ET. Choi and Choi (22) observed a higher incidence of consecutive ET in children younger than 4 years compared with those older than 4 years, although the difference was not statistically significant. Considering the potential disadvantages of consecutive ET, it may be prudent to delay surgery in children with immature visual function unless there is a marked increase in deviation or poor fusional ability (23). Conversely, other studies (8,24) have suggested that XT surgery can be performed safely in children both younger and older than 4 years, with no adverse impact on motor or sensory outcomes. In this study, all participants were older than 5 years at the time of surgery, so our findings do not fully address outcomes in younger children. However, our results align with those of Buck et al. (17), indicating that surgery at a relatively older age is not a significant risk factor for consecutive ET.

The association between binocular visual function and consecutive ET is also debated. Lee and Hwang (9) reported that poor preoperative stereopsis was associated with a higher risk of consecutive ET. In contrast, several other studies (4,5,8) found no significant relationship between binocular function and postoperative outcomes. In the present study, preoperative binocular visual functions did not appear to influence the development of consecutive ET. Most patients demonstrated im-

provement in binocular visual function after surgery compared with preoperative levels. While Group 1 showed no significant change in stereopsis, likely due to already high preoperative levels, Group 2 demonstrated a significant postoperative improvement. Additionally, fusion rates improved significantly in both groups, consistent with findings reported by Kim et al. (5).

Diplopia associated with consecutive ET can cause substantial discomfort and affect daily life, making both patients and surgeons hesitant to proceed with surgery. However, in most cases, preoperative diplopia resolves when orthotropia is achieved after XT surgery (5). In this study, the initially high rate of preoperative diplopia in Group 1 decreased significantly by the final follow-up. Conversely, the initially low rate of diplopia in Group 2 increased, correlating with the higher incidence of consecutive ET. These results may be attributed to the higher preoperative deviation angles, higher rates of amblyopia, and greater surgical amounts in Group 2.

Few studies have specifically investigated the relationship between refractive error, amblyopia, and consecutive ET. Kim and Choi (4) and Heo and Lambert (10) identified amblyopia as a significant risk factor for consecutive ET, and Jang et al. (8) suggested that high myopia and amblyopia predispose patients to its development. In contrast, Kim et al. (5) reported that refractive errors, amblyopia, and anisometropia were not significant predictors. In the present study, amblyopia alone was not found to be a significant factor; however, refractive error, anisometropia, and visual acuity, which can contribute to amblyopia, were significant risk factors. These findings emphasize the importance of appropriate refractive correction and amblyopia treatment before XT surgery, as recommended by Ding et al. (21).

This study has certain limitations. It was retrospective in nature, with a relatively short follow-up period, and the study population included a wide range of ages. Future prospective studies with larger, more homogeneous populations and longer follow-up times are needed to better evaluate the impact of various risk factors on the development of consecutive ET. A notable strength of the study is that all surgeries and postoperative evaluations were performed by a single surgeon, which minimized variability and ensured consistent surgical techniques and assessments.

Conclusion

Consecutive ET is a relatively common complication following XT surgery. Its development is likely influenced by multiple factors acting individually or in combination. Although early postoperative overcorrection tends to decrease over time, patients with high refractive errors, anisometropia, large preoperative deviation angles, greater surgical amounts, and high early postoperative deviation angles should be closely monitored for the development of consecutive ET.

Disclosures

Ethics Committee Approval: *This study adhered to the principles of the Declaration of Helsinki. As this was a retrospective study, ethics committee approval was waived.*

Informed Consent: Written informed consent was obtained from the patients or their guardians before surgery.

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Vessel-Sparing Rectus Plication Surgery vs Recession/ Resection: A Comparative Optical Coherence Tomography Angiography (OCT-A) Analysis of Iris Vessel Density Changes

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Abstract

Objectives: To compare the iris vessel density results before and after rectus plication, a vessel-sparing procedure, and resection/recession surgery using a non-invasive method, optical coherence tomography angiography (OCT-A).

Methods: This single-center, prospective observational study was held in Beyoglu Eye Research and Training Hospital. Ten patients were included in the study after excluding patients with systemic or ocular diseases, nystagmus or fixation loss. The anterior segment module of the OCT-A was utilized, and the eye-tracking feature was disabled to obtain the highest image quality. OCT-A imaging was performed one day before or on the day of the surgery and within three days after surgery.

Results: Ten patients (8 females) were included in the study. Five had esotropia, meanwhile 5 had exotropia. Two patients received muscle plication in one eye, and the other three received one rectus plication and antagonist recession on the same eye. Preoperative and postoperative images were analyzed both qualitatively and quantitatively with device software and ImageJ. The vessel density near the plicated rectus decreased less after surgery. The mean preoperative and postoperative vessel densities were 53.68% and 49.62% in the plication group ($p>0.05$). However, they were 60.19% preoperatively and 54.26% postoperatively in the resection/recession group ($p=0.043$).

Conclusion: In this study, OCT-A was utilized for the first time to evaluate the qualitative and objective quantitative changes in iris vessel density after rectus plication and recession/resection surgeries. The quantitative comparisons demonstrated that the iris vessel density decreased less after vessel-sparing surgery. Iris OCT-A shows promise for evaluating changes in iris vessel density.

Keywords: Iris vessels, Image J, Optical coherence tomography angiography, Plication, Strabismus surgery

Introduction

Anterior segment ischemia (ASI) is one of the most feared complications of strabismus surgery. Fortunately, it is a rare complication mostly seen after disinsertion of more than

two muscles (1). However, there are reports of ASI after disinsertion of two rectus muscles (2).

Vessel sparing techniques have improved over the years and results showed that they are equally effective as tradi-

* This study was partially (only plication patients' results) presented before in the Subspecialty Day in WSPOS, ESCRS 2023 in Vienna.

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tional strengthening procedures (3). Plication has the advantage of sparing ciliary vessels, thus not disturbing the anterior circulation if performed carefully (1). Especially in patients with a higher risk of ASI, such as patients with previous strabismus and retinal detachment surgery history, thyroid orbitopathy, atherosclerosis, hematological disorders increasing blood viscosity, limbal conjunctival incision, vessel sparing techniques should be considered. Studies revealed that the anterior segment is less disturbed after plication surgery (1).

Plication procedure is also supported to have other advantages. There is no risk of a lost muscle, less risk of trauma and bleeding. Pattern deviations might also be corrected with a technique described as plication with transposition (4).

The gold standard to assess iris circulation is fluorescein and indocyanine angiography. However, these procedures are invasive and have risks, such as allergic reactions, anaphylaxis, and even death. In recent years, there have been a few studies on anterior segment Optical Coherence Tomography-Angiography (OCT-A) due to its non-invasive nature. (5-7). Iris vessel imaging with OCT-A still has some limitations as image artifacts, pupil movements and dark iris color. Nevertheless, it has potential for anterior vasculature imaging as well as retinal imaging.

In a study assessing iris vessel density, OCT-A detected vascular filling defects in the quadrant adjacent to the operated muscle (6). In this study, iris vessel changes were assessed with OCT-A after strabismus surgery. In addition to that, to our knowledge, it is the first study to compare vessel sparing surgery with resection/recession surgery in terms of iris vessel density on OCT-A. Comparisons were made qualitatively and also quantitatively with ImageJ. (<https://imagej.nih.gov/ij/>) There is no funding used and there is no conflict of interest.

Methods

Participants

This is a prospective observational study including 10 (8 females, 2 males) strabismus patients. The subjects were selected from the outpatient clinic of the strabismus unit of Beyoglu Eye Research and Training Hospital. All included patients were operated on by the same surgeon. The Institutional Review Board (IRB) approved this study as it adhered to the ethics tenets of the Declaration of Helsinki. Data acquisition and analysis were performed in compliance with the protocols approved by the Ethical Committee of Marmara University. (Ethical approval number 09.2023.821) All the subjects gave informed consent after being informed in detail.

All subjects were assessed with a detailed ophthalmological examination, including deviation angle measurements

with prisms. Deviation measurements were performed by the prism occlusion test or Krimsky, according to the patient's fixation status. Inclusion criteria were to be diagnosed with strabismus, to be a candidate for strabismus operation, to be older than 18 years, not to have a history of any ophthalmological operations, and not to have a systemic disease affecting blood circulation. Exclusion criteria were to have nystagmus and other fixation problems, to have previous strabismus or other ophthalmological surgeries, and not want to sign the informed consent.

Anterior Segment OCT-A Imaging

All detailed ophthalmological examinations were made before the operation and within three days after surgery. Anterior segment OCT-A images were obtained according to tips and protocols described by Iovino et al. (5) Triton DRI-OCT (Topcon Corporation, Tokyo, Japan) was used. It is an SS-OCTA that reaches up to 100,000 A-scans per second, and the algorithm it uses is called the OCTARA. To focus on the AS, the manufacturer provides an anterior segment-specific lens and a headrest attachment. It is also recommended to disable the eye tracking feature. The 6×6 macular cube is said to be the best scan size that allows to visualize iris with vascular details (Fig. 1). It is also possible to obtain 3×3 and 9×9 scan images. Mydriatic eye drops were avoided because pupil dilation worsens the image quality. An ambient room lighting was provided to create miosis and the same light setting was used at each visit in order to avoid variations due to pupil size. We could not obtain a scan of all quadrants separately because this process was frustrating for patients, especially in the postoperative period. We obtained images of the area adjacent to the operated muscle.

Image Processing

All the OCT-A images were analyzed with two protocols. Firstly, automated vascular density software analysis was used, which was commercially available in the OCT device, performing vascular density software analysis. It was used to calculate vessel density for selected quadrants preoperatively and postoperatively.

Secondly, all the OCT-A images were processed and analysed using ImageJ and Fiji applications. All the images were converted to 8-bit grayscale images by using a predefined formula [$V=0.299R+0.587G+0.114B$ ($V=Y$; $R=red$; $G=green$; $B=blue$)] (8). Brightness was adjusted in a standardized way. So, only the bright vessels were highlighted. All images were then processed using a combination of Gaussian filters, spectral bandpass filters and intensity thresholding to remove non-specific, non-contiguous artifacts (Fig. 2). Reflectivity of the vessels was measured with the ImageJ software, by which the gray scale images' reflectivity values were given as intensity per pixel.

