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Impact of smoking on glaucoma

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Abstract

Purpose of review: Assessing whether lifestyle related factors play a role in causing primary open-angle glaucoma (POAG) is of great value to clinicians, public health experts and policy makers. Smoking is a major global public health concern and contributes to ocular diseases such as cataracts, and age-related macular degeneration through ischemic and oxidative mechanisms. Recently, smoking has been investigated as a modifiable risk factor for glaucoma. In the presence of an association with glaucoma, provision of advice and information regarding smoking to patients may help reduce the burden of disease caused by POAG. Therefore, the aim of this review is to summarize the current evidence regarding the effect of smoking in the pathogenesis of glaucoma and its incidence, progression as well as the benefits of smoking cessation.

Recent findings: While the association between glaucoma development and smoking history is controversial, in the last decade, several recent studies have helped to identify possible effects of smoking, especially heavy smoking, in regard to glaucomatous progression. Smoking cessation may possibly be protective against glaucoma progression.

Summary: Smoking may play a role in glaucoma progression and long-term smoking cessation may be associated with lower glaucoma progression. The dose-response relationship between smoking and glaucoma as well as therapeutic potential of smoking cessation needs to be further validated with both preclinical and rigorous clinical studies.

Introduction

Glaucoma is a progressive optic neuropathy and a leading cause of irreversible blindness worldwide, characterized by retinal ganglion cell (RGC) degeneration and associated visual field (VF) damage.[1]The chronic, progressive, and irreversible nature of damage in glaucoma makes the timely detection of disease progression and understanding of its potential risk factors highly important.[2] A myriad of factors, including older age[3], abnormal systemic blood pressure,[4] elevated intraocular pressure (IOP)[3], and disc hemorrhage (DH)[5] are known to contribute to the disease.

Knowing patients' risk factors, especially modifiable risk factors for glaucoma development and progression, allows clinicians to identify high-risk individuals who can be targeted for closer monitoring or more aggressive treatment. Risk factors can also provide insight into disease mechanisms and may help identify other potential treatment approaches, potentially reducing the economic burden of glaucoma.[6] However, IOP has been known to be the only proven modifiable risk factor for both the development and progression of glaucoma.[7, 8] Nevertheless, many patients with glaucoma still develop progressive functional loss despite relatively low IOP levels.[9]

Evaluating the potential impact of lifestyle-related factors in the development of POAG holds significant importance for clinicians, public health experts, and policymakers. If an association is established, providing advice and information to patients regarding these factors could potentially alleviate the burden associated with POAG.

Smoking

Recently, smoking has been emphasized as a modifiable risk factor for glaucoma.[10] Smoking is a major global public health concern that has been associated with many chronic diseases and has been known to contribute to other ocular diseases such as cataracts, age-related macular degeneration (AMD), and anterior ischemic optic neuropathy through ischemic and oxidative mechanisms. [11-13]

Tobacco use has been linked to vascular dysfunction, as it has been demonstrated to lead to atherosclerotic plaques and intimal thickening that cause occlusion of arterial lumina,[14] as well as decreased blood flow to the optic nerve head.[11, 15] Smoking can also increase inflammation, and oxidative stress as a potential mechanism for initiating vascular dysfunction.[16, 17] Moreover, the high oxidative stress associated with the production of free radicals from smoking has been known to damage trabecular meshwork cells (TMC) and RGCs, decreasing the outflow of the aqueous humor.[18-20] Smoking can also induce vasoconstriction of the episcleral veins and reduce the aqueous outflow.[21] Therefore, according to previous evidence, it seems that the damage caused by smoking may be similar to a putative pathophysiological mechanism of POAG.

In this review, we aim to summarize the latest evidence regarding the effect of smoking on glaucoma as an environmentally modifiable factor, highlighting the potential mechanism of smoking on the pathogenesis of glaucoma and its impact on glaucoma incidence and progression, as well as the current literature's implications for how this risk may be modified through lifestyle changes.

