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Glaucoma

Symptomatic Presbyopia may Develop Earlier in Patients With Glaucoma—A Cross-Sectional Retrospective Cohort Study

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Purpose: The purpose of this study was to explore risk factors for symptomatic presbyopia, defined as near add power ≥1.50 diopters, in patients with glaucoma.

Methods: Treated glaucoma (n = 56), untreated glaucoma (n = 21), and control individuals (n = 376), aged 40 to 55 years at first visit, were enrolled in the study, and near add power, retinal thickness, and visual field were examined. The association between near add power and ocular parameters and the odds ratios (ORs) for symptomatic presbyopia were investigated. Survival analysis for symptomatic presbyopia was conducted.

Results: Age, astigmatic power, mean deviation, and ganglion cell complex thickness were associated with near add power. The OR for symptomatic presbyopia was significant for age (OR = 1.51), astigmatism (OR = 1.01), mean deviation (OR = 0.72), ganglion cell complex thickness (OR = 0.98), treated and untreated glaucoma (OR = 2.09), and use of glaucoma eye drops (OR = 3.33). Survival analysis showed that the treated glaucoma group reached the near add power endpoint of ≥1.50 D (symptomatic presbyopia) significantly earlier than the other two groups, and there was no difference between the control and untreated glaucoma groups.

Conclusions: Glaucoma patients treated with eye drops may start near correction earlier.

Translational Relevance: Symptomatic presbyopia may develop earlier in patients with glaucoma, and our findings could further contribute to better management and understanding of presbyopia with glaucoma.

Introduction

Glaucoma is a typical geriatric disease with a prevalence of 4.1% in Japanese adults over the age of 40.[1] It is a leading cause of irreversible blindness, affecting more than 70 million people globally.[2,3] Because of its chronic nature and visual field defects, quality of life deteriorates,[4] and the risk of falls[5] and motor accidents may increase.[6] Reduction of intraocular pressure (IOP) is the only proven treatment,[7] and currently a number of medications are available for glaucoma, including prostaglandin F (FP) receptor agonists, beta-blockers, and carbonic anhydrase inhibitors. The IOP-lowering mechanisms of action of these medications include modifying the uveoscleral (unconventional) outflow route (e.g., FP receptor agonists) or aqueous humor production (e.g., beta-blockers).[8] Glaucoma patients mostly tolerate medical treatment well, but common side effects of glaucoma eye drops, such as ocular surface symptoms, lid and iris pigmentation, and deepening of the upper eyelid sulcus, may occur.[9,10]

Presbyopia is also a typical aging disease with progressive loss of amplitude of accommodation.[11–13]

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It is a global burden in our super-aging society,[14] and the economic impact from productivity loss caused by uncorrected presbyopia is significant.[15,16] After the mean age of 47, near add is necessary to see clearly at near distance in presbyopes,[17] and this increases with age. Accommodation is mostly driven by ciliary muscle contraction and morphological changes in the crystalline lens.[18] With aging, lens hardening is a major factor causing loss of accommodative amplitude.[18] Risk factors for presbyopia include aging[11,19] and, within similar age groups, diabetes,[20] smoking,[21] and dry eye.[22,23]