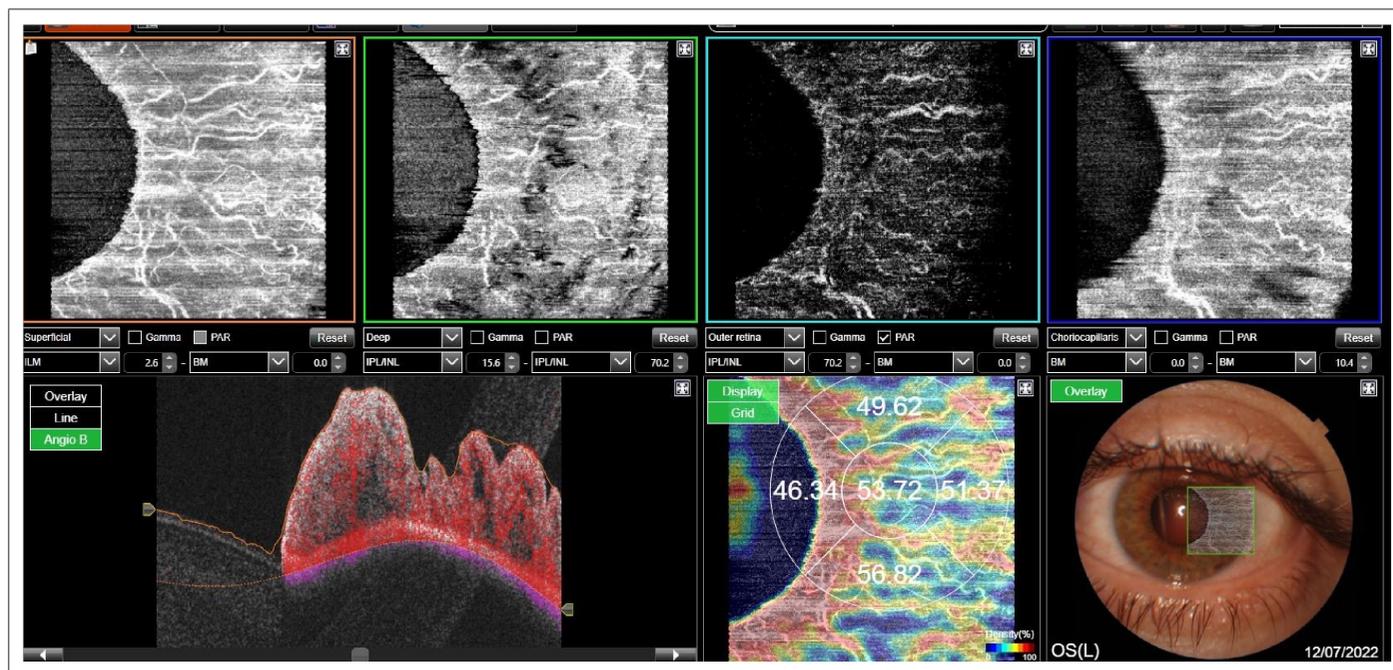


Figure 1. Preoperative 6x6 iris OCT-A images of a patient with Topcon Triton SS OCT-A device.

Statistical Evaluation

Descriptive statistics were given as mean, standard deviation, median, minimum, maximum, frequency, and ratio values where relevant. The distribution of data was analyzed with the Shapiro-Wilks test. The distribution of data did not meet the condition of normality. Non-parametric tests were used. The Wilcoxon test was used in the analysis of dependent quantitative data. The chi-square test was used to analyze qualitative independent data, and the Fischer test was used when the chi-square test conditions were not met. The analysis was made using the SPSS program version 28.0 (SPSS Inc, Chicago, IL). The significance level was set as $p < 0.05$.

Results

The participants of this study were 80% female ($n=8$) and 20% ($n=2$) male, whose mean age was 38 ± 15 (Median: 44, 17-60)

years. The clinical characteristics of the patients and operations were given in Table 1. The mean visual acuity (Snellen) was 0.80 ± 0.32 (Median: 1, Min-Max: 0.05- 1) in the right eyes, and 0.73 ± 0.40 (Median: 1, Min-Max: 0.05-1) in the left eyes of the subjects. Mean pre-operative angle of deviation (AD) was 36.5 ± 14.73 (Median: 30, 20-60) prism diopters (PD) in near, and 36.6 ± 16.89 (Median: 35, 16-70) PD in distance. Post-operative mean AD in near was 11.6 ± 11.19 (Median: 11, 0-30) PD and 11.0 ± 9.33 (Median: 12, 0-25) PD in distance.

Preoperative and postoperative vessel density measurements obtained by using the OCT-A internal software and image processing tool, Image J, are given in Table 2. It was noted that in resection/recession patients, the mean vessel density was reduced up to 6% postoperatively (Fig. 3). Even though it did not reach statistical significance, a reduction of up to 4% in the mean vessel density was also noted in the plication group. The measurements with Image J show

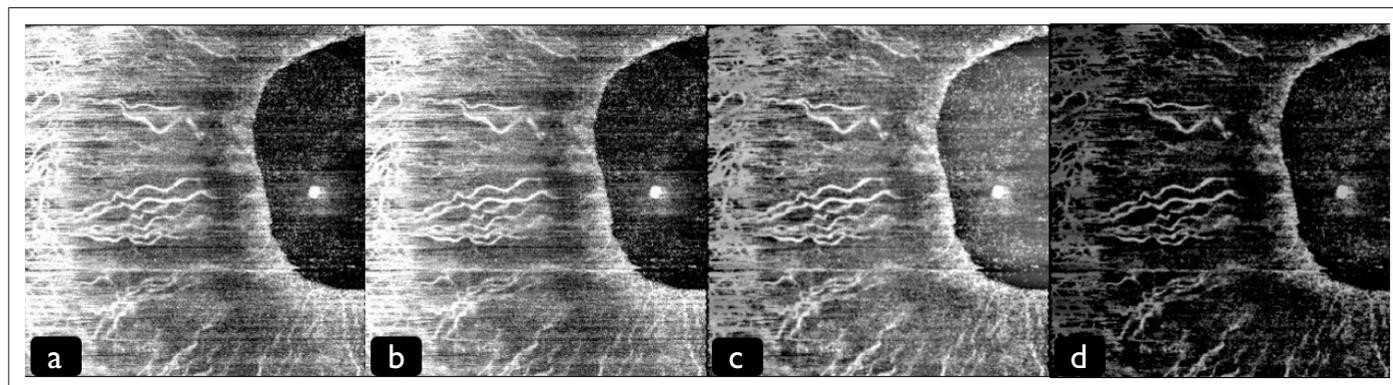


Figure 2. (a) 6x6 iris OCT-A image (b) Image transformed into 8-bit version (c) After bandpass filters applied (d) After brightness adjustment.

Table 1. Vessel density measurement with internal software in OCT-A device and Image J

	Preoperative Median (Min-Max) Mean±SD	Postoperative Median (Min-Max) Mean±SD	p*
Software			
Plication	61.64 (59.75- 69.63) 64.0±4.42	64.20 (59.75-69.62) 63.81±4.16	0.89
Resection- Recession	65.08 (62.15- 76.49) 66.92±5.86	60.16 (53.72-69.66) 60.37±5.23	0.08
Image J			
Plication	52.69 (42.99-66.96) 53.68±9.84	49.38 (39.31-60.01) 49.62±8.46	0.08
Resection- Recession	62.66 (24.52-90.22) 60.19±28.02	59.88 (15.66-89.66) 54.26±32.42	0.043

*Wilcoxon signed ranks test.

that there was a reduction in vessel densities in both groups, but the reduction in vessel density in the resection/recession group reached a statistically significant level (p=0.043).

Discussion

After strabismus surgery, what happens to iris circulation fed by anterior ciliary and long posterior ciliary vessels has been an interesting subject since years. First, researchers examined the iris vessels by fluorescein angiography and indocyanine angiography, which are still the gold standard to visualise iris vessels. It has been shown that a certain amount of iris filling defects might be seen postoperatively, especially at the quadrant adjacent to the operated muscle (6). It is also hypothesised that two long posterior ciliary arteries running

in the horizontal recti, make horizontal midline more resistant to ischemia compared to vertical quadrants.

Even though it is a rare complication, anterior segment ischemia is a significant risk when several rectus muscles are included in the operation plan. This complication might have mild symptoms as mild iritis or severe changes, such as iris atrophy, keratopathy, posterior synechiae, cataracts, and phthisis bulbi (9).

In order to prevent postoperative ischemia, vessel sparing techniques as muscle-to-sclera plication have been studied in terms of effectiveness and safety (3). Not only was plication found as effective as resection, but it was also found to have other advantages as no risk of lost muscle, reversibility, relative simplicity and shorter operation time, less risk of trauma and hemorrhage (10).

The changes in the blood circulation of the anterior segment after muscle-to-sclera plication, recession and resection were investigated with iris angiography studies. It was shown that plication spared the ciliary muscles and blood circulation, especially in horizontal rectus operations (1). However, in a clinical setting, we know that it is difficult to perform iris angiography due to multiple obstacles, such as its invasive nature and the need for a skilled technician. It is also time-consuming. Because the iris is the slowest filling circulation compared to the choroid and retina and more time is needed to visualise the vessels (11). Another limitation is it can not be performed in patients with an allergy to dye, liver or kidney diseases and pregnant women (5).

Despite its own limitations, it was noted that iris OCT-A can produce high-resolution cross-sectional images, allowing visualization of iris circulation. In the near future, it has the potential to be improved with an eye-tracking system and sophisticated segmentation software (5). It has already been

Table 2. Characteristics of patients included in the study

Patient	Sex	Age	VA (RE)	VA (LE)	Operation	Preop AD N (PD)	Preop AD D (PD)	Postop AD N (PD)	Postop AD D (PD)
No. 1	F	48	I	I	L/MR 4.5 mm rec+LR 5 mm res	30	30	0	0
No. 2	F	52	I	I	R/MR 5 mm rec+LR 6 mm plic	30	40	6	12
No. 3	F	60	0.7	0.7	R/LR 6 mm plic	25	20	12	12
No. 4	F	44	I	I	L/MR 5.5 mm rec+LR 5 mm plic	55	40	30	25
No. 5	F	44	0.7	0.05	L/MR 6.5 mm plic	60	70	30	25
No. 6	M	45	I	I	L/MR 5 mm plic+LR 7 mm rec	45	50	0	0
No. 7	F	27	I	0.05	L/LR 7.5 mm rec+MR 6 mm res	50	50	14	14
No. 8	F	25	I	I	L/LR 4.5 mm rec+LR 5 mm res	30	30	10	8
No. 9	M	17	0.5	0.5	R/LR 6 mm plic	20	20	14	14
No. 10	F	20	0.05	I	R/LR 6 mm rec	20	16	0	0

VA: Visual acuity, RE: Right eye, LE: Left eye, F: Female, M: Male, AD: Angle of deviation, N: Near, D: Distant, MR: Medial rectus, LR: Lateral rectus, Rec: Recession, Res: Resection, Plic: Plication.