Smoking and Intraocular Pressure

Previous findings regarding the impact of smoking on IOP are equivocal.[22-27] Data from the Blue Mountain Eye Study consisting of 3172 mostly Caucasian residents in Australia

(15.8% current smokers and 35.6% ex-smokers) suggested a moderate positive association between smoking and increased IOP (P = 0.02).[28] In a retrospective study by Lee et al. examining 12.5 million patients utilizing the Intelligent Research in Sight Registry, they found that compared with never smokers, current and past smokers showed a statistically significantly higher IOP by 0.92 mmHg (95% confidence interval [CI], 0.88-0.95 mmHg) and 0.77 mmHg (95% CI, 0.75-0.79 mmHg), respectively, after adjustment for confounding factors. The difference in IOP between current and never smokers was the highest in the fourth decade of life, regardless of the glaucoma status (glaucoma group, 1.14 mmHg [95% CI, 1.00-1.29 mmHg]; without glaucoma group, 0.68 mmHg [95% CI, 0.65-0.71 mmHg]).[26] In contrast, an Australian population-based cross-sectional study of 4576 participants did not find any association between smoking and IOP in participants with or without glaucoma.[25] Moreover, Mahmoudinezhad et al. did not find any association between average IOP and VF progression in former smokers in their study on 511 eyes of 354 POAG patients.[29] Nevertheles, many of the patients in aformentioned studies may be under aggressive therapy and this complicates the evaulation of the effect of smoking on IOP. It has been suggested that the association of smoking with IOP, if any, can potentially be due to reduced aqueous outflow resulting from vasoconstriction of episcleral veins and inhibition of aqueous outflow from the trabecular meshwork.[15, 17, 30] On the other hand, the impact of smoking on glaucoma in smokers may also stem from toxic compounds, triggering ischemic or oxidative mechanisms.[18, 20, 31] As a result, reaching a consensus on asscoiation of smoking and IOP remains challenging. Therefore, further investigation into this topic is warranted to gain a clearer understanding of the relationship between smoking and IOP.

Smoking and Glaucoma Incidence

Several studies investigating the link between smoking and ocular diseases have suggested that the development of POAG may be related to smoking status.[17, 31] However, some large well-designed studies, such as the Beaver Dam Eye Study[32], the Proyecto VER[33], the Los Angeles Latino Eye Study[34], and the Rotterdam Study[35], have failed to show a relationship between glaucoma and cigarette consumption.

Some studies have also demonstrated a potential link between the intensity of tobacco smoking and glaucoma incidence, particularly with heavy smoking use. Law et al. report that in smokers, greater pack/day of smoking history was associated with statistically significantly higher odds of glaucoma (OR=1.70, 95% CI=1.08–2.67, *P*=0.02) in a population-based analysis of the United States National Health and Nutrition Examination Survey database consisting of 3864 participants.[36] In addition, the Black Women's Health Study, a large prospective cohort study following 32,570 African American women from 1995-2007 for incident POAG, found a trend toward significance for heavy smokers under the age of 50.[37]

In contrast, some studies reported a protective effect from smoking.[38-40] Animal model studies have suggested that nicotinic acetylcholine receptor activity may have a neuroprotective effect against the development of glaucoma.[39, 40] In a large prospective study from 1986 to 2010 by Kang et al. analyzing participants of the Nurses' Health Study (NHS) (77,157 women) and the Health Professionals follow-up study (42,773 men), the authors reported that cigarette smoking was inversely correlated with POAG paracentral VF loss subtype (Hazard ratio (HR) = 0.92 [95% CI: 0.87, 0.98] and peripheral VF loss subtype (HR = 0.98 [95% CI: 0.94, 1.01].[41] Nevertheless, Law et al., proposed that the protective effects of smoking, if there are any, may be eliminated in heavy smoking.[36] This may be due to the cumulative toxic effect of tobacco on the optic nerve.[29, 42] This inconsistency in the effect of smoking on glaucoma can also be explained by different levels of nicotine absorption or a

difference in end-organ response to the combination of chemicals in tobacco smoke in various duration and severity of smoking.[43, 44] Furthermore, the discrepancies in the results between various studies investigating the dose–response effect of smoking may be partially explained by the difficulty in accurately measuring smoking dose and being reliant on self-reporting of smoking status, which may be subject to a high degree of recall bias.

