acta medica

ORIGINAL ARTICLE

Evaluation of Risk Factors Affecting Progression in Primary Open-Angle Glaucoma and Exfoliation Glaucoma in a Turkish Population

Abdullah Ağın[1]
ORCID: 0000-0001-7173-8617

Murat İrkeç[2]
ORCID: 0000-0001-8892-4811

Sibel Kocabeyoğlu[2]
ORCID: 0000-0001-6595-3687

Jale Karakaya[3]
ORCID: 0000-0002-7222-7875

[1]University of Health Science, Haseki Training and Research Hospital, Department of Ophthalmology, Istanbul, Türkiye.

[2]Hacettepe University Faculty of Medicine, Department of Ophthalmology, Ankara, Türkiye.

[3]Hacettepe University Faculty of Medicine, Department of Biostatistics, Ankara, Türkiye.

Corresponding Author: Sibel Kocabeyoğlu
E-mail: sibelkocabeyoglu@gmail.com

Received: 17 July 2022, Accepted: 9 December 2022, Published online: 27 December 2022

ABSTRACT

Objective: To evaluate the effects of risk factors on progression in primary open-angle glaucoma (POAG) and exfoliation glaucoma (XFG).

Materials and methods: The study included 139 patients with POAG and XFG followed up at Hacettepe University Faculty of Medicine, Department of Ophthalmology, Glaucoma Unit. A number of factors were evaluated through a cross-sectional design for all the patients, including age, sex, hypertension, diabetes, thyroid disease, cardiovascular disease, migraine, alcohol, smoking, family history, affected side, lens status, central corneal thickness (CCT), number of medications, body mass index (BMI), cup-to-disc (C/D) ratio, intraocular pressure (IOP), computerized automated visual field mean deviation (MD), and prior surgery.

Results: The patients were divided into two groups, POAG and XFG, and further divided into the following two subgroups: progressive and non-progressive. Of the patients, 75 (53.9%) had POAG, and 64 (46.1%) had XFG. In the patients followed up, annual MD change was 0.96 ± 1.5 dB/year, baseline MD was −5.06 ± 5.61 dB, and IOP was 15.94 ± 1.93 mmHg. Potential risk factors for progression in the whole group were evaluated, but no significant difference was found between the groups with and without progression for all factors. Subgroup analysis revealed that in the POAG group, BMI was significantly higher in the non-progressive disease subgroup (p=0.01); furthermore, in the XFG group, IOP was significantly higher in the progressive disease subgroup (p=0.02). According to multiple logistic regression analysis, a 1-unit decrease in BMI in the POAG group increased the risk by 1.3 times (p=0.01), and smoking in the XFG group resulted in a 6-fold reduction in the risk of progression (p=0.04).

Conclusion: Although mean IOP was higher in XFG group, the present study found BMI in POAG and smoking in XFG as independent factors that reduced progression in our series.

Keywords: primary open-angle glaucoma, exfoliation glaucoma, progression, risk factors.

INTRODUCTION

Glaucoma is a leading cause of irreversible blindness and affects more than 60 million people worldwide. Although it is a multifactorial disease, its etiopathogenesis has not been fully elucidated. Intraocular pressure (IOP) is the most important identifiable risk factor implicated in the development and progression of the disease, and a decrease in IOP does not definitively prevent progression [1]. Progression may also occur in patients with low IOP. Primary open-angle glaucoma (POAG) is the most common type of glaucoma and occurs without any underlying trauma, inflammation, or secondary eye disease. Main risk factors are high IOP, age, race, and family history [2]. Exfoliation Syndrome (XFS) is an important ocular manifestation of a systemic disease and is the most common cause of secondary open-angle glaucoma [3,4]. In these patients, mean IOP is higher, and glaucomatous optic neuropathy and coronary artery disease are more relatively common [3,4]. Compared to POAG, it progresses more rapidly and requires a more aggressive treatment. There are inconsistent results regarding the risk factors affecting the progression of glaucoma in the literature. The aim of this study was to evaluate the effect of potential risk factors on progression in patients with POAG and Exfoliation Glaucoma (XFG).