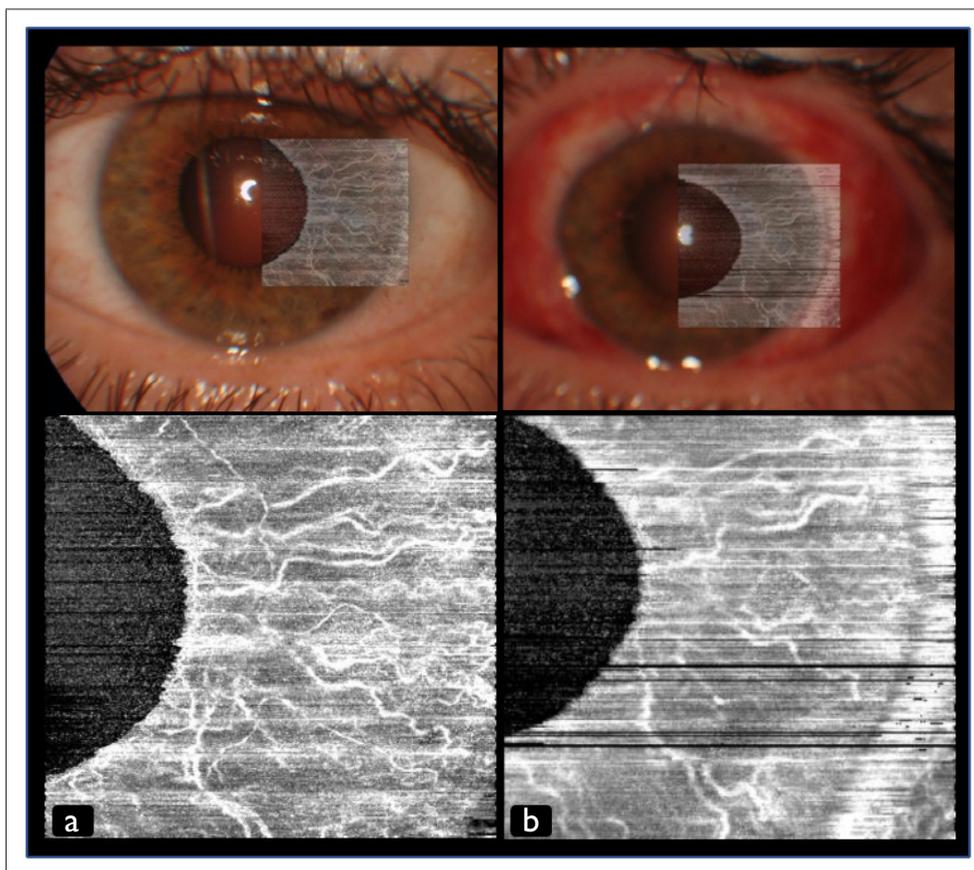


Figure 3. (a) Preoperative and (b) Postoperative 6x6 iris OCT-A images of a patient before and after lateral rectus recession.

studied in patients with anterior segment ischemia risk and after recession/resection surgeries. (6,12). However, to our knowledge, it is the first study comparing plication and resection/recession surgeries with OCT-A both qualitatively and quantitatively with Image J. Iris OCT-A has advantages like non-invasive, fast image capture. On the other hand, it has limitations, such as no eye tracking and no sequential image registration, which leads to artifacts and difficulty in locating the same area of interest. Secondly, the ocular tissue refraction affecting anterior OCT-A image parameters. Thirdly, non-parallel segmentation and pigment epithelium induced a mirror artifact. Moreover, the iris vessel caliber, density and tortuosity is affected by pupillary dilation, and despite trying to have the same ambient illumination conditions, pupil size is not constant during imaging. All of these factors have an influence on reproducibility and comparisons (5,12).

In this study, we used a swept-source OCT-A (SS OCT-A) system with a longer wavelength (1050 nm), enabling better penetration to deeper layers of the eye (13). It is a serious problem to obtain good-quality OCT-A images in pigmented irides. Ang et al. compared spectral domain OCT-A to SS OCT-A in showing iris neovascularization and normal vasculature in pigmented irides. They concluded that both

systems were comparable in showing superficial neovascularizations, but SS OCT-A was better in visualizing normal iris vessels in stroma of pigmented irides (14). Thus, unlike previous studies on anterior segment circulation after strabismus surgeries, we did not use spectral domain OCT-A. Triton SS OCT-A was used in this study to better visualization in pigmented irides.

The vascular density calculated by OCT-A software is sensitive to variation in location and programmed to detect vessel segmentations in the posterior segment of the eye. Without eye tracking and modifications for anterior segment vessel segmentation, these calculations are not very reliable and reproducible. On the other hand, we found similar vascular densities to those found by Velez et al. and Vanlangenaeker et al (6,12). In the subgroup analysis of 3x3 images, Vanlangenaeker et al. found a mean decrease of 4.622%, which were mostly observed adjacent to recessed rectus areas. These findings were comparable to our results.

It was noted that both with internal software and Image J measurements, postoperatively, there is a decrease in vessel density in vessel sparing and non-sparing techniques, 6% and 4%, respectively. The clinical implication of this immediate decrease on the anterior segment is not known (12). Al-

though the difference does not always reach a level of statistical significance, the vessel sparing technique seems to affect anterior segment circulation less. Previous iris angiography studies have shown this result. After image processing, our results supported angiography findings as the vessel density decrease in the vessel sparing technique was less ($p=0.043$).

Conclusion

In our study, image processing software, ImageJ, was used in order to compare internal software measurements and to compare preoperative to postoperative vessel densities. Standardized image processing techniques, described in the literature, were used to clean various artifacts (7). The results obtained with image processing techniques also supported measurements of internal software.

The advantages of this study are that first time in the literature vessel sparing and recession/resection techniques were compared in terms of anterior circulation changes. A non-invasive OCT-A technology and image processing were used. On the other hand, the limitations of this study were its small sample size, not including the long-term effects of surgery and not comparing OCT-A results with conventional iris angiograms.

To conclude, with this study, the iris vessel density changes in OCT-A after different surgical techniques were compared for the first time with an objective qualitative method. In the future, anterior segment OCT-A might be used more frequently after some modifications, such as eye tracking and anterior segment-adjusted software systems.

Disclosures

Ethics Committee Approval: This study was approved by the Marmara University Ethics Committee (Date: 25.09.2023, Number: 09.2023.821) and conducted in accordance with the tenets of the Declaration of Helsinki.

Informed Consent: Informed consents were obtained from all patients.

Conflict of Interest: None declared.

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Author Contributions: Concept – D.D.Y., A.I., C.G., Z.H., T.Y., S.G.C., O.A., M.T., B.G.; Design – D.D.Y., A.I., C.G., Z.H., T.Y., S.G.C., O.A., M.T., B.G.; Supervision – D.D.Y., A.I., C.G., Z.H., T.Y., S.G.C., O.A., M.T., B.G.; Resource – D.D.Y., A.I., C.G., Z.H., T.Y., S.G.C., O.A., M.T., B.G.; Data Collection and/or Processing – D.D.Y., A.I., S.G.C.; Analysis and/or Interpretation – D.D.Y., A.I., S.G.C.; Literature Search – D.D.Y.; Writing – D.D.Y.; Critical Reviews – D.D.Y., A.I., S.G.C.

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Surgical Outcomes of Blepharoptosis in Ocular Prosthesis Patients

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Abstract

Objectives: To evaluate the surgical outcomes of blepharoptosis in patients with no light perception (NLP) who used prostheses and to assess eyelid symmetry and functional improvement following appropriate surgical management.

Methods: This retrospective study included 15 patients with prosthesis-related ptosis treated between 2020 and 2024. Demographic characteristics, prosthesis type and duration of use, type of ptosis, preoperative levator function, and surgical technique were recorded. Margin reflex distance I (MRD-I) was measured preoperatively and at postoperative 1 week, 1 month, 3 months and 6 months, using standardized digital photographs. Eyelid symmetry, complications, and need for revision surgery were evaluated. Repeated measurements were analyzed using the Friedman test with Wilcoxon signed-rank post hoc comparisons.

Results: The mean age was 40.13 ± 17.41 years (range 15–70 years); 10 patients were female and 5 were male. The mean preoperative levator function was 11.80 ± 3.52 . Regarding the underlying causes of eye loss/prosthesis use, 9 (60.0%) were due to trauma, 1 (6.7%) was due to infection, 2 (13.3%) were due to glaucoma, and 3 (20.0%) were due to other causes. 12 patients had evisceration, and 3 patients used a prosthesis over a phthisis bulbi eye. 13 patients underwent Müller Muscle-Conjunctival Resection (MMCR) and 2 patients underwent levator surgery. MRD-I increased significantly from 1.20 ± 0.94 mm preoperatively to 3.27 ± 0.70 mm at 6 months. Further analysis to determine the source of the difference revealed statistically significant differences between preoperative MRD-I and postoperative MRD-I at 1 week, 1 month, 3 months, and 6 months. The Friedman test showed a significant improvement over time ($p < 0.001$). Technique comparisons were exploratory due to the small levator subgroup. No significant difference was found between the duration of eye prosthesis use and preoperative MRD-I ($p = 0.761$).

Conclusion: MRD-I improved from 1.20 ± 0.94 mm preoperatively to 3.27 ± 0.70 mm at 6 months, and eyelid symmetry (≤ 1 mm) was achieved in 86.6% of patients, demonstrating that ptosis of the upper eyelid in ocular prosthesis patients can be effectively corrected with appropriately selected surgical techniques based on levator function.

Keywords: Eyelid symmetry, margin reflex distance-I, müller muscle conjunctival resection, ocular prosthesis, phenylephrine test

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Introduction

Blepharoptosis is defined as the abnormal drooping of the eyelid during straight gaze, which can affect vision and appearance. It can be unilateral, bilateral, congenital or acquired. Ptosis occurs in 4.7% to 13.5% of the adult population, and this rate may increase with age (1–3). The upper eyelid typically covers the cornea by 1–2 mm. Ptosis can be minimal (1–2 mm), moderate (3–4 mm) or severe (>4 mm) and the pupil may be completely covered. Treatment for ptosis varies depending on age, aetiology, whether one or both eyelids are affected, the severity of ptosis, levator function, and the presence of ophthalmological/neurological comorbidities.