Smoking and Visual Field Damage

Various cross-sectional and prospective studies have also investigated the effect of smoking on VF damage.[41, 45, 46] In a study by Asaoka et al., including 409 eyes from 268 patients over 5.5 years of follow-up from the Japanese Archive of Multicentral Databases in Glaucoma (JAMDIG), smoking status was related to glaucomatous VF progression in all sectors of the inferior hemifield.[45] This may reflect the effects of ischemia associated with smoking, given that non-arteritic anterior ischemic optic neuritis has been reported to cause similar inferior altitudinal defects.[47] Nevertheless, the reason for why smoking was not a risk factor for progression in the superior hemifield remained unclear. The large prospective study described previously by Kang et.al., also showed that smokers with greater pack-years were significantly more likely to have a peripheral VF than paracentral VF defect in POAG.[41]

In healthy chronic heavy smokers, retinal sensitivity was found to be decreased, although the central vision was not affected, possibly due to a cumulative effect of chronic smoking onto the retinal and/or optic nerve functions without clinically evident optic neuropathy.[42] Akarsu et al.,[46] showed that moderate cigarette smoking (10–20 cigarettes per day for at least the past 5 years) is associated with both diffuse and localized reductions in retinal sensitivity using white on white perimetry. Therefore, there appears to be evidence that smoking can lead to functional loss in glaucoma and the VF loss may be related to the smoking intensity, especially with moderate to heavy smoking.

Smoking and Retinal Thickness Thinning

Controversy exists regarding the effects of pack-years on retinal thickness in glaucoma patients across several cross-sectional studies.[44, 48-51] In the study by Moschos et al., where they recruited 31 smokers and 25 age and sex matched non-smoker control, chronic smokers for more than 25 years showed thinner ganglion cell complex thicknesses than control subjects.[48] In addition, Kumar et al. evaluated the effects of moderate to heavy smoking on RNFL thickness and found significantly thinner RNFL in smokers compared to never smokers only in the nasal quadrant.[50] However, a cross-sectional study by Duman et al. examining 108 subjects (54 smokers of at least 10 pack-year and 54 never-smoker) did not find any difference in RNFL thickness between smokers (average of 22 pack-years) and never smokers, possibly due to small sample size.[49] Other studies also did not find any association between smoking status and RNFL thickness.[44, 51] These observations could shed light on the fact that the cumulative effect of smoking may need a higher intensity and possibly longer time to impact retinal thickness in glaucoma patients. Nevertheless, this evidence suggested that moderate to heavy intensity of smoking may be associated with retinal thinning, adding value to the evaluation of smoking intensity in the assessment of glaucoma patients.

Smoking and Retinal Vessel Density Loss

The decreased optic disk perfusion in smokers may also affect glaucoma,[52] as an increase in the incidence, prevalence and progression of glaucoma has been reported to be associated with reduced ocular blood flow.[53-56] In an earlier case-control study by Aayhan et al, consisting of 40 smoker-eyes and age/sex matched controls, the authors reported that smoking acutely reduced macular blood flow. However, macular vessel density did not change one hour after smoking.[43] The authors thus suggested smoking may only acutely induce macula hypoxia. However, in a recent retrospective cross-sectional study by Eslani et al.,[52] the authors reviewed 432 eyes of 271 glaucoma patients followed up by OCTA and reported

each 10 pack-year increase in smoking intensity was associated with a decrease of 0.54% in optic nerve head capillary density (P=0.041) Another study by Ciloglu et al. reported similar results, where participants with more than 10 pack-years have reduced superficial and deep foveal vessel density as well as enlargement of foveal avascular zone compared to those who smoke less than 10 pack-years.[57] The effect of smoking on ocular capillary density loss may be attributed to smoking related microinfarction and decreased capillary blood flow.[52] Therefore, evidence thus far suggests smoking may affect glaucoma status in part through ocular vessel density loss, and clinicians should closely monitor glaucoma patients' smoking habits and intensity.