Previously, we documented that the FP receptor agonist, latanoprost, could exacerbate the progression of presbyopia by comparing near add power between a control group without any medication, and glaucoma patients treated with 0.005% latanoprost eye drops.[24] Using Kaplan-Meyer survival analysis, we showed that the latanoprost group reached the endpoint of 3.00 D near add power earlier than the control group. This clinical finding is supported by many prior investigations in young individuals[25] and animal experiments.[26] It is hypothesized that glaucoma may have a causal effect on presbyopia. In our previous study, near add power was measured as a primary outcome because it is a clinically relevant and useful parameter that can be easily measured in general practice. Age-related loss of accommodation (presbyopia) occurs throughout life, and accommodation is completely lost by age 50, when the function of the accommodative apparatus is almost completely lost. In addition, presbyopia is complete by the age of 50 (at the onset of most glaucoma cases). Nevertheless, near add power can fluctuate even after the age of 50 and become almost constant after the age of 55. Near add power is a composite value involving pupil size, refraction, aberration, retinal sensitivity, and central function in addition to accommodative amplitude. In this sense, changes in various components of near vision could be retrieved with analysis of near add power. Accordingly, our previous results might suggest that glaucoma is one of the potential contributory factors of presbyopia, especially in younger populations when the clinical onset and progression of both pathologies overlap. The association between glaucoma and presbyopia is also suggested by other investigators to be due to the major pathophysiological factors of both diseases that occur at the ciliary body, including the uveoscleral outflow, ciliary muscle, lens zonule, and crystalline lens.[27,28] Kaufman and colleagues[27,28] have documented how the ocular anterior and posterior segments are linked, both structurally and functionally, and extralenticular changes with age may play an important role in the pathophysiology of presbyopia, glaucomatous optic neuropathy, and impaired aqueous outflow. Using rhesus monkeys, they further demonstrated that the contractility of isolated ciliary muscle does not diminish with age, but the posterior ciliary muscle attachments stiffen, suggesting a possible mechanism for restricting muscle and, consequently, lens movement during accommodation.[29] Additionally, Croft et al.[30,31] described accommodative pressure and tension spikes at the optic nerve head, which may have implications for glaucoma, because glaucoma occurs in individuals even in the normal IOP range. Romano and Lograno[32] used a myograph system of the human isolated ciliary muscle to construct concentration-response curves for bimatoprost, anandamide, PGF2α, latanoprost, and travoprost, and inferred evidence for the involvement of cannabinoid CB1 receptors in bimatoprost-induced contractions. Taken together, there is substantial evidence to suggest presbyopia may be associated with glaucoma and glaucoma medications.

The aim of this study was to explore risk factors for symptomatic presbyopia, defined as a near add power $\geq$1.50 D, in control and glaucoma patients. We focused particularly on potential long-term effects, such as chronic contraction of the ciliary muscle, which may affect accommodation, especially in middle-aged glaucoma patients. We measured the near add power in control, untreated glaucoma, and glaucoma patients prescribed with antiglaucoma ophthalmic solution and conducted regression analysis and survival analysis to identify ocular parameters that were risk factors for increasing near add power at the same age. We enrolled individuals aged from 40 to 55 years when presbyopia is presumably in a linear progression stage for the majority of individuals before reaching the plateau stage, although our previous study[24] analyzed individuals aged from 40 to 69 years when some of the participants may have been in the plateau stage. This age range would be relevant for comparing presbyopia at each age and exploring any progressive factors for presbyopia.

Methods

Study Design, Patient Recruitment, and Institutional Review Board Approval

This was a hospital-based, cross-sectional cohort study conducted from April 2015 to March 2023. Outpatients were consecutively recruited to the study from the Tsukuba Central Hospital (Ibaraki, Japan) from April 2015 to March 2020 and the Otake Eye Clinic (Kanagawa, Japan) from December 2018 to March 2023. The institutional review boards and ethics

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committees of the Tsukuba Central Hospital (approved December 12, 2014, permission number 141201) and the Kanagawa Medical Association (approved November 12, 2018, permission number krec2059006) approved this study, and it was conducted in accordance with the Declaration of Helsinki. The need for consent was waived by the institutional review boards. The institutional review board and ethics committee of Keio University School of Medicine approved this study (June 28, 2021; approval number 20210080) to permit authorship for authors with appointments at Keio University School of Medicine (KN, AH and MA). All the data collected in this study, including patient interviews, were collected as part of routine standard of care. Authors had access to information that could identify individual participants during and after data collection.

Inclusion and Exclusion Criteria

Consecutive bilateral phakic patients aged from 40 to 55 years with best-corrected visual acuity ≥20/25 in both eyes were initially enrolled in the study. Patients examined by Humphrey field analyzer or optical coherence tomography (OCT) for measurement of retinal thickness were selected and analyzed (Fig. 1). Exclusion criteria were macular diseases and glaucoma surgery.