Ptosis treatment generally comprises follow-up, medication, and surgical procedures. Surgically, for mild to moderate ptosis, Müller muscle conjunctival resection (MMCR) or the Fasanella-Servat procedure is recommended in patients with mild to moderate ptosis who respond to the 2.5% phenylephrine test and have levator function >10 mm. Levator muscle procedures are recommended for ptosis with levator function >5 mm. Brow/frontal suspension is recommended for severe ptosis with levator function <4 mm (4).

Ptosis in patients with ocular prostheses may occur either alone or as part of socket syndrome following enucleation and is a common finding. Post Enucleation Socket Syndrome (PESS) was first described in 1982 (5). It is a multifactorial, variable syndrome resulting from the rotational displacement of the orbital contents from the top to the back and from the posterior to the inferior, the retraction of the extraocular muscles, and the possible volume loss due to resorption of the orbital implant if it is made of hydroxyapatite. These orbital changes occur rapidly in the months following eye loss and continue at a reduced rate for the rest of the patient's life. It is more pronounced in cases where the orbital implant is very small during surgery or if no implant is used. PESS typically results in posterior tilting of the superior fornix, a deep superior sulcus, pseudo-ptosis, elongation and laxity of the lower eyelid, a shallower inferior fornix, and enophthalmos, and may prevent the fitting of ocular prostheses (6).

In patients undergoing evisceration, the most common clinical findings in the eyelid are deepening of the superior sulcus and ptosis (35.0%), while lower eyelid entropion and lower eyelid retraction are the second most common findings (25.0%). Among patients who underwent enucleation, the most common eyelid change was lower eyelid entropion (45.5%). Ptosis and lower eyelid socket contracture were the second most common changes (36.4%) (7).

Prosthetic application is a procedure performed to alleviate aesthetic concerns in patients with no functional expectations; therefore, the ptosis and asymmetry that develop in these patients are critical. A previous study reported that

participants were equally concerned about discharge, visual perception, and appearance in the first 3 months after eye loss and at least 2 years later, although concerns decreased. Older participants were less concerned about appearance, while women were more concerned about current discharge and appearance (8). Appearance and concealability are among the most important concerns for patients with prosthetic eyes (9).

The aim of this study was to evaluate the surgical success of ptosis in patients with prosthetic eyes based on the margin reflex distance-I (MRD-I) and symmetry status, compare different surgical techniques in this patient population, and to evaluate intraoperative and postoperative complications.

Methods

Data on 15 patients with ptosis associated with ocular prosthesis use who were treated at the Oculoplasty Clinic of Beyoglu Eye Training and Research Hospital between 2020 and 2024 were retrospectively extracted from their files.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Non-Interventional Clinical Research Ethics Committee of Istanbul Training and Research Hospital (date: 07/25/2025; no:196). Written informed consent was obtained from all patients prior to surgery. Written consent was also obtained for the use of clinical images and documented in the medical records.

The following data were evaluated and recorded: patient age; sex; type of prosthesis used; duration of prosthesis use; type of ptosis; preoperative levator function; preoperative and postoperative 1-week, 1-month, 3-month, and 6-month MRD-I; whether additional surgery was performed with ptosis surgery; symmetry between both eyelids; follow-up periods; development of postoperative complications; and whether revision surgery was required. Surgical success was defined as a postoperative MRD-I ≥ 3.0 mm at 6 months without the need for revision surgery. Eyelid symmetry was defined as an absolute inter-eyelid MRD-I difference ≤ 1.0 mm.

Patients with good socket-prosthesis fit, adequate fornix width, ptosis associated with ocular prosthesis, regular prosthesis use, no previous ptosis surgery, and comprehensive records were included in the study. Patients with insufficient sockets, narrow fornices, ptosis or ptosis surgery prior to prosthesis use, or incomplete records were excluded.

To determine the MRD-I, standardized frontal photographs were obtained in primary gaze under consistent lighting conditions. MRD-I was measured digitally using Fiji (ImageJ, National Institutes of Health, USA). All measurements were obtained by the same investigator and independently verified by a second investigator. Masking was not applied due to the retrospective design. Regardless of levator function, 2.5% phenylephrine hydrochloride was administered

to every patient with an ocular prosthesis. An appropriate surgical plan was developed for each patient based on the response to the phenylephrine test.

All patients were first evaluated at the prosthesis center. Socket volume deficiencies or prosthesis-related problems were corrected prior to ptosis surgery. Surgical intervention was considered only after prosthesis optimization. In levator surgery, levator reinsertion was performed through an upper eyelid crease incision. In MMCR, the amount of resection of the Müller-conjunctiva complex was adjusted according to the phenylephrine response. Where MRD₁ became symmetrical with the contralateral eye after 5 minutes, a 9 mm resection was planned; a 10 mm resection was performed where the ptotic eyelid remained lower despite a positive response. Conversely, where the ptotic eyelid reached a position higher than the contralateral side without significant unmasking of the Hering phenomenon in the fellow eye, an 8 mm resection was selected (1). No significant ptosis was observed in the contralateral eye due to the Hering effect during the intraoperative and postoperative periods.

Statistical Analysis

Analyses were performed using SPSS version 22.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistical methods (mean, standard deviation, median, minimum, maximum) were used. Normality was assessed using the Shapiro-Wilk Test. Repeated MRD-I measurements were analyzed using the Friedman test. Where significant, pairwise post hoc comparisons were performed using Wilcoxon signed-rank tests with Holm-Bonferroni correction. A p-value<0.05 was considered statistically significant.

Results

The mean patient age was 40.13±17.41 years (min 15–max 70 years). Of the 15 patients included, 10 (66.6%) were female and 5 (33.3%) were male. The preoperative levator function was 11.80±3.52. Examining the causes of eversion, it was found that 9 cases (60.0%) were due to trauma, 1 case (6.7%) was due to infection, 2 cases (13.3%) were due to glaucoma, and 3 cases (20.0%) were due to other causes. A total of 12 patients had eversion, while 3 patients used prostheses on phthisic bulbi eyes. The average follow-up period was 86.00±63.57 months (12-180 months); the average prosthesis usage period for patients was 28.64±41.22 months (1-156 months) (Table 1).

Differences between preoperative MRD-I (1.20±0.94 mm) and postoperative MRD-I values at 1 week (2.40±0.63 mm), 1 month (2.93±0.70 mm), 3 months (3.20±0.67 mm), and 6 months (3.27±0.70 mm) were statistically significant (p<0.001) (Table 2). Further analyses revealed statistically significant differences between preoperative and postoperative MRD-I values at week 1, month 1, month 3, and month

Table 1. Findings regarding some sociodemographic characteristics and prosthetic ptosis surgery in patients

	n	%
Gender		
Female	10	66.7
Male	5	33.3
Average age	40.13±17.41 years (min 15- max 70 years)	
Preoperative levator function	11.80±3.52 mm	
Etiology of ptosis		
Mechanical	1	6.7
Aponeurotic	14	93.3
Cause of anophthalmia		
Trauma	8	57.1
Infection	1	7.1
Glokoma	2	14.3
Due to other reasons	3	21.4

Table 2. Relationship between preoperative and postoperative (1 week, 1 month, 3 months, 6 months) MRD-I

Time Point	MRD-I (mm), mean±SD
Preoperative	1.20±0.94
Week 1	2.40±0.63
Month 1	2.93±0.70
Month 3	3.20±0.67
Month 6	3.27±0.70
p value*	<0.001

* Friedman test. MRD-I: Margin reflex distance-I, SD: Standard deviation.

6. The Friedman test showed a significant improvement over time (p<0.001). No significant difference was found between the duration of ocular prosthesis use and preoperative MRD-I levels (p=0.761).

A total of 13 patients (86.6%) underwent MMCR (Figure 1), and 2 (13.4%) underwent levator surgery (Figure 2). Technique comparison was exploratory only, as the levator group was too small to allow meaningful statistical inference.

Eyelid symmetry (MRD-I difference≤1.0 mm) was achieved in 13 patients (86.6%); asymmetry was present in 2 patients (13.4%). Revision surgery was recommended for these 2 patients but they declined as they were satisfied with their appearance. Revision surgery was not performed on any of the 15 patients and no intraoperative complications were encountered. Ecchymosis and edema were detected at varying levels in the surgical area in all patients during the postoperative period; These resolved with medical treatment.

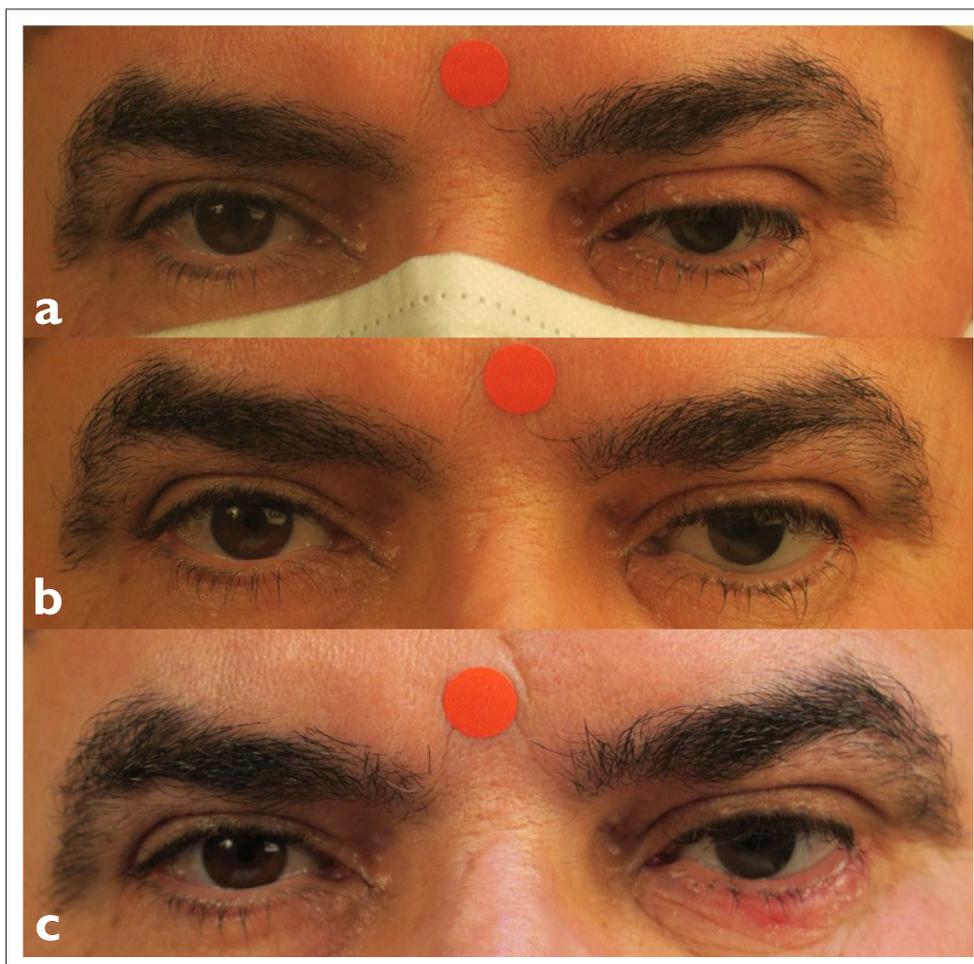


Figure 1. Preoperative left upper eyelid ptosis (a); elevation of the left upper eyelid 10 minutes after instilling 2.5% phenylephrine (b); and postoperative result at 3 months after MMCR surgery (c).