MATERIALS AND METHODS

We included 139 patients with POAG and XFG followed between January 2013 and March 2017 at Hacettepe University Faculty of Medicine, Department of Ophthalmology, Glaucoma Unit. Ethics committee approval for the study was obtained from Hacettepe University Non-Invasive Clinical Research Ethics Committee, approval no GO 17/389 of 16.05.2017. This study was conducted in accordance with the tenets of the Declaration of Helsinki. Medical records of patients who were followed regularly for the last 3 years for POAG and XFG and who underwent at least 5 visual field tests were screened to extract and record systemic findings, diseases, ocular findings, and diagnostic test results. Height and weight measurements were performed using a digital measuring device (Seca 767+220, Seca GmbH, Hamburg, Germany) during patient visits for glaucoma. These parameters were compared in groups with and without progression based on and regardless of the type of glaucoma. Patients were included in the study if they had a regular follow-up of at least 3 years with a diagnosis of POAG or XFG, and they were excluded if they had an eye disease such as uveitis, scleritis, herpetic eye disease, and diabetic retinopathy. Reliable visual field test criteria were a false positive and negative rate and fixation loss of <30% and <20%, respectively [5,6]. Glaucoma staging was performed using Hodapp-Parrish-Anderson criteria based on visual field loss [7].

Visual acuity, cup/disc (C/D) ratio and CCT were evaluated based on data from 3 years ago; IOP and number of medications were evaluated based on mean numbers. Smoking was considered positive if patients smoked at least 1 cigarette per day for 1 year. Cardiovascular diseases considered for evaluation included hypercholesterolemia, hypertriglyceridemia, ischemic and valvular heart disease, transient ischemic attack, arrhythmia, heart failure, and peripheral vascular, cerebrovascular, and thromboembolic diseases. Furthermore, we recorded whether the patients used alcohol regularly for the last 1 year or longer. The patients were based on progressive and non-progressive disease in the whole group (Table 1), as well as in the POAG (Table 2), and XFG (Table 3) group. The criterion for progression was a change in MD value by ≥1 dB/year. The worse eye of the patients (the eye more affected by glaucoma) was used in evaluation. Visual field values were obtained from the standard automated perimeter (Humphrey Field Analyzer 2, Carl Zeiss Meditec, Jena, Germany). The visual field test administered to all patients was the 24-2 SITA Standard method.

All statistical analyses were performed on IBM SPSS Statistics 23.0 program. The Kolmogorov–Smirnov test was used to check whether the numerical variables were normally distributed or not. Descriptive statistics were given in mean and standard deviation for normally distributed variables, and in median (minimum–maximum) values for non-normally distributed variables. Two sets of numerical data were compared using the t-test of significance for the difference between the two means for normally distributed variables, the Mann–Whitney U test for non-normally distributed variables, and the Chi-square test (Pearson, Yates

corrected) or Fisher exact test for comparing categorical variables.

Multiple logistic regression analysis was performed to examine the effects of independent variables such as age, sex, hypertension, diabetes, thyroid disease, cardiovascular disease, migraine, alcohol, smoking, family history, affected side, lens status, number of medications, body mass index (BMI), and IOP on the risk of progression. Backward stepwise (Wald) method was used to remove non-significant terms from the model. Odds ratios and confidence intervals were calculated as a result of the analysis. Statistical significance was set at $P<0.05$.

RESULTS

The mean age of the 139 patients included in the study was 68.84 ± 10.6 years (37–92 years). 67 (48.2%) of the patients were male and 72 (51.8%) were female. Risk factors were evaluated comparatively for the progressive and non-progressive disease groups regardless of the glaucoma type, and for the progressive and non-progressive disease subgroups in the POAG and XFG groups. A total of 31 patients (41.3%) in the POAG group and 33 patients (51.5%) in the XFG group had progressive disease. Statistical analyses were performed on the eyes of patients with progressive disease. The whole group assessment found a median (minimum–maximum) value of –0.76 (–7.12–4.97) dB for annual MD change, a mean (±SD) value of –5.06 ± 5.6 dB for baseline MD, and a mean (±SD) value of 15.94 ± 1.9 mmHg for IOP. According to the Hodapp-Parrish-Anderson Classification, 105 patients were in Stage 1, 18 patients in Stage 2, 8 patients in Stage 3 and 8 patients in Stage 4 [7].

In patients with XFG, the median (minimum–maximum) value for mean IOP was 16 (10–19) in the progressive disease group and 16 (13–18) in the non-progressive disease group (p=0.02). In the POAG group, the median (minimum–maximum) value for BMI was 25.7 (18.6–30.2) in the progressive disease group and 26.7 (21.2–36.9) in the non-progressive disease group (p=0.01). According to multiple logistic regression analysis, a 1-unit decrease in BMI in the POAG group increased the risk by 1.3 times (p=0.01), and smoking led to a 6-fold reduction in the risk (p=0.04). Other evaluated factors had no significant effect on progression in glaucoma. Table 1 shows the results for the whole group of patients. Table 2 and Table 3 show the results of the subgroup analyses for patients with POAG and XFG.