Patient Interviews for Common Eye Symptoms

Participants were interviewed for the presence or absence (yes/no) of three common visual symptoms, namely eye strain, blurred vision, and photophobia. These questions were selected from items on the Dry Eye–Related Quality-of-Life Score questionnaire[33] as the most prevalent symptoms seen in outpatient eye clinics at Keio University Hospital.

Ophthalmological Examinations and Diagnosis of Glaucoma

Glaucoma was diagnosed using a visual field test (Humphrey Visual Field Analyzer 30-2 standard program; Carl Zeiss, Jena, Germany) and OCT (RC3000; Nidek, Gamagori, Japan), which was used to measure the thickness of the ganglion cell complex (GCC), peripapillary nerve fiber layer (NFL), and full macula. Routine ophthalmological examinations were also performed. Individuals with primary open-angle glaucoma and normal-tension glaucoma were screened for eligibility with a battery of ophthalmic examinations, including slit-lamp biomicroscopy, funduscopy, gonioscopy, IOP measurements, and visual field analysis using the 30-2 Standard Swedish Interactive Threshold Algorithm Strategy with the Humphrey Field Analyzer. Primary open-angle glaucoma and normal-tension glaucoma were diagnosed when the following three conditions were present: (1) glaucomatous optic cupping represented by notch formation, generalized enlargement of cupping, senile sclerotic disc or myopic disc, or NFL defects; (2) reproducible typical glaucomatous visual field defects, such as Bjerrum scotoma, nasal step, or paracentral scotoma compatible with optic disc appearance; and (3) open angle observed on gonioscopy or slit-lamp biomicroscopy.

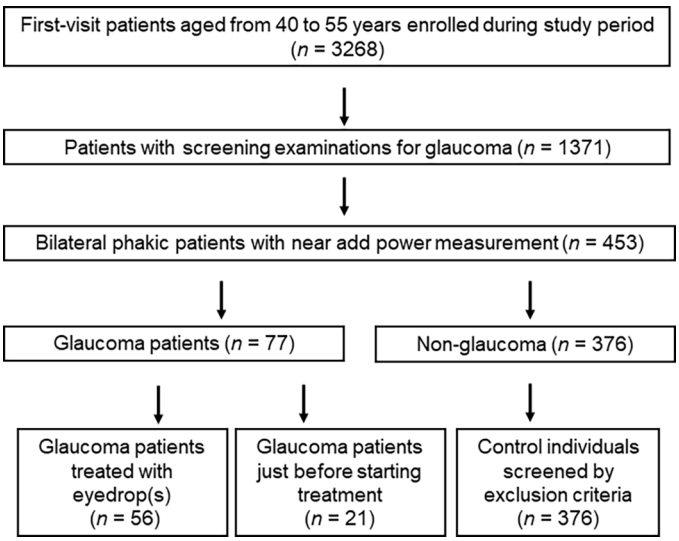

Figure 1. Flow diagram of patient enrolment and inclusion process for the study.

Topical glaucoma medications used were 0.005% latanoprost, a fixed combination of 0.005% latanoprost and 0.5% timolol maleate, 0.0015% tafluprost, 0.5% timolol maleate, 0.4% ripasudil hydrochloride hydrate, or 0.1% brimonidine tartrate. One of the authors (MA) examined all glaucoma patients and controls and checked patient compliance by confirming the frequency and duration of visits. Six months of eye drop use was considered a sufficient period of use because previous studies observed participants for one and 30 days to confirm significant effects.[25,26] Evaluation of control participants included best-corrected visual acuity measurements, autorefractometry, slit-lamp biomicroscopy, funduscopy, IOP measurements with a noncontact tonometer or Goldmann applanation tonometer, OCT, or Humphrey Field Analyzer. This group consisted mostly of individuals who visited the clinic for visual symptoms.