Discussion

Ocular prostheses are artificial eyes designed to restore appearance and psychological well-being in individuals who have lost an eye due to trauma, disease, or congenital causes. Prostheses are manufactured through processes requiring significant skill, time, and craftsmanship, often resulting in variable quality and accessibility (10,11). Recent advances in digital technologies such as computer-aided design, 3D printing, and imaging have revolutionized this field by enabling the more precise, repeatable, and efficient production of customized ocular prostheses (12–14).

Blepharoptosis is a common complication following eye removal (15). Psychosocial adjustment and patient satisfaction are influenced by factors such as prosthesis mobility, appearance, and the quality of care provided (16–18). Blepharoptosis is associated with significant functional, cosmetic, and psychosocial effects (19–21). Aesthetically favourable results are achievable in many patients without the need for additional surgical intervention. Enlarging the upper part of the prosthesis can mechanically elevate or curve the upper

eyelid. However, this may be limited due to lower eyelid retraction, hypoglobus, and loss of mobility (5,22). Socket rehabilitation is achievable by changing the prosthesis to increase orbital volume. A thicker prosthesis can generally lift the upper eyelid with the help of posterior support; however, prosthesis thickness is inversely proportional to mobility. Thick or heavy prostheses may result in a hypoglobus appearance or lower eyelid retraction, or both (23).

Volume deficiency can be corrected using autologous or alloplastic orbital implants (24,25). There is a direct relationship between the residual volume replacement percentage and ptosis formation: the likelihood of ptosis occurring in patients with a volume replacement of 40.0% is 2.27 times higher than in patients with a volume replacement of 80.0%. Ptosis resolved in 30.0% of patients following orbital volume replacement (26). It is recommended that upper eyelid blepharoptosis is corrected after volume deficiency is addressed (15). There was no orbital volume deficiency in the patients in the present study, and each patient was evaluated for prosthesis suitability. In patients with prosthesis



Figure 2. Preoperative left upper eyelid ptosis (a); postoperative appearance at 1 month after levator reinsertion (b); and postoperative appearance at 6 months after levator reinsertion (c).

incompatibility, related procedures were performed prior to ptosis surgery. Patients whose ptosis did not improve were referred for surgery and the appropriate surgical approach was selected.

Ptosis in anophthalmic eyes may result from various factors such as volume loss, soft tissue rotation, lower eyelid laxity, and socket fibrosis. PESS is characterized by fat atrophy, soft tissue rotation, lower eyelid laxity, and socket fibrosis; ptosis and an upper lid deep sulcus appearance are frequently observed in PESS. Clinical symptoms usually onset within the first 2 years after enucleation (5). In this study, PESS findings were present in 12 (80.0%) of the patients. No fornix insufficiency or socket volume deficiency was observed.

Detachment or dysfunction of the levator palpebrae superior insertion site can be considered as one of the main causes of anophthalmic blepharoptosis. Despite adequate orbital volume, ptosis was reported in 18.0% of anophthalmic patients (n=66); the cause of ptosis in these cases was attributed to a shift in the center point of the levator palpebra superior muscle and the resulting mechanical imbalance (15). In a series of 32 cases, levator function was significantly lower on the anophthalmic side (10.43 ± 1.48 mm) than on the

normal side (12.74 ± 1.81 mm). In this study, levator function was also found to be significantly lower on the anophthalmic side (11.80 ± 3.52) than on the normal side (14.01 ± 2.05). The cause of the ptosis mechanism can be similarly explained. Levator function was better in those eyes with appropriate height in suitable prostheses. Levator function in anophthalmic eyes was directly proportional to the increase in the anterior surface of the implant and the increase in implant size, and inversely proportional to age and superior sulcus deepening (15).

A study evaluating 186 patients following enucleation demonstrated that 62.3% of postoperative complications could be treated by adjusting the prosthesis (25). Procedures performed during prosthesis adjustment may increase the weight of the prosthesis, potentially limiting its mobility and causing deformities. In this study, all patients were evaluated by the prosthesis center specialist who was consulted prior to the establishment of the surgical indication. No socket volume deficiency or prosthesis-related problems were noted; ptosis was identified as requiring surgical correction.

Downward shift of the lower eyelid and socket tissues can occur at the upper weight limit for prosthesis enlargement. In a series of 70 cases, it was reported that the prosthesis

volume ranged from 0.75-4.2 mL, with the ideal volume being 2.2 mL at the lower limit and 4.2 mL at the upper limit. (22) Smaller prostheses are associated with implant malposition and socket narrowing. Larger prostheses are associated with ptosis and lower eyelid laxity.

In a case series, blepharoptosis was the most common postoperative enucleation complication and required surgical intervention in 7.0% of patients (25). The reported consensus was that in surgical repair, upper eyelid ptosis in anophthalmia should be addressed after volume deficiency and lower eyelid malposition have been corrected (15). In another study, blepharoptosis was corrected in 12 of 18 patients after volume replacement with dermal fat grafting; the other 6 patients subsequently required surgery to correct eyelid ptosis (27) In the present study, patients with volume deficiency or prosthesis incompatibility were excluded if their upper eyelid ptosis resolved after volume replacement or prosthesis-related problems were addressed. Patients who underwent upper eyelid ptosis surgery, despite all problems being resolved, were included.

As surgical interventions, techniques used to correct upper eyelid ptosis in anophthalmic sockets include levator reinsertion, frontal suspension, and MMCR (24,28,29). Levator surgery was once the most frequently used method for correcting ptosis in anophthalmia. The internal approach has also become common in recent years (28–30). Phenylephrine is commonly used for pupil dilation (mydriasis) and diagnostic purposes in ptosis. Both 2.5% and 10.0% phenylephrine produce upper eyelid elevation, with 10.0% inducing a slightly greater effect (0.2 mm more) than 2.5% (31). Both concentrations are considered safe, with no significant changes in blood pressure or heart rate following single-dose administration in healthy individuals (32,33). Karesh et al. (34) performed MMCR on 35 patients with anophthalmic ptosis who responded to 10.0% phenylephrine eye drops. Postoperative symmetry was observed in both eyelids in 31 patients, overcorrection in 2 patients, and undercorrection in 2 patients. No patient experienced socket dryness or upper fornix narrowing. In this study, patients underwent surgical levator reinsertion and MMCR was performed in those who responded to 2.5% phenylephrine eye drops. Levator reinsertion was performed in 2 patients and MMCR was performed in 13 patients. Eyelid symmetry was achieved in 13 patients. Undercorrection developed in 2 patients; overcorrection did not develop in any patient. There were no surgical complications in the postoperative period, and the postoperative success rate was consistent with the literature. Following prosthesis optimization, surgical correction of ptosis in properly fitted sockets resulted in stable MRD-I improvement at 6 months. MMCR did not result in socket dryness or fornix narrowing.

Limitations of this study include the small sample size, the unequal distribution of surgical techniques which precluded meaningful comparison between procedures, and the lack of patient-reported satisfaction outcomes.

Conclusion

In conclusion, insufficient orbital volume is important in the pathophysiology of anophthalmic socket ptosis. The consensus in the literature is that orbital volume is key in ptosis of the anophthalmic socket; treating orbital volume can correct ptosis. Adjusting the prosthesis can provide volume change. This adjustment can elevate the upper eyelid but may impact the fit or mobility of the prosthesis. Persistent ptosis despite an appropriate prosthesis and adequate socket volume can be successfully treated surgically.

Disclosures

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of Istanbul Training and Research Hospital (Date: 07/25/2025, Number: 196) and conducted in accordance with the tenets of the Declaration of Helsinki.

Informed Consent: Written informed consents were obtained from all patients.

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Clinical Findings of Rare Ocular Metastasis in a Patient Diagnosed with Epithelioid Sarcoma

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Abstract

Epithelioid sarcoma is a rare type of tumor that primarily affects young men and accounts for less than 1% of all soft tissue sarcomas. In this case, a patient diagnosed with epithelioid sarcoma and systemic metastases presented with complaints of decreased vision and eye pain. Examination revealed a mass lesion involving the conjunctiva, iris and lens, accompanied by conjunctival hyperemia, corneal edema and hyphema. Ocular metastasis was suspected, and samples were obtained through excisional biopsy of the conjunctival nodule and aspiration of fluid from the anterior chamber. Pathological examination confirmed that the conjunctival nodule represented an ocular metastasis of epithelioid sarcoma. Although there are reported cases of primary orbital epithelioid sarcoma, we present this report because it demonstrates a unique example of extra-orbital primary disease with subsequent ocular metastasis.

Keywords: Epithelioid sarcoma, ocular metastasis, conjunctival nodule

Introduction

Epithelioid sarcoma mainly affects the soft tissue of the hand, forearm, and pretibial regions in young adults and usually shows slow growth. It tends to develop from facial structures and tendons (1). Although it constitutes less than 1% of all soft tissue sarcomas, it has a high recurrence rate. The location of the tumor is the most critical factor affecting survival in epithelioid sarcoma, and the disease occurs more frequently in men (2,3). The proximal type is linked to poorer outcomes compared to the classical type. Because it grows slowly and painlessly, patients may present months or even years after disease onset (3,4). Radical excision with a negative surgical margin and perioperative radiotherapy are

preferred for treating local disease. Local recurrence, which often occurs within one to two years after treatment, is the primary factor leading to treatment failure (3,5). Due to the frequent occurrence of lymph node spread, sentinel lymph node biopsy may be conducted in certain selected cases. Metastases in the lungs and pleura are the most common. Perioperative chemotherapy can be utilized for large, high-grade masses and cases with metastases (5). Tumor cells frequently exhibit immunoreactivity with cytokeratin (CK) and CD34, which is genetically linked to the loss of SMARCB1/INI1 protein expression (6). In this report, we describe a rare case of ocular metastasis originating from an extra-orbital primary epithelioid sarcoma.