DISCUSSION

In glaucoma, knowledge of systemic and ocular risk factors that may affect progression provides a significant contribution to designing the treatment plan and follow-up of patients. Several have investigated glaucomatous progression, and most have highlighted MD change as a criterion. The authors observed that these studies, essentially based on pointwise linear regression analysis, found an annual change of 1 dB to have high specificity and sensitivity for glaucomatous progression regardless of the stage of the disease, and they evaluated progression on the basis of these studies [8,9].

In the present study, we found that mean IOP in the XFG group was higher in the progressive disease group; BMI in POAG and smoking in XFG emerged as independent risk factors with negative relationship with glaucomatous progression. Some studies in the literature investigating risk factors have reported that IOP affects progression, as observed in our study. Leske et al. showed that a 10%–19% decrease in IOP was effective in slowing down progression [10]. Another study with 557 patients with POAG and XFG reported that mean IOP and more intensive treatment were associated with progression [11]. In a study with 167 patients with XFG, Konstas et al. showed mean IOP to be associated with progression, with a progression rate of 28% for ≤17 mmHg, 43% for 18–19 mmHg, and 70% for ≥20 mmHg [12]. A study by Hollo et al. with 134 patients with XFG reported progression at a rate of 40% at ≤17 mmHg, and 70% at >17 mmHg [2]. Another study by Hollo et al. with 201 patients with XFG showed progression to occur at a rate of 33% for ≤13 mmHg, 54% for 14–21 mmHg, and 84% for ≥22 mmHg [13]. Our study concluded that mean IOP in the XFG group was significantly higher in the progressive disease group, but evaluation for both the POAG and the whole group revealed no significant intergroup differences in terms of mean IOP.

Many studies in the literature mentioned the protective effect of increased BMI in POAG and

Table 1. Comparison of risk factors for the whole group

	Non-progressive (n=75)	Progressive (n=64)	p value
Mean Age (±SD)	66.7 ± 10.9	70.4 ± 10	0.40
Mean CCT (±SD)	540.7 ± 43.2	529.6 ± 35.7	0.10
Sex			
Male	34 (%45.3)	33 (%51.5)	0.46
Female	41 (%54.6)	31 (%48.5)	
Hypertension	43 (%57.3)	37 (%57.8)	0.95
Diabetes	25 (%33.3)	15 (%23.4)	0.27
Thyroid disease	12 (%16)	6 (%9.37)	0.36
Cardiovascular disease	24 (%32)	24 (%37.5)	0.61
Migraine	5 (%6.66)	2 (%3.1)	0.40
Alcohol consumption	10 (%13.3)	6 (%9.3)	0.64
Smoking	16 (%21.3)	10 (%15.6)	0.52
Positive family history	24 (%32)	18 (%28.1)	0.75
Affected side			
Unilateral	10 (%13.3)	11 (%17.1)	0.69
Bilateral	65 (%86.7)	53 (%82.9)	
Lens			
Phakic Patient	58 (%77.3)	41 (%64)	0.12
Pseudophakic Patient	17 (%22.7)	23 (%36)	
Number of Medications (median-min-max)	1.0 (0-4)	2.0 (0-4)	0.06
BMI (median-min-max)	25.8 (20.3-40)	25.8 (18.3-33.5)	0.5
C/D ratio (median-min-max)	0.4 (0.2-0.8)	0.5 (0.2-1)	0.36
Mean IOP (median-min-max) mmHg	16 (13-18)	16 (10-25)	0.65
History of surgery			
Cataract extraction	15 (%20)	17 (%26.5)	0.17
Trabeculectomy	6 (%8)	8 (%12.5)	
No surgery	52 (%69.3)	33 (%51.5)	
Cataract extraction and trabeculectomy	2 (%2.66)	6 (%9.3)	