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Table 1. Patient Demographics and Ophthalmological Parameters

	Control	Untreated Glaucoma	Treated Glaucoma	*P* Value*
Number (% men)	376 (28.2)	21 (42.4)	56 (42.9)	0.46
Baseline characteristics				
Age, y	48.6 ± 4.3	48.8 ± 4.4 (0.85)†	48.5 ± 3.4 (0.91)†	0.79
Spherical equivalent, D	−3.36 ± 3.16	−5.30 ± 2.87 (0.01)†	−4.15 ± 3.65 (0.08)†	0.21
Astigmatism, D	0.53 ± 0.57	0.58 ± 0.59 (0.74)†	0.56 ± 0.60 (0.70)†	0.94
Anisometropia, D	0.59 ± 0.85	0.68 ± 0.74 (0.65)†	0.46 ± 0.54 (0.25)†	0.16
Near add power, D	1.53 ± 0.80	1.51 ± 0.54 (0.94)†	1.64 ± 0.63 (0.30)†	0.40
Symptomatic presbyopia (near add power ≥ 1.5 D)	64.6%	61.9% (0.80)†	82.1% (0.01)†	0.06
Glaucoma-related clinical features				
Intraocular pressure, mmHg†	14.9 ± 3.3	16.8 ± 4.3 (0.02)†	14.4 ± 2.9 (0.31)†	0.01
Mean deviation, dB†	−1.68 ± 2.70	−7.47 ± 7.68 (< 0.01)†	−6.11 ± 5.67 (< 0.01)†	0.42
Cup/disc ratio†	0.59 ± 0.16	0.71 ± 0.16 (< 0.01)†	0.79 ± 0.11 (< 0.01)†	0.02
GCC thickness, µm†	92.1 ± 18.8	57.8 ± 16.4 (< 0.01)†	69.6 ± 13.8 (< 0.01)†	0.01
Peripapillary NFL thickness, µm†	106.0 ± 19.5	72.8 ± 20.8 (< 0.01)†	82.0 ± 13.6 (< 0.01)†	0.11
Full macular thickness, µm†	256.2 ± 21.8	246.8 ± 52.2 (0.34)†	259.3 ± 21.4 (0.64)†	0.48
Dry eye-related clinical features				
Tear break-up time, s	3.5 ± 3.0	3.7 ± 3.0 (0.65)†	4.0 ± 3.0 (0.13)†	0.64
Short tear break-up time (≤ 5 s)	67.4%	66.7% (0.95)†	63.8% (0.65)†	0.84
Superficial punctate keratitis	22.0%	23.5% (0.85)†	35.4% (0.02)†	0.32
Use of dry eye medication	26.5%	5.3% (0.04)†	14.3% (0.04)†	0.44

Data are presented as mean ± standard deviation unless specified otherwise.
*P value (untreated vs. treated).
†P value in parentheses vs. control; unpaired *t*-test or χ^2 test (Yates's correction for N ≤ 5) as appropriate.
‡Worse eye.

Board-certified ophthalmologists tested participants for vital staining of the cornea and fluorescein tear break-up time following procedures described in detail elsewhere.[34] Prescribed eye drops for dry eye were 0.1% hyaluronate, 3% diquafosol, and 2% rebamipide.

Binocular near add power was measured by a blinded examiner at a distance of 30 cm using a Bankoku near-acuity chart (Handaya Inc., Tokyo, Japan). After determining the patient's distance refractive correction, the minimal additional power required to achieve near acuity better than 20/25 was measured in 0.25 D increments and was recorded as near add power.