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Case Report

A 20-year-old male patient presented with complaints of decreased vision and pain in his right eye, which had worsened over the past month. During the examination, the best corrected visual acuity measured using the Snellen chart was recorded as hand movements in the right eye and 0.8 in the left eye. Intraocular pressure was measured at 45 mmHg in the right eye and 17 mmHg in the left eye using Goldmann applanation tonometry. A biomicroscopic examination revealed a nodular mass measuring 3 mm in length and 2 mm in width located in the superior bulbar conjunctiva of the right eye (Fig. 1). Additionally, there was corneal edema and a hyphema graded at 1/10. Obviously, due to corneal edema, the existing 1/10 hyphema cannot be seen very clearly and there was no rubeosis iridis, nor was any neovascularization or hemorrhage observed in the anterior chamber angle. The examination also showed a protruding mass in the iris at the 11 o'clock position, diffuse small nodular lesions, and a mass extending into the anterior chamber in the central area of the anterior capsule (Fig. 2). Due to corneal edema, the examination of the fundus was unable to be performed; however, both the vitreous and retina appeared normal on ultrasonography. When his comorbidities were assessed, it was revealed that he had been diagnosed with epithelioid sarcoma originating from the right shoulder region approximately two and a half years ago. He was currently receiving treatment in the medical oncology service due to hemoptysis and had multiple metastatic foci in the lungs, lymphatic system, and bones. Due to a preliminary diagnosis of ocular metastasis, cranial and orbital magnetic resonance imaging (MRI) were ordered. The MRI results revealed no mass formation in the orbit; however, small nodular lesions in the brain parenchyma were noted, which raised suspicion for metastasis. Subsequently, a fluid sample from the anterior chamber was

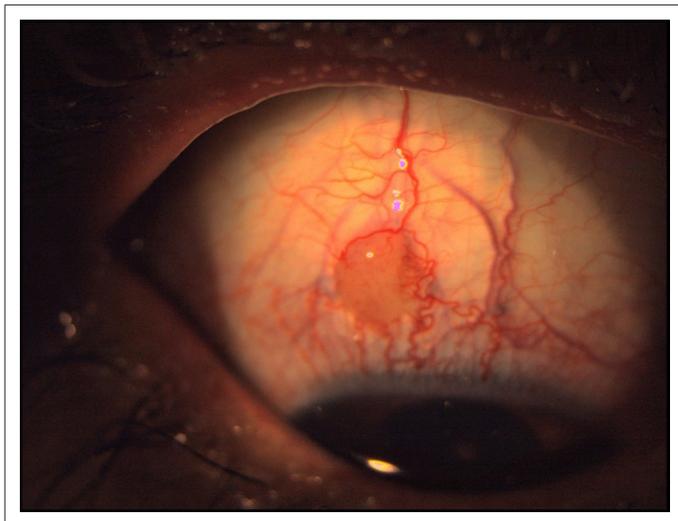


Figure 1. Nodular mass located in the superior bulbar conjunctiva.

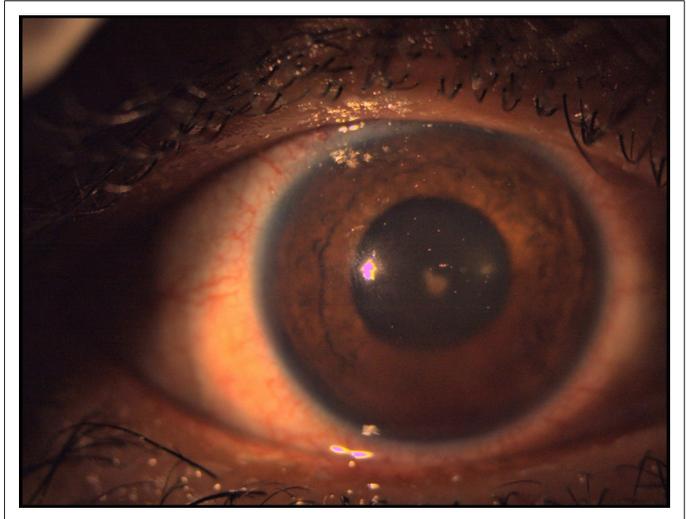


Figure 2. Mass formations on the iris and anterior capsule and hyphema which are hazy due to corneal edema.

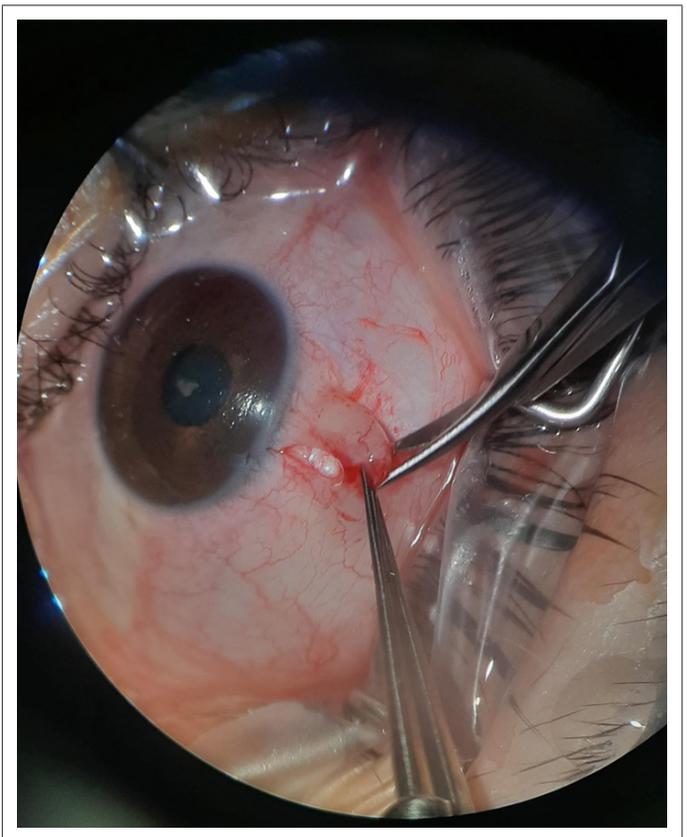


Figure 3. Excisional biopsy from the conjunctival mass.

obtained using a 26-Gauge needle. An excisional biopsy was carried out on the conjunctival lesion, ensuring a clean surgical margin of 3-4 mm (Fig. 3). A sample of anterior chamber fluid and an excised mass, placed in formaldehyde, were sent for pathological examination. Cryotherapy was applied to the conjunctiva at the margins of the excision. The excised area was reconstructed using an amniotic membrane.

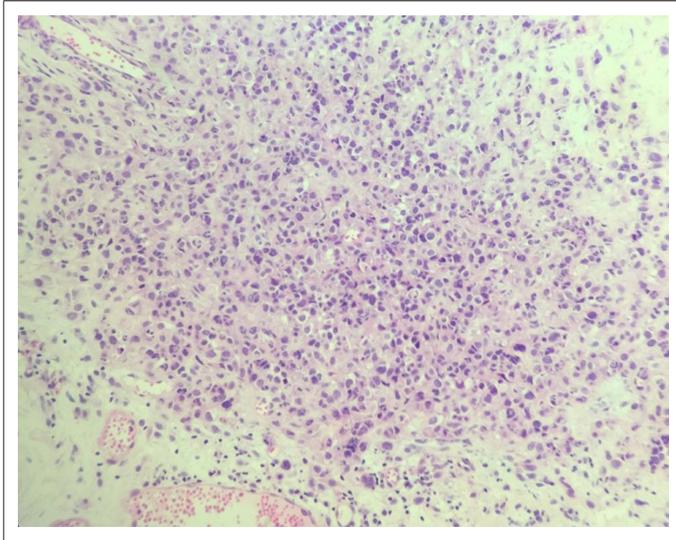


Figure 4. Pathology specimen consisting of cells with an epithelioid appearance.

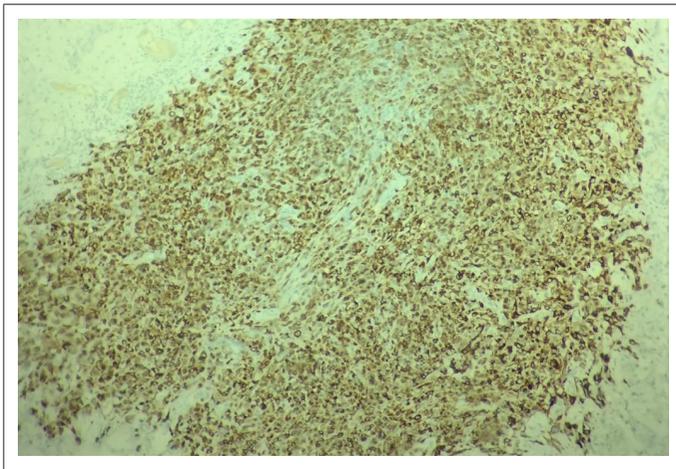


Figure 5. Pancytokeratin positivity immunohistochemically in tumor cells.

The anterior chamber fluid showed acellular cytology, while the conjunctival biopsy demonstrated epithelioid malignant tumoral infiltration (Fig. 4). Tumor cells exhibited strong and diffuse immunostaining for pan-cytokeratin (panCK) (Fig. 5) as well as CD34 (Fig. 6). Surgical margins were reported as free of tumor. A surgical procedure was not recommended due to widespread metastasis in the lungs, bones, and lymphatic system, along with the patient's poor general condition. The patient's systemic treatment in the oncology department is ongoing, and topical antiglaucomatous drop therapy has been initiated.