suggested various mechanisms to explain this [14-19]. In a large-series study involving 787777 women and 41352 men, Pasquale et al. evaluated the association between anthropometric measurements and the incidence of POAG, and showed higher BMI in women to be associated with lower incidence of POAG, but they could not find the same association in men [14]. Adipose tissue can act as an endocrine organ and secrete paracrine factors that can affect the death of retinal ganglion cells [20]. One possible mechanism that has been suggested is that increased estrogen in circulation in people with high BMI binds to receptors in retinal ganglion cells and exerts a protective effect [21]. However, the Singapore Eye Study showed low BMI to be associated with a large vertical C/D ratio in men [22]. The Barbados Eye Study found higher BMI in men and women to have protective effects against the risk of POAG, and suggested this might be due to genetic differences in people with higher BMI [23]. Gasser et al. found that people with lower BMI had an increased predisposition to developing glaucoma [24]. Similarly, Zheng et al. and Xu et al. reported that people with a predisposition to glaucoma were tall people with low BMI [15,16]. Springelkamp et al. showed that tall, thin, and low-BMI people had a greater C/D ratio and a smaller neuroretinal rim area, and in parallel with other studies, they showed increased BMI to be a protective factor for POAG [17]. Trans-lamina cribrosa pressure results from the difference between IOP and cerebrospinal fluid (CSF) pressure, and its increase is associated with glaucomatous nerve damage in the optic disc [18]. Since BMI is correlated with CSF pressure, low CSF pressure and low BMI are thought to be involved in the pathogenesis of glaucomatous optic neuropathy [18,19]. In parallel with this information, two

Table 2. Comparison of risk factors in the Primary Open-Angle Glaucoma group

	Non-progressive (n=44)	Progressive (n=31)	p value
Mean Age (±SD)	63.43 ± 11.44	67.29 ± 10.78	0.14
Mean CCT (±SD)	549.75 ± 43.60	533.54 ± 33.19	0.86
Sex			
Male	19 (%43.1)	11 (%35.4)	0.66
Female	25 (%56.9)	20 (%64.6)	
Hypertension	24 (%54.5)	16 (%51.6)	0.98
Diabetes	13 (%29.5)	7 (%22.5)	0.68
Thyroid disease	8 (%18.1)	4 (%12.9)	0.75
Cardiovascular disease	15 (%34)	11 (%35.4)	0.83
Migraine	4 (%9)	2 (%6.5)	0.51
Alcohol consumption	5 (%11.3)	1 (%3.2)	0.39
Smoking	5 (%11.3)	1 (%3.2)	0.39
Positive family history	19 (%43.1)	13 (%41.9)	0.89
Affected side			
Unilateral	5 (%11.3)	4 (%12.9)	0.87
Bilateral	39 (%88.7)	27 (%87.1)	
Lens			
Phakic Patient	34 (%77.2)	21 (%67.7)	0.51
Pseudophakic Patient	10 (%22.8)	10 (%32.3)	
Number of Medications (median-min-max)	1 (0-2)	1 (0-4)	0.41
BMI (median-min-max)	26.7 (21.2-36.9)	25.7 (18.6-30.2)	**0.01***
C/D ratio (median-min-max)	0.4 (0.2-0.8)	0.5 (0.2-1)	0.35
Mean IOP (median-min-max)	16 (13-18)	16 (12–25)	0.13
History of surgery			
Cataract extraction	10 (%22.7)	7 (%22.5)	0.13
Trabeculectomy	2 (%4.5)	3 (%9.6)	
No surgery	32 (%72.7)	18 (%58)	
Cataract extraction and trabeculectomy	0 (%0)	3 (%9.6)	

studies by Berdahl et al. showed that CSF pressure was lower in patients with POAG compared to the control group, and stated that low CSF pressure may have the same effect as increased IOP in the development of glaucoma [25,26]. Although there is no data in the literature evaluating progression in connection with BMI in POAG and XFG patients; our study showed that low BMI was associated with progression of glaucoma in patients with POAG, but could not demonstrate the same association in patients with XFG, which might be attributable to the different mechanisms involved in the development of the two glaucoma subtypes. New research supports the hypothesis of presence of a paravascular pathway in the eye, similar to the recently discovered "glymphatic system" of the brain, a functional waste clearance pathway that promotes the removal of solutes, including amyloid-β, from the brain through paravascular channels. This discovery has provided a different and strong insight into the pathophysiology of the disease [27]. Amyloid-β increases with chronic elevation in IOP in animals with experimentally induced ocular hypertension and causes the death of retinal ganglion cells [28]. Lower CSF pressure and increased trans-lamina cribrosa pressure gradient lead to restriction in normal glymphatic flow at the level of lamina cribrosa, possibly resulting in accumulation of toxic substances such as amyloid-β. These mechanisms strongly support the association between low BMI and progression in POAG.