Statistical Analysis

Participants were classified into control, untreated glaucoma, or treated glaucoma groups. Patients diagnosed with glaucoma and treated with topical medication for more than six months were categorized as the treated glaucoma group. Patients diagnosed with glaucoma but who had not yet started topical treatment were categorized as the untreated glaucoma group. Some patients were diagnosed with glaucoma on the day of the visit but had yet to start topical treatment. Usually, treatment was initiated on the same day when treatment was indicated. These patients were categorized as the untreated glaucoma group. Participants without glaucoma were categorized as the control group. Patient demographics, prevalence of ocular symptoms, and ophthalmological parameters were compared using *t*-tests and χ^2 tests. Regression analysis of near add power and ocular parameters and comparison of odds ratios (ORs) for risk factors of symptomatic presbyopia were conducted. Near add power with an endpoint of 1.50 D was compared among treated and untreated glaucoma and control groups using Kaplan-Meier survival analysis and the results analyzed with the Cox-Mantel test. Data are presented as mean ± standard deviation or as percentages where appropriate. All analyses were performed using StatFlex (Atech, Osaka, Japan), with $P < 0.05$ considered to indicate a significant difference.

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Results

Out of 3268 patients aged from 40 to 55 years who visited the study institutes during the study period, 376 control individuals, 21 untreated glaucoma patients, and 56 treated glaucoma patients were finally included in the analysis following the stated inclusion and exclusion criteria (Fig. 1). FP receptor agonists and their fixed combination with beta blockers were prescribed to 46 glaucoma patients (82.9%), and beta blockers and their fixed combination with carbonic anhydrase inhibitors were prescribed to 24 patients (42.9%). All patients were treated with an FP receptor agonist, beta blocker, carbonic anhydrase inhibitor, or their fixed combination, with one patient also receiving 0.4% ripasudil and 0.1% brimonidine. The mean number of glaucoma medications was 1.1 ± 0.5. There were no significant differences in age, gender, spherical equivalent, astigmatism, or anisometropia between the groups, whilst the prevalence of symptomatic presbyopia was greater in the treated glaucoma group than in the control group (Table 1).

For glaucoma-related clinical features, the IOP of the untreated glaucoma group was higher than the control ($P < 0.01$) and treated glaucoma ($P < 0.01$) groups (Table 1). There was no difference in mean deviation, peripapillary NFL thickness or full macular thickness between treated and untreated glaucoma groups, whereas the disc/cup ratio was larger ($P = 0.02$) and GCC thickness thinner ($P < 0.01$) in the untreated glaucoma group compared to the treated glaucoma group. For dry eye-related clinical features, the prevalence of superficial punctate keratitis was greater in the treated glaucoma group than controls ($P = 0.02$) and the use of dry eye medication was greater in the control group than the untreated ($P = 0.04$) and treated glaucoma groups ($P = 0.04$; Table 1).

Table 3. Association Between Near Add Power and Ocular Parameters

	Beta	*P* Value
Baseline characteristics and refractive status		
Age in years	0.67	<0.01
Sex (men = 1)	0.01	0.77
Spherical equivalent	0.02	0.49
Astigmatism	0.09	<0.01
Anisometropia	−0.03	0.33
Glaucoma-related clinical features		
Intraocular pressure*	−0.06	0.06
Mean deviation*	−0.11	0.01
Cup/disc ratio*	−0.01	0.83
GCC thickness*	−0.12	<0.01
Peripapillary NFL thickness*	−0.06	0.28
Full macular thickness*	−0.04	0.46
Number of glaucoma medications	0.04	0.24
Diagnosed glaucoma	0.03	0.26
Dry eye-related clinical features		
Tear break-up time	−0.04	0.30
Superficial punctate keratitis	0.01	0.63
Use of dry eye medication	−0.01	0.68

Standardized partial regression coefficient, adjusted for age and sex.
*Worse eye.

Ocular symptoms were generally less prevalent in the untreated and treated glaucoma groups than the control group (Table 2). Specifically, the prevalence of dryness was lowest in the treated glaucoma group, whereas eye strain had the highest prevalence in the control group.