Discussion

We present a case of ocular metastasis in a patient with epithelioid sarcoma, where the primary tumor is located outside the orbit and has disseminated metastases. While

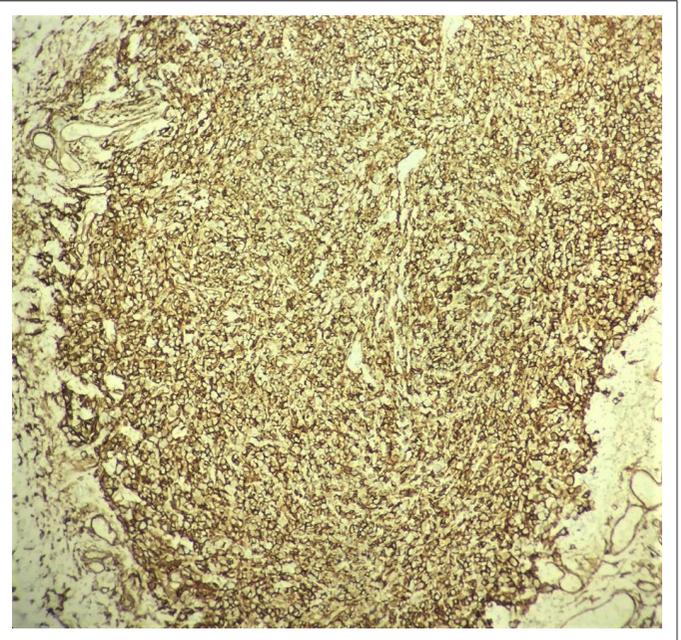


Figure 6. CD34 positivity immunohistochemically in tumor cells.

there are reported cases of primary orbital epithelioid sarcoma, our case is unique, as it involves ocular metastasis from a primary tumor that originates distant from the orbital area.

When examining the reported cases of primary orbital tumors, it is observed that there are very few cases involving patients of various ages. In a case report by Alkatan et al. (7), an extraconal orbital mass was detected on an MRI conducted for a 5-month-old healthy infant. The infant exhibited inferior dystopia and conjunctival chemosis in the right eye for one month. Following a biopsy, the diagnosis of epithelioid sarcoma was confirmed. Despite undergoing chemotherapy and orbital exenteration surgery, the patient experienced intracranial spread of the recurrent tumor. In another report by Kaya et al. (8), an 87-year-old female patient underwent a biopsy after a soft tissue mass was found in the orbit. This finding was accompanied by the lateral displacement of intraocular structures noted on a computed tomography (CT) scan, which was associated with ectropion of the lower eyelid caused by a mass in the medial orbit of her left eye. The patient also presented with a rapidly growing mass in the medial orbit that resulted in epiphora. After diagnosing her with epithelioid sarcoma, she underwent orbital exenteration surgery, and there was no recurrence observed during the follow-up.

Additionally, a case report by Jurdy et al. (9) highlighted a 39-year-old female patient who was diagnosed with epithelioid sarcoma. A biopsy of a mass in her left eye demonstrated possible involvement of the medial rectus muscle. This mass was identified through an MRI due to her symptoms, which included recurrent conjunctival hemorrhage, headaches, and pain in

the left periorbital region. The patient was presented with the option of orbital exenteration; however, she refused this treatment. Instead, radical resection of the tumor was performed, and follow-up examinations revealed no signs of recurrence.

In the study conducted by White et al. (10), a 17-year-old female patient was referred due to a mass in the temporal area of her right upper eyelid. Upon examination, inferonasal dystopia of the globe was observed. A CT scan revealed a superior and inferolateral mass, and a biopsy confirmed the diagnosis of epithelioid sarcoma. There was no systemic metastasis. The patient underwent exenteration surgery on the orbit, and for three years of follow-up, no recurrence was noted. Additionally, a 34-year-old female patient had a biopsy for a right superolateral orbital mass that had persisted for nine months, leading to a diagnosis of epithelioid sarcoma. Following the biopsy, she also underwent exenteration surgery. Radiotherapy was administered due to positive surgical margins. However, ten months later, a CT scan demonstrated recurrence, although no systemic metastasis was observed.

Conjunctival metastases from malignancies originating in extraocular tissues are extremely rare. In a study examining ten cases of tumors that metastasized to the conjunctiva, Kiratlı H. (11) et al. reported the following findings: breast cancer was identified in four cases, lung cancer in two cases, laryngeal cancer in one case, cutaneous melanoma in two cases, and metastasis from an unknown primary cancer in one case. Among the patients, solitary metastasis was observed in eight patients. The metastasis occurred in the bulbar conjunctiva for six patients and in the palpebral conjunctiva for two patients. Additionally, metastasis to other ocular tissues was noted in eight patients.

Conclusion

Our case is significant as it represents the first documented example of conjunctival metastasis from epithelioid carcinoma with a primary focus located distant from the eye. Patients presenting with metastatic malignancy, decreased vision, eye pain, hyphema, and nodular structures in the iris and conjunctiva may need further examination and treatment due to the suspicion of ocular metastasis.

Disclosures

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Arygrosis in Lens Capsule: A Case Report

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Abstract

To report a case of long-standing occupational ocular argyrosis with histopathological confirmation during cataract surgery. A 57-year-old male silver worker with a 16-year history of ocular argyrosis and progressive visual deterioration underwent comprehensive ophthalmological examination and phacoemulsification with intraocular lens implantation. The anterior lens capsule obtained during capsulorhexis was submitted for histopathological examination. Clinical examination revealed bilateral diffuse corneal deposits, periocular pigmentation, and characteristic findings consistent with chronic silver deposition patterns. The right eye demonstrated a mature cataract with complete cortical opacity. Phacoemulsification was performed successfully without complications. Histopathological analysis confirmed characteristic silver deposits within the capsular matrix, providing a definitive diagnosis of ocular argyrosis. Postoperative visual acuity improved from hand motion to 0.9. This case demonstrates successful cataract surgery outcomes in a patient with long-standing occupational ocular argyrosis. Histopathological examination of surgical specimens provides invaluable diagnostic confirmation and demonstrates the systemic nature of silver deposition. The case emphasizes the importance of long-term monitoring in patients with occupational silver exposure and confirms that cataract surgery can be performed safely with excellent visual outcomes in patients with concurrent ocular argyrosis.

Keywords: Argyria, cataract, lens, ocular argyrosis, phacoemulsification

Introduction

Silver exposure in occupational settings has emerged as a significant health concern, particularly in industries involving jewelry manufacturing, photography, and metallurgy (1).

Argyria is a rare systemic disorder characterized by the pathological deposition of silver particles in various tissues following chronic exposure to silver compounds (2). The condition develops through multiple exposure routes, including ingestion, inhalation, and dermal absorption, with occupational exposure representing the most frequent etiology in contemporary clinical practice (3). The pathophysiological mechanism involves the reduction of absorbed silver ions to insoluble metallic silver particles, which are subsequent-

ly sequestered in tissues rich in elastic fibers and basement membranes (2).

Ocular argyrosis represents the most frequently encountered form of localized argyria, characterized by pathognomonic gray discoloration of ocular structures (4). The deposition of silver salts results in skin discoloration around the eyes; the affected area becomes gray or bluish-gray. Silver precipitates are distributed in the elastic fibers of the connective tissue and basement membranes, including the eyelids, conjunctiva, lacrimal sac, lens, ciliary body and Bruch's membrane, and are also noted within Bowman's membrane, corneal stroma, Descemet's membrane, and lens capsule, causing characteristic tissue discoloration (5). While the majority of patients remain asymptomatic, some individuals

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may experience nyctalopia or visual field abnormalities (2). Ocular argyrosis diagnosed during a thorough ophthalmic examination may be the first sign of generalized argyria. The disease may also develop following the use of silver-containing eye drops, certain eyelash and eyebrow dyes (6). Diagnosis is primarily established through clinical examination and occupational history (3). Histopathological examination remains the gold standard for definitive diagnosis when tissue samples are available (7). Herein a case of ocular argyrosis in a patient who underwent cataract surgery with histopathological analysis of the anterior lens capsule confirming silver deposition is reported.

Case Report

A 57-year-old male patient presented with a 4-year history of progressive visual deterioration in the right eye. The patient was a long-standing silver worker who had been diagnosed with ocular argyrosis 16 years earlier. His past medical history was significant for hypertension and myocardial infarction. Current medications included antidepressant therapy and acetylsalicylic acid.

Best-corrected visual acuity measured with the Snellen chart was hand motion in the right eye and 0.6 in the left eye with optical correction. Slit-lamp examination revealed characteristic findings of ocular argyrosis bilaterally. The periocular skin and ocular surface displayed diffuse black-gray pigmentation in both eyes. Corneal examination showed patchy pigmentation in the stroma and Descemet's membrane bilaterally, with highly reflective punctiform deposits extending from the anterior to mid-stroma and increasing in density toward the corneal endothelium (Fig. 1a). Due to the intense stromal silver deposits, proper evaluation of the corneal endothelium was not possible. The right eye demonstrated a mature cataract with complete cortical opacity, while the left eye showed nuclear sclerosis (Fig. 1b). The anterior segment optical coherence tomography (AS-OCT) also demonstrated silver accumulation in the cornea (Fig. 1c). Fundus examination was not possible in the right eye due to the dense cataract. However, the left eye fundus appeared normal with no pigmentation. Intraocular pressure was within normal limits in both eyes. Ocular ultrasonography of the right eye confirmed no retinal detachment and revealed normal posterior segment anatomy. Based on the clinical findings of corneal silver deposits and visually significant cataract, the patient was scheduled for phacoemulsification with intraocular lens implantation (IOL) in the right eye. The biometry was performed using optical coherence biometry, showing axial length: 24.02 mm, K1: 43.49 D, K2: 45.06 D, and anterior chamber depth: 3.51 mm. The IOL was 18.5 D.