Vascular factors are thought to be involved in the pathogenesis of glaucoma owing to changes in blood flow in the optic nerve head. Although some studies have shown that smoking is associated with the development of glaucoma,[29] other studies

Table 3. Comparison of risk factors in the Exfoliation Glaucoma group

	Non-progressive (n=31)	Progressive (n=33)	p value
Mean Age (±SD)	71.3 ± 8.4	71.3 ± 8.4	0.33
Mean CCT (±SD)	528 ± 40	528 ± 40	0.83
Sex			
Male	15 (%48.3)	15 (%48.3)	0.22
Female	16 (%51.7)	16 (%51.7)	
Hypertension	19 (%61.2)	19 (%61.2)	0.94
Diabetes	12 (%38.7)	12 (%38.7)	0.32
Thyroid disease	4 (%12.9)	4 (%12.9)	0.66
Cardiovascular disease	9 (%29)	9 (%29)	0.54
Migraine	1 (%3.2)	1 (%3.2)	0.48
Alcohol consumption	5 (%16.1)	5 (%16.1)	0.81
Smoking	5 (%16.1)	5 (%16.1)	0.81
Positive family history	5 (%16.1)	5 (%16.1)	0.81
Affected side			
Unilateral	5 (%16.1)	5 (%16.1)	0.84
Bilateral	26 (%83.9)	26 (%83.9)	
Lens			
Phakic Patient	24 (%77.4)	24 (%77.4)	0.23
Pseudophakic Patient	7 (%22.6)	7 (%22.6)	
Number of Medications (median-min-max)	1 (0-3)	1 (0-3)	0.12
BMI (median-min-max)	25.3 (20.3-40.0)	25.3 (20.3-40.0)	0.22
C/D ratio (median-min-max)	0.5 (0.3-0.8)	0.5 (0.3-0.8)	0.06
Mean IOP (median-min-max)	16 (13-18)	16 (13-18)	**0.02***
History of surgery			
Cataract extraction	5 (%16.1)	5 (%16.1)	0.73
Trabeculectomy	4 (%12.9)	4 (%12.9)	
No surgery	20 (%64.5)	20 (%64.5)	
Cataract extraction and trabeculectomy	2 (%6.4)	2 (%6.4)	

have found no association [30,31]. Furthermore, association between smoking and progression in glaucoma is controversial in the literature, and data are scarce on this issue. Asaoka et al. argued that there is a positive correlation between smoking and progression in glaucoma in patients with POAG, and showed that visual field damage in smoking patients with POAG was more pronounced in the lower quadrant, similar to non-arteritic anterior ischemic optic neuropathy [32]. Chiotoroiu et al. reported that glaucoma progressed faster in smokers, without specifying which type of glaucoma patients were included in the study [33]. However, the newly published UK Glaucoma Treatment study showed that glaucomatous damage in the visual field decreased with active or previous smoking in patients with POAG and XFG [34]. This is possibly the first study that included patients with XFG and evaluated glaucomatous progression in connection with smoking, and its results are in line with our study [34] The UK Prospective Diabetes Study demonstrated that smokers have a lower incidence of retinopathy and a lower risk of retinopathy progression compared to non-smokers [35]. The researchers in that study emphasized that the strength of the association alone was unlikely to be a coincidence, and that nicotine itself or one of the many other active compounds found in tobacco smoke may have an independent effect. Hollo, however, reported that smoking did not have an acute effect on peripapillary and macular vessel density in middle-aged smokers [36]. These data are supported by the Nurses' Health Study and the Health Professionals Follow-up Study that found an inverse correlation between pack-year and incidence of glaucoma, in line with our findings [37]. Unadjusted analysis in the National Health and Nutrition Examination Survey reported that current

smokers had a lower odds of glaucoma compared to non-smokers and ex-smokers, but this association lost statistical significance in the adjusted models [38]. The authors hypothesized that the possible protective effects of smoking could be negated by heavy smoking [38]. In addition, there appears to be an inverse dose-response relationship between Parkinson's disease and smoking, which is supported by meta-analyses [39]. The protective effect of smoking on neurodegenerative diseases including glaucoma should not be underestimated. Despite the known adverse effects of smoking or nicotine on ocular circulation and tissues, nicotine is also thought to have protective mechanisms on the blood supply of the optic nerve. Nicotine may cause the release of nitric oxide from perivascular nitric oxide (NO)-dependent nitrergic neurons, leading to vasodilation [40] A case-control study based on data from the Nurses' Health Study and the Health Professionals Follow-Up Study showed that smoking has an effect on glaucoma associated with nitric oxide synthase 3 (NOS3) gene variations [41]. Although XFG is known to be associated with molecules that affect NO-dependent pathways such as sirtuin, apelin and asymmetric diarginine,[42,43] smoking, which increases NO production, can be expected to affect the progression in XFG. If the inverse correlation between smoking and XFG is to be confirmed, further research into the mechanisms involved could provide a better understanding of the disease and ultimately help us identify treatment targets. Although the protective effect of not smoking is consistent with some epidemiological evidence for glaucoma and other types of neurodegeneration, the evidence is mixed and complex. Therefore, additional research could help clarify associations.