Regression analysis of near add power and ocular parameters indicateing age, astigmatism, mean deviation, and GCC thickness were significantly associated with near add power (Table 3). Comparison of ORs

Table 2. Prevalence of Subjective Symptoms

Symptoms	Control	Untreated Glaucoma	Treated Glaucoma	*P* Value (Untreated Vs. Treated)
Dry sensation	34.8	27.8 (0.55)*	7.7 (<0.01)*	<0.01
Foreign-body sensation	20.8	11.1 (0.33)*	11.5 (0.07)*	0.78
Ocular pain	10.8	0.00 (0.21)*	0.00 (0.01)*	
Eye strain	45.2	16.7 (0.03)*	30.8 (0.03)*	0.36
Sensitivity to bright light	20.1	0.00 (0.04)*	13.5 (0.29)*	0.15
Blurring	27.0	33.3 (0.56)*	19.2 (0.23)*	0.23

Values are percentage prevalence.
*P value in parentheses vs. control; χ^2 test (Yates's correction for N ≤ 5).

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Table 4. Comparison of ORs for Risk Factors of Symptomatic Presbyopia

Risk Factors	OR	Upper Limit of 95% CI	Lower Limit of 95% CI
Baseline characteristics and refractive status			
Age	1.517**	1.405	1.637
Sex (men = 1)	0.964	0.564	1.649
Spherical equivalent	1.000	0.999	1.001
Astigmatism	1.006*	1.001	1.010
Anisometropia	0.998	0.994	1.001
Glaucoma-related clinical features			
Intraocular pressure†	0.973	0.906	1.045
Mean deviation†	0.720**	0.609	0.851
Cup/disc ratio†	1.001	0.986	1.015
GCC thickness†	0.984*	0.971	0.998
Peripapillary NFL thickness†	0.991	0.972	1.010
Full macular thickness†	0.995	0.974	1.017
Use of glaucoma medication	3.335**	1.405	7.915
Diagnosed glaucoma	2.094*	1.031	4.252
Dry eye-related clinical features			
Tear break-up time	1.097	0.592	2.033
Superficial punctate keratitis	1.502	0.800	2.821
Use of dry eye medication	1.297	0.713	2.363

CI, confidence interval; OR, odds ratio.
* $P < 0.05$, adjusted for age and sex.
** $P < 0.01$, adjusted for age and sex.
† Worse eye.

for risk factors of symptomatic presbyopia revealed the OR for symptomatic presbyopia (near add power ≥ 1.50 D) was significant for age (OR = 1.51), astigmatism (OR = 1.01), mean deviation (OR = 0.72), GCC thickness (OR = 0.98), diagnosed glaucoma (treated and untreated; OR = 2.09), and use of glaucoma eye drops (OR = 3.33; Table 4). A Kaplan-Meier survival plot showed the age at which individuals in the three groups reached the near add power endpoint of 1.50 D, defined as symptomatic presbyopia. Treated glaucoma patients reached the endpoint of 1.50 D significantly earlier than those in the control ($P < 0.0$, Cox-Mantel test) and untreated glaucoma groups ($P = 0.02$). There was no difference between control and untreated glaucoma groups ($P = 0.83$; Fig. 2).

Discussion

The current study identified risk factors for symptomatic presbyopia in glaucoma patients and suggests symptomatic presbyopia may develop earlier in glaucoma patients with medication. Contractility of isolated ciliary muscle does not diminish with age,[35] and so it can be hypothesized that, first, long-term glaucomatous ocular change and aging induce stiffened posterior ciliary muscle attachments, producing a possible mechanism for restricting muscle and, consequently, lens movement during accommodation.[27,28] Second, glaucoma medications may enforce continuous contraction of ciliary muscle,[27,28] leading to decreased muscle function because of circulatory disorders. These pathologies could be linked to the development of early symptomatic presbyopia. We also speculate that FP receptor agonists induce weak pseudomyopia and accommodation spasm that may be reversible in young people[25,26] but become irreversible in the elderly.[35] Beta blockers have also been suggested to reduce accommodation.[24] We speculate on two additional possible factors for presbyopia progression in glaucoma. First, visual function may decrease in glaucoma because of deteriorating retinal function, as suggested by electro-retinography[36] and OCT.[37] Second, dry eye, as a side effect of glaucoma medication, may also contribute to the development of focusing difficulty in terms of accommodative micro-fluctuation,[38] irregular astigmatism, and higher-order aberration.[39] The current study indicates that astigmatism is a significant risk factor for developing