The patient underwent uncomplicated phacoemulsification with posterior chamber intraocular lens implantation

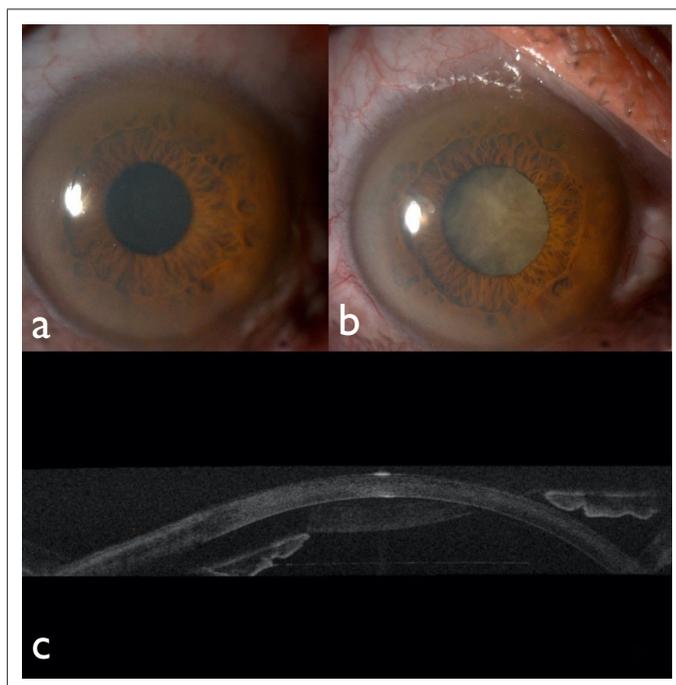


Figure 1. (a) Corneal examination showing patchy pigmentation in the stroma and Descemet's membrane, with highly reflective punctiform deposits extending from the anterior to mid-stroma and increasing in density toward the corneal endothelium. (b) Right eye showing mature cataract with complete cortical opacity. (c) Anterior segment optical coherence tomography demonstrating silver accumulation in the cornea.

under topical anesthesia. During the capsulorhexis procedure, the anterior lens capsule tissue was carefully collected and submitted for histopathological examination. The surgical procedure was completed with no complications. Postoperatively, the patient was treated with routine topical antibiotic and corticosteroid therapy. The recovery was uneventful with no signs of inflammation or other complications during the follow-up period. Histopathological analysis of the anterior lens capsule revealed characteristic silver deposits consistent with ocular argyrosis, confirming the clinical diagnosis (Fig. 2). The silver particles were identified within the capsular matrix, providing definitive evidence of silver accumulation in the ocular tissues.

The patient demonstrated excellent visual recovery following cataract surgery, with best-corrected visual acuity improving to 0.9 with optical correction (+0.75 -1.25 100), and no postoperative complication was observed.

Informed consent was obtained from all individual participants included in the study.

Discussion

Ocular argyrosis constitutes a rare ophthalmic manifestation of systemic silver toxicity, characterized by pathological silver accumulation within diverse ocular structures. The incidence has markedly decreased due to enhanced industrial safety

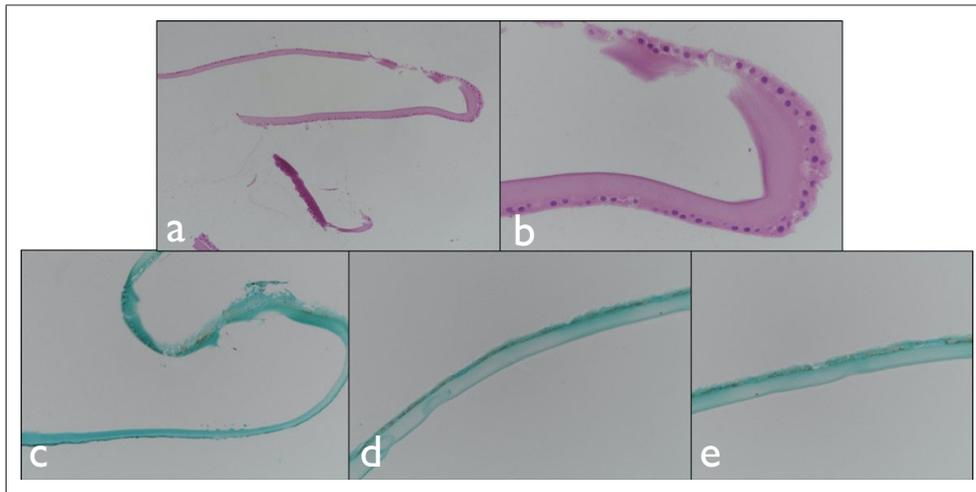


Figure 2. Histopathological examination of the anterior lens capsule. **(a, b)** Hematoxylin and eosin (H&E) staining showing the anterior lens capsule with single-layered endothelial cells at low magnification (a, $\times 40$) and higher magnification (b, $\times 200$). **(c-e)** Methenamine silver staining demonstrating fine granular pigmented silver particles within the capsular matrix and endothelial cells. (c, $\times 40$; d, $\times 100$; e, $\times 100$).

measures and discontinuation of silver-containing medications (8). Despite these preventive measures, silver compounds maintain widespread industrial applications across metallurgical processes, photographic technologies, jewelry manufacturing, and specialized medical devices, perpetuating potential occupational exposure (9). This case highlights the importance of histopathological confirmation in cases of suspected ocular argyrosis and demonstrates successful surgical outcomes in patients with this rare condition.

The pathophysiological mechanisms involve systemic uptake of silver particles, which form stable molecular complexes with endogenous proteins, DNA and RNA structures (3). These silver-protein conjugates demonstrate selective tissue tropism, accumulating preferentially in highly vascularized ocular tissues, particularly the choroidal vasculature and ciliary body. In contrast to systemic exposure, topical silver exposure typically results in localized ocular argyrosis with predominant intracellular accumulation within conjunctival epithelial cells and extracellular precipitation at the Descemet's membrane level (10). Silver deposits selectively accumulate within elastic fibers of connective tissue and basement membrane structures, involving the eyelids, conjunctiva, lacrimal sac, crystalline lens, ciliary body, and Bruch's membrane. Corneal deposition occurs across multiple anatomical layers, involving Bowman's membrane, corneal stroma, and Descemet's membrane, resulting in characteristic tissue discoloration (1,7,9). Clinical studies demonstrate a direct correlation between exposure duration and corneal deposit density (11,12).

The clinical spectrum demonstrates considerable phenotypic heterogeneity, with numerous patients exhibiting asymptomatic corneal silver deposition (13). However, Sta-

feeva et al. (4) reported that some individuals may develop nyctalopia secondary to photoreceptor cellular dysfunction. Sarnat-Kucharczyk et al. (2) described additional manifestations including visual field deficits and decreased visual acuity, though these complications are relatively infrequent. Additionally, Palamar et al. (14) reported in their case report that bilateral ocular surface pigmentation and black tears were observed in a case of argyrosis due to occupational silver exposure. The most frequent finding consists of conjunctival hyperpigmentation, particularly in the nasal region and caruncle (8).

The current case presents a scenario of occupational ocular argyrosis in a long-standing silver worker with 16 years of known disease progression. This case demonstrates the chronic, progressive nature of silver deposition and highlights the importance of long-term monitoring in patients with occupational exposure. Bilateral corneal deposits, periocular pigmentation, and systemic tissue involvement were consistent with characteristic silver deposition patterns as described in the literature (7,13,15).

Contemporary imaging technologies have fundamentally transformed diagnostic paradigm and morphological characterization. AS-OCT emerged as a valuable non-invasive tool, identifying silver deposits as hyperreflective bands at Bowman's layer and Descemet's membrane levels (10,12,16). Dudeja et al. (12) demonstrated novel AS-OCT application in a 67-year-old photographic film manufacturer with chronic silver-halide exposure, revealing distinct hyperreflective bands that distinguish ocular argyrosis from other metallic deposition diseases such as Wilson's disease or drug-induced corneal verticillata. In vivo confocal microscopy has proven invaluable in characterizing corneal silver accumulation, re-

vealing distinctive hyperreflective precipitates with granular morphological patterns (11,15). Mora et al. (16), utilizing in vivo confocal microscopy, demonstrated that argyrosis typically does not stimulate corneal inflammatory reactions, with most patients remaining asymptomatic, consistently showing absence of activated keratocytes and dendritic cells.

Surgical management of cataract in ocular argyrosis patients requires careful consideration. Our patient underwent successful phacoemulsification with IOL implantation, achieving excellent visual outcomes with best-corrected visual acuity improving to 0.9 postoperatively. This demonstrates concordance with previously published reports advocating safety and efficacy of cataract extraction in argyrosis patients (17). Dudeja et al. (12) reported a 56-year-old silversmith with bilateral ocular argyrosis who underwent cataract surgery with histopathological confirmation of silver deposits in the lens nucleus, raising important questions regarding whether silver deposits occur in senile cataracts or if cataracts are induced by silver deposition itself. Agarwal et al. (17) highlighted challenges in IOL power calculation, noting that Scheimpflug imaging results may be erroneous due to light blockage by silver deposits, while optical and ultrasonic biometry remain reliable, with recommendations for monofocal IOLs until long-term results of premium IOLs are established. Nevertheless, theoretical concerns warrant consideration, including potential bioactivity of silver particles within aqueous humor, possible mobilization of corneal silver deposits during surgical manipulation, and unknown long-term biocompatibility interactions between silver compounds and IOL biomaterials. Histopathological validation of silver deposits within our patient's anterior lens capsule provided definitive diagnostic confirmation. This approach has been emphasized as the gold diagnostic standard, particularly in ambiguous or atypical presentations (8). Microscopic identification of silver particles within the capsular matrix confirms the systemic nature of silver deposition.

Differential diagnostic considerations encompass alternative metallic deposition disorders, including Wilson's disease with pathognomonic copper accumulation, ocular chrysiasis characterized by gold particle deposition, and siderosis involving iron precipitation (10). Conditions associated with abnormal ocular pigmentation, including primary acquired melanosis and malignant melanoma, require systematic exclusion (18). Pharmacologically-induced corneal deposits secondary to medications such as amiodarone and antimalarial agents may demonstrate morphologically similar presentations (1). This case emphasizes the critical importance of comprehensive ophthalmological evaluation and long-term monitoring in patients with occupational silver exposure. The successful surgical outcome demonstrates that cataract extraction can be performed safely in

patients with concurrent ocular argyrosis. Histopathological examination of surgically obtained specimens provides invaluable diagnostic information and should be considered when clinically feasible.

The long-term visual prognosis remains generally favorable, particularly when future silver exposure is effectively prevented. However, existing metallic deposits are considered irreversible and permanent, emphasizing the paramount importance of early clinical recognition and appropriate occupational counseling when applicable (2). Comprehensive long-term studies evaluating potential interactions between silver deposits and intraocular lens materials following cataract surgery remain absent in current literature, highlighting an important area for future research.

Conclusion

This case demonstrates successful cataract surgery in a patient with chronic occupational ocular argyrosis, with histopathological confirmation of silver deposits in the anterior lens capsule, providing a definitive diagnosis. The excellent visual outcome (BCVA 0.9) confirms that phacoemulsification can be safely performed in patients with silver deposition. Early recognition of occupational silver exposure and appropriate monitoring remain crucial, as existing deposits are irreversible despite a favorable long-term visual prognosis when further exposure is prevented.

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