Cataract surgery in eyes with POAG and XFG is known to cause significant changes in anterior segment parameters such as IOP, CCT, anterior chamber depth, and number of endothelial cells [44,45] The effects of these factors on progression in patients with POAG and XFG have been evaluated in numerous studies in the literature [1,2,10,13,32,46]. Our study found no significant difference between the groups in terms of age, sex, hypertension, diabetes, thyroid disease, cardiovascular disease, migraine, alcohol use, family history, affected side, CCT, number of medications, and previous surgery. In a study with 134 patients with XFG, Hollo et al. achieved results similar to those in our study and found no significant difference between the groups with progressive and non-progressive disease in terms of cardiovascular disease, HT, diabetes, age, and sex [2]. In that study, progression was determined based on clinician's evaluation rather than on quantitative values (thinning of the neuroretinal rim, glaucomatous visual field loss, total cupping, diffuse visual field loss, decrease in best-corrected visual acuity) [2]. In the Early Manifest Glaucoma Trial, however, examination of 126 patients with open-angle glaucoma found that age, bilateral disease, exfoliation, cardiovascular disease, and IOP were risk factors for progression, and thinning of CCT caused increased risk of progression in patients with high IOP [10]. However, CCT has been found to have no significant effect in the previously published Early Manifest Glaucoma Trial [1] This has been thought to be related to the small number of patients with progressive disease included in the former study [1]. In the Early Manifest Glaucoma Trials, all cases of open-angle glaucoma were evaluated in the same group, and the presence of exfoliation was considered as a parameter. In both of these studies, age of >68 years was considered a risk factor for progression [1,10]. In the study by Konstas et al. with 167 patients with XFG, however, multivariate analysis revealed that C/D ratio at the time of diagnosis, number of trabeculectomies and mean IOP were correlated with progression [12]. In that study, similar to the aforementioned study by Hollo et al.,[2]. progression was evaluated based on clinical criteria. The study by Asaoka et al. investigated the effects of age, mean IOP, HT, migraine, presence of family history, and smoking on progression in glaucoma, and found that only age and smoking had an effect on progression [32]. Another study by Hollo et al. showed that age, sex, visual acuity, and presence of cardiovascular disease had no effect on progression, which is in line with our study [13].

The most important limitation of our study is the limited number of patients included in this study and the retrospectively design of evaluation. Adequate data could not be extracted from the records about presence of disc hemorrhage and detailed smoking history consisting of the number of cigarettes smoked per day or information as to whether patients smoked regularly during the evaluation period. Refractive errors and differences in axial length can affect the visual field, but these parameters could not be evaluated owing to the lack of fully adequate data in the records.

In conclusion, our study determined that mean IOP in the XFG group was higher in the progressive disease group. It also found BMI in POAG and smoking in XFG as independent factors with a protective effect on progression of glaucoma. Different parameters have been used in studies as criteria for progression, and different results have been achieved in terms of risk factors affecting progression. This difference in results might have been caused by factors such as genetics, population included in the study, differences in follow-up, and differences in drug compliance; these factors should be evaluated more extensively in larger series.

Author contribution

Study conception and design: AA, MI and SK; data collection: AA, MI, and SK; analysis and interpretation of results: AA, MI, SK, and JK; draft manuscript preparation: AA, MI, SK and JK. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Non-interventional Clinical Researches Ethics Board (Protocol no. GO 17/389 / 16.05.2017).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Leske MC, Heijl A, Hyman L, Bengtsson B, Komaroff E. Factors for progression and glaucoma treatment: the Early Manifest Glaucoma Trial. Curr Opin Ophthalmol. 2004;15(2):102-106.

[2] Hollo G, Quaranta L, Cvenkel B, et al. Risk factors associated with progression in exfoliative glaucoma patients. Ophthalmic Res. 2012;47(4):208-213.

[3] Irkec M. Exfoliation and carotid stiffness. Br J Ophthalmol. 2006;90(5):529-530.

[4] Sekeroglu MA, Bozkurt B, Irkec M, Ustunel S, Orhan M, Saracbasi O. Systemic associations and prevalence of exfoliation syndrome in patients scheduled for cataract surgery. Eur J Ophthalmol. 2008;18(4):551-555.

[5] Lee JM, Caprioli J, Nouri-Mahdavi K, et al. Baseline prognostic factors predict rapid visual field deterioration in glaucoma. Invest Ophthalmol Vis Sci. 2014;55(4):2228-2236.