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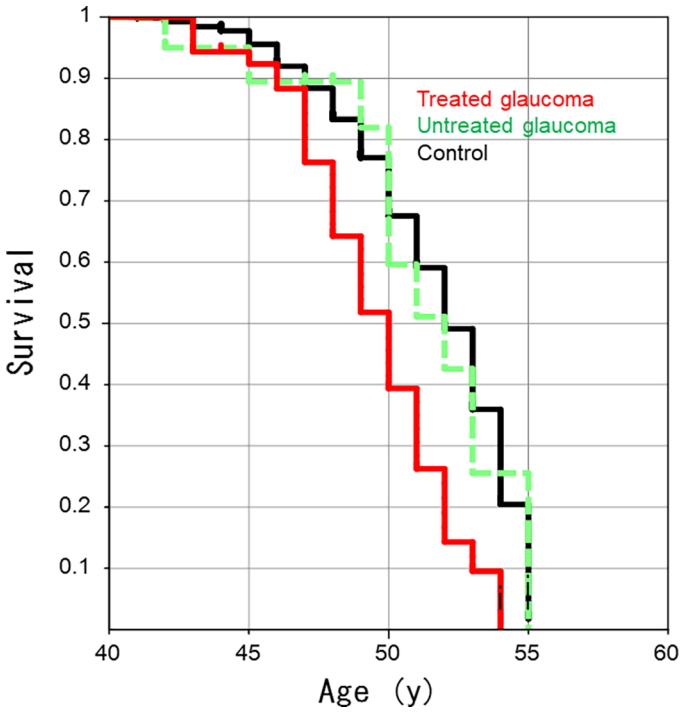

Figure 2. Kaplan-Meier survival plot showing the age at which individuals in the treated glaucoma (red line), untreated glaucoma (green), and control (black) groups reached the near add power endpoint of 1.50 D, defined as symptomatic presbyopia. Treated glaucoma patients reached the endpoint of 1.50 D significantly earlier than individuals in the control group ($P < 0.01$; Cox-Mantel test) and untreated glaucoma group ($P = 0.02$). There was no difference between control and untreated glaucoma groups ($P = 0.83$).

symptomatic presbyopia, and this is supported by a previous investigation reporting that astigmatism aggravates vision[40] and relevant astigmatic correction should be considered in presbyopia.

Middle-aged patients treated with FP receptor agonists may not be aware of their exacerbated presbyopia progression. If they suffer from focusing difficulty, changing from an FP receptor agonist to another medication with less effects on accommodation is recommended. Alternatively, pilocarpine-containing eye drops[41] and contact lenses or eyeglasses with near add power may be prescribed for symptomatic cases. Many pharmacological treatments for presbyopia have been proposed.[41–43] Anti-cataractogenesis treatment for lens hardening could have a substantial benefit for presbyopia treatment,[41,44] and, indeed, suppression of presbyopia progression with pirenoxine eye drops has been seen in clinical and animal studies.[41] Given that FP receptor agonists worsen presbyopia by a continuous contraction force followed by stiffening of the ciliary muscle, alteration or modulation of this mechanism might be a potential treatment strategy for presbyopia.

The present study has several limitations. First, the patients analyzed in this study may be biased toward those with severe glaucoma-related symptoms or concerns to some extent. If the general public, aged 40 to 55, were included in the analysis, the impact of glaucoma and medications could be more accurately assessed. Second, further measurement of pupil diameter, which is significantly involved in accommodation, would allow accurate evaluation of presbyopia status. Third, other possible factors, such as systemic comorbidities, should also be investigated as potential contributors to presbyopia progression.

In conclusion, the current study suggests that symptomatic presbyopia may develop earlier in glaucoma patients using topical medication. Our findings may help further the understanding of the association between glaucoma and presbyopia and better serve glaucoma patients with visual problems.

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