Risk Factors for Glaucoma Needing More Attention

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Abstract: Glaucoma is defined as a chronic progressive optic neuropathy, for which elevated intraocular pressure (IOP) is the only modifiable risk factor. Emerging research indicates that modifiable factors besides IOP may be associated with the presence of glaucoma. In this review, we discuss the role of modifiable determinants, specifically socioeconomic status, nutritional intake, body mass index and obesity, exercise, smoking, and sleep apnea, in the presence of glaucoma. Preliminary studies suggest that associations may exist between these non-inherent factors and glaucoma although research had significant limitations. The mechanisms of influence are unknown or understudied. Research needs to incorporate the broader behavioral and social factors that may affect glaucoma status.

INTRODUCTION

Given the detrimental effects of glaucoma [1-5], we need to understand the various factors that affect its presence. Glaucoma is a condition, for which elevated intraocular pressure (IOP), is currently the only modifiable risk factor. Demographic factors (also known as non-modifiable or inherent determinants) are related to the prevalence of glaucoma. Blacks are four to five times more likely to have glaucoma than whites [4]. The rates of primary angle closure glaucoma are higher in Asians than in Whites [6]. Women may be slightly more likely to suffer from glaucoma than men, when adjusting for age [7].

Considerable interest exists in preventive measures for the development of glaucomatous optic nerve damage and visual field loss, other than IOP lowering. Emerging research indicates that modifiable factors besides IOP may be associated with the presence of glaucoma. In this review, we discuss the role of modifiable (including behavioral and societal) characteristics in the presence of glaucoma, specifically socioeconomic status (SES), nutritional intake, body mass index (BMI) and obesity, exercise, smoking, and sleep apnea.

SOCIOECONOMIC STATUS (SES)

Research regarding the association between SES and glaucoma is scarce. Some studies have examined the relationship between SES and knowledge of or attitudes towards glaucoma. The 2005 Survey of Public Knowledge, Attitudes, and Practices Related to Eye Health and Disease, which involved 3,180 telephone interviews with randomly selected adults, aged 18 and older, found that having heard of glaucoma is associated ($p<.001$) with having insurance, higher annual household income, and higher education [8]. Those with higher SES, as defined by greater educational attainment, are more likely to know of glaucoma and its pathophysiology, treatment, and consequences, controlling for age, sex, and duration of glaucoma [9]. Lack of awareness about glaucoma in a general eye clinic was associated with lower educational attainment [10]. Another study investigated the association between SES and the presence of glaucoma. This case-control study of 220 glaucoma cases, recruited in the UK, found that individuals with advanced glaucoma were more likely to be of "lower occupational class," lack vehicles, and rent instead of own their houses [11].

Recently, we proposed a conceptual model to explain the visual functioning of individuals and communities [12]. In the conceptual framework, the income disparities in the prevalence of visual impairment are explained by lower access to care, and limited individual knowledge regarding eye diseases and negative attitudes towards receipt of eye care among various groups [12]. African Americans, who may have lower access to health care, are less likely to undergo glaucoma surgery [13]. Treatment for glaucoma was problematic in African American beneficiaries due to lower access to care in one study [14].

Prior research found that SES primarily explained racial/ethnic disparities in functioning once individuals had chronic diseases; SES moderately explained differences in disease prevalence [15]. Therefore, SES may especially contribute to our understanding in disparities among individuals with late glaucoma since the lack of timely identification and treatment for glaucoma in individuals with low SES may result in the economic differences in the presence of the disease.

Research regarding the relationship between glaucoma and SES used different definitions of SES. Some studies only investigated the influence of SES on knowledge

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regarding glaucoma instead of glaucoma presence. SES may interact with other factors, such as race/ethnicity, family history of glaucoma, and time since last visit to an ophthalmologist. Unfamiliarity with glaucoma has been associated with being African American and Latino [10]. The relationship between SES and glaucoma has been explained by recall of family history of glaucoma and time since last visit to ophthalmologist [11]. Research needs to assess the importance of other factors, such as demographics and health care utilization patterns, when examining the influence of SES.

NUTRITIONAL INTAKE

Intake of Antioxidants

Reactive oxygen species (ROS) are related to the pathogenesis of primary open angle glaucoma. Oxidative DNA damage in the ocular epithelium that regulates the trabecular meshwork is more severe in glaucoma patients compared to controls [16]. Theoretically, oxidative stress is related to the neuronal cell death affecting the optic nerve [17].

Two large studies investigated the relationship between the intake of antioxidants and glaucoma. In the Nurses' Health Study and Health Professionals Follow-up Study, there were 474 self-reported, confirmed glaucoma cases. The mean age of females was 48 years and that of males was 54 years. Using the Block food frequency questionnaires to assess dietary intake, investigators found no strong associations between primary open-angle glaucoma (POAG) diagnosis and the consumption of citrus foods, cruciferous vegetables, yellow vegetables, green leafy vegetables, all fruits combined, and all vegetables combined, and Vitamins A and C, and alpha- and beta-carotenes