[6] Viswanathan D, Goldberg I, Graham SL. Relationship of change in central corneal thickness to visual field progression in eyes with glaucoma. Graefes Arch Clin Exp Ophthalmol. 2013;251(6):1593-1599.

[7] Hodapp EP, RK II ; Anderson, DR. Clinical Decisions in Glaucoma. The CV Mosby Co. 1993;52–61.

[8] Chan TCW, Bala C, Siu A, Wan F, White A. Risk Factors for Rapid Glaucoma Disease Progression. Am J Ophthalmol. 2017;180:151-157.

[9] Nouri-Mahdavi K, Hoffman D, Ralli M, Caprioli J. Comparison of methods to predict visual field progression in glaucoma. Arch Ophthalmol. 2007;125(9):1176-1181.

[10] Leske MC, Heijl A, Hyman L, et al. Predictors of long-term progression in the early manifest glaucoma trial. Ophthalmology. 2007;114(11):1965-1972.

[11] Heijl A, Buchholz P, Norrgren G, Bengtsson B. Rates of visual field progression in clinical glaucoma care. Acta Ophthalmol. 2013;91(5):406-412.

[12] Konstas AG, Hollo G, Astakhov YS, et al. Factors associated with long-term progression or stability in exfoliation glaucoma. Arch Ophthalmol. 2004;122(1):29-33.

[13] Hollo G, Cvenkel B, Teus MA, et al. Is there any difference in target intraocular pressure for exfoliative glaucoma patients with cardiovascular disease history? Eur J Ophthalmol. 2010;20(6):1000-1006.

[14] Pasquale LR, Willett WC, Rosner BA, Kang JH. Anthropometric measures and their relation to incident primary open-angle glaucoma. Ophthalmology. 2010;117(8):1521-1529.

[15] Zheng Y, Cheung CY, Wong TY, Mitchell P, Aung T. Influence of height, weight, and body mass index on optic disc parameters. Invest Ophthalmol Vis Sci. 2010;51(6):2998-3002.

[16] Xu L, Wang YX, Wang S, Jonas JB. Neuroretinal rim area and body mass index. PLoS One. 2012;7(1):e30104.

[17] Springelkamp H, Wolfs RC, Ramdas WD, et al. Incidence of glaucomatous visual field loss after two decades of follow-up: the Rotterdam Study. Eur J Epidemiol. 2017.

[18] Ren R, Wang N, Zhang X, Tian G, Jonas JB. Cerebrospinal fluid pressure correlated with body mass index. Graefes Arch Clin Exp Ophthalmol. 2012;250(3):445-446.

[19] Ren R, Jonas JB, Tian G, et al. Cerebrospinal fluid pressure in glaucoma: a prospective study. Ophthalmology. 2010;117(2):259-266.

[20] Gimeno RE, Klaman LD. Adipose tissue as an active endocrine organ: recent advances. Curr Opin Pharmacol. 2005;5(2):122-128.

[21] Munaut C, Lambert V, Noel A, et al. Presence of oestrogen receptor type beta in human retina. Br J Ophthalmol. 2001;85(7):877-882.

[22] Amerasinghe N, Wong TY, Wong WL, et al. Determinants of the optic cup to disc ratio in an Asian population: the Singapore Malay Eye Study (SiMES). Arch Ophthalmol. 2008;126(8):1101-1108.

[23] Leske MC, Connell AM, Wu SY, et al. Incidence of open-angle glaucoma: the Barbados Eye Studies. The Barbados Eye Studies Group. Arch Ophthalmol. 2001;119(1):89-95.

[24] Gasser P, Stumpfig D, Schotzau A, Ackermann-Liebrich U, Flammer J. Body mass index in glaucoma. J Glaucoma. 1999;8(1):8-11.

[25] Berdahl JP, Allingham RR, Johnson DH. Cerebrospinal fluid pressure is decreased in primary open-angle glaucoma. Ophthalmology. 2008;115(5):763-768.

[26] Berdahl JP, Fautsch MP, Stinnett SS, Allingham RR. Intracranial pressure in primary open angle glaucoma, normal tension glaucoma, and ocular hypertension: a case-control study. Invest Ophthalmol Vis Sci. 2008;49(12):5412-5418.

[27] Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. Sci Transl Med. 2012;4(147):147ra111.

[28] Ito Y, Shimazawa M, Tsuruma K, et al. Induction of amyloid-beta(1-42) in the retina and optic nerve head of chronic ocular hypertensive monkeys. Mol Vis. 2012;18:2647-2657.