Smoking and Glaucoma Progression

A consistent longitudinal relationship between smoking and VF progression previously has not been reported.[29, 58-60] A few studies reported that cigarette smoking might have a protective effect against glaucoma in a lower dose.[58, 59] For example, in the longitudinal United Kingdom Glaucoma Treatment Study (UKGTS), a double-masked, placebo-controlled and randomized trial with 516 participants across 10 different United Kingdom centers, the authors found that smoking (current or previous) was associated with a reduced risk for VF deterioration (HR, 0.59; 95% CI, 0.37-0.93; P = 0.023).[59] However, in a recent longitudinal study by Mamoudinezhad et al., on 511 eyes of 354 POAG patients over 12.5 years of follow up, heavy smokers were found to have higher rates of VF progression as compared to mild and moderate smoker.[29] Of note, heavy smokers (more than 20 pack-years) had 2.2 times higher odds of developing VF progression relative to never-smokers (OR, 2.21; 95% CI, 1.02–4.76; P = 0.044).[29]

Similarly, in a longitudinal study by Nishida et al., the authors analyzed 466 eyes of 314 patients who had followed up over 6.6 years and found a dose-response relationship between smoking intensity and faster rate of RNFL thinning. (−0.06 μm/year per 10 pack-year higher; p=0.031). In

addition, RNFL thinning became significantly faster when smoking intensity was more than 8 pack-year.[60] Therefore, heavy smokers in particular seem to have a higher risk of glaucoma progression when compared to moderate or mild smokers.

One of the advantages of the UKGTS was its standardization of treatments and control over the analysis. This allowed for a consistent evaluation of various factors that could potentially affect the deterioration of VF and interestingly, some of these factors were found to have a potential association with smoking history. For instance, the study investigated the impact of sleep apnea, migraine, Reynaud's phenomenon, heart attack, cardiovascular disease, angina, and claudication on VF deterioration.[59], representing potential mediating mechanisms behind how smoking may facilitate glaucoma progression. For example, smoking has been linked to cardiovascular disease, which in turn may contribute to the development or progression of glaucoma. However, it's worth noting that the UKGTS only collected information on smoking history for a two-year follow-up period. Thus, the protective effects observed may be eliminated by heavy smoking over a longer duration. [29, 59]

Nevertheless, careful interpretations are needed while interpreting published longitudinal studies because of the existence of confounders in these studies. For example, it is possible that smoking may be associated with other unmeasured factors, such as nicotine replacement therapy, which affects rates of VF progression.[29, 59] Smokers may also be less adherent to medication or have other poor health behaviors, and poor diet and health may interact with some of the variables evaluated in the previous studies as confounding factors, especially among heavy smokers.[29]

Smoking and Glaucoma Development

Few studies have also shown that smoking increases the odds of glaucoma development.[26, 61] In a study by Pérez-de-Arcelus et al. on a large cohort (16,797

participants) who initially were found not to have glaucoma, current smokers had a significantly higher risk (HR 1.88, 95% CI: 1.26–2.81]) of glaucoma compared to participants who had never smoked after controlling for potential confounders after 8.5 years of follow-up.[61] A nonsignificant increased risk was found among former smokers. Moreover, the authors found a dose–response relationship between pack-years and the risk of glaucoma with the highest quintile (HR: 1.70 [95% IC: 1.10–2.64]) having a higher risk than the first quintile. However, no relationship was found between passive smokers (those that are exposed to smokers but do not smoke themselves) and glaucoma.[61] Moreover, in a retrospective study by Lee et al. examining 12.5 million patients utilizing the Intelligent Research in Sight Registry, they found compared to never smokers, current smokers had a 0.92 mmHg higher IOP and were 88% more likely to develop glaucoma (hazard ratio, 1.88; 95% CI, 1.26–2.81; P = 0.002) after adjustment for confounding factors. No significant associations were found between past and never smokers.[26] In a recent study by Mahmoudinezhad et al. on 825 eyes of 542 glaucoma suspect patients over 9 years of follow-up, age was a significant modifier of the relationship between smoking and glaucomatous VF defects (P=0.048). The risk of developing glaucoma in smokers (HR =1.73; 95% CI, 1.10-2.72; P = 0.02) was significantly greater than never smokers after adjustment for confounding factors in older patients (age>61 years).[62] All this evidence adds to the importance of glaucoma risk assessment among smokers.

Smoking and Genetics

The genetic association between smoking and glaucoma is an area of on-going investigation. In the latest research on this topic, Tran et al. conducted a large-scale analysis utilizing publicly available genetic datasets consisting of eight studies with genome-wide association studies (GWAS) summary statistics. They found that genetically predicted smoking initiation was associated with lower IOP (−0.18 mm Hg per SD, 95% confidence interval [CI] = −0.30 to −0.06, P = 0.003).They also found genetically predicted smoking intensity was

associated with decreased open angle glaucoma (OAG) risk (odds ratio [OR] = 0.74 per SD, 95% CI = 0.61 to 0.90, P = 0.002).[63] However, when the authors adjusted their analysis for IOP, the association between the smoking initiation genetic risk score and reduced risk of OAG persisted but lost significance.[63] The authors overall suggested genetically predicted smoking initiation may decrease the odds of glaucoma via an IOP-dependent pathway.

On the other hand, Stamenkovic et al. found that among smokers, glutathione S-transferase mu 1(GSTM1)-null and glutathione S-transferase theta1 (GSTT1)-active genotypes may be associated with higher risk of POAG, suggesting potential gene-environment interaction in glaucoma development.[64] Moreover, Kang et al.[65] recently found that the associations with cigarette smoking status differed significantly depending on gene variants (p = 0.004). Compared with CC homozygotes who never smoked, CC homozygotes who were past or current smokers were at significantly higher risk of POAG (RR, 1.63 [95 % CI 1.15–2.31]).[65]

Overall, POAG exhibits considerable phenotypic heterogeneity, and the disease phenotype is likely the result of many genetic and acquired processes and their interactions. An important distinction to note is that the biologic response to an exposure may have a larger role than the exposure itself in triggering the disease.[66] The identification of these gene-environment interactions related to POAG could lead to genotype-specific lifestyle modification strategies in the future that may reduce the burden of glaucomatous visual loss.[66]

Smoking Cessation and Glaucoma

Studies on the effects of smoking cessation on glaucoma are scarce. In a recent retrospective study by Mahmoudinezhad et al., on 511 eyes of 354 POAG patients from the Diagnostic Innovations in Glaucoma Study (DIGS) and the African Descent and Glaucoma Evaluation Study, the authors compared 211 Eyes of 149 Former Smokers (smoking cessation over 25 years) with 300 eyes of 205 never smokers and reported no significant difference in risk

of VF progression between former heavy smokers (≥20 pack-year smoking history) who has quit smoking for more than 25 years and never smokers (P=0.43). However, a significantly higher proportion of VF progression was found in heavy smokers who quit < 25 years compared with heavy smokers who quit ≥25 years by Kaplan-Meier analysis (P =<0.001).[67] Therefore, smoking cessation may potentially alter glaucoma risk, but more investigation is needed on this topic to inform clinical guidelines.

Conclusions

Despite controversies on the effect of smoking status on glaucoma, several studies have found smoking, particularly moderate to heavy smoking, may be associated with the progression of glaucomatous disease. Therefore, it is crucial for clinicians to actively encourage glaucoma patients to adopt healthy lifestyle habits, which include abstaining from smoking. Such an approach not only enhances overall health but also potentially benefits eye health, particularly in individuals experiencing glaucoma progression even at low IOPs.

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Key points:

1. Discrepancy in the literature exists regarding the association of development of glaucoma and history of smoking and might be related to definition of smoking, smoking intensity, and different levels of nicotine absorption among smokers.
2. Heavy smokers are more likely to suffer from visual field progression in glaucoma.
3. The risk of developing glaucoma among smokers suspected of having glaucoma was influenced by age, with older individuals having a higher risk than younger individuals.
4. Long-term smoking cessation may be associated with lower VF progression in glaucoma patients.
5. Patients suspected of having glaucoma or those diagnosed with glaucoma can benefit from screening for smoking and advice on quitting smoking in routine practice.

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▪▪ of outstanding interest

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