[29] Zanon-Moreno V, Garcia-Medina JJ, Zanon-Viguer V, Moreno-Nadal MA, Pinazo-Duran MD. Smoking, an additional risk factor in elder women with primary open-angle glaucoma. Mol Vis. 2009;15:2953-2959.

[30] Bonovas S, Filioussi K, Tsantes A, Peponis V. Epidemiological association between cigarette smoking and primary open-angle glaucoma: a meta-analysis. Public Health. 2004;118(4):256-261.

[31] Quigley HA, West SK, Rodriguez J, Munoz B, Klein R, Snyder R. The prevalence of glaucoma in a population-based study of Hispanic subjects: Proyecto VER. Arch Ophthalmol. 2001;119(12):1819-1826.

[32] Asaoka R, Murata H, Fujino Y, et al. Effects of ocular and systemic factors on the progression of glaucomatous visual field damage in various sectors. Br J Ophthalmol. 2016.

[33] Chiotoroiu SM, Pop de Popa D, Stefaniu GI, Secureanu FA, Purcarea VL. The importance of alcohol abuse and smoking in the evolution of glaucoma disease. J Med Life. 2013;6(2):226-229.

[34] Founti P, Bunce C, Khawaja AP, et al. Risk Factors for Visual Field Deterioration in the United Kingdom Glaucoma Treatment Study. Ophthalmology. 2020;127(12):1642-1651.

[35] Stratton IM, Kohner EM, Aldington SJ, et al. UKPDS 50: risk factors for incidence and progression of retinopathy in Type II diabetes over 6 years from diagnosis. Diabetologia. 2001;44(2):156-163.

[36] Hollo G. No Acute Effect of Smoking on Peripapillary and Macular Vessel Density in Healthy Middle-aged Smokers. J Glaucoma. 2019;28(5):e86-e88.

[37] Kang JH, Pasquale LR, Rosner BA, et al. Prospective study of cigarette smoking and the risk of primary open-angle glaucoma. Arch Ophthalmol. 2003;121(12):1762-1768.

[38] Law SM, Lu X, Yu F, Tseng V, Law SK, Coleman AL. Cigarette smoking and glaucoma in the United States population. Eye (Lond). 2018;32(4):716-725.

[39] Breckenridge CB, Berry C, Chang ET, Sielken RL, Jr., Mandel JS. Association between Parkinson's Disease and Cigarette Smoking, Rural Living, Well-Water Consumption, Farming and Pesticide Use: Systematic Review and Meta-Analysis. PLoS One. 2016;11(4):e0151841.

[40] Topouzis F, Wilson MR, Harris A, et al. Risk factors for primary open-angle glaucoma and pseudoexfoliative glaucoma in the Thessaloniki eye study. Am J Ophthalmol. 2011;152(2):219-228 e211.

[41] Kang JH, Wiggs JL, Rosner BA, Haines J, Abdrabou W, Pasquale LR. Endothelial nitric oxide synthase gene variants and primary open-angle glaucoma: interactions with hypertension, alcohol intake, and cigarette smoking. Arch Ophthalmol. 2011;129(6):773-780.

[42] Bezci Aygun F, Kocabeyoglu S, Irkec M, Dikmen ZG, Umaroglu MM, Konstas AGP. Serum Apelin and Asymmetric Dimethylarginine Levels in Patients With Exfoliation Syndrome or Exfoliative Glaucoma. J Glaucoma. 2020;29(7):593-597.

[43] Yucel Gencoglu A, Irkec M, Kocabeyoglu S, Dikmen ZG, Karakaya J, Konstas AGP. Plasma levels of sirtuin and adiponectin in patients with primary open-angle glaucoma, exfoliative glaucoma, and healthy controls. Eur J Ophthalmol. 2021:11206721211065216.

[44] Elgin U, Sen E, Simsek T, Tekin K, Yilmazbas P. Early Postoperative Effects of Cataract Surgery on Anterior Segment Parameters in Primary Open-Angle Glaucoma and Pseudoexfoliation Glaucoma. Turk J Ophthalmol. 2016;46(3):95-98.

[45] Bozkurt B, Guzel H, Kamis U, Gedik S, Okudan S. Characteristics of the Anterior Segment Biometry and Corneal Endothelium in Eyes with Pseudoexfoliation Syndrome and Senile Cataract. Turk J Ophthalmol. 2015;45(5):188-192.

[46] Canadian Ophthalmological Society Glaucoma Clinical Practice Guideline Expert C, Canadian Ophthalmological S. Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of glaucoma in the adult eye. Can J Ophthalmol. 2009;44 Suppl 1:S7-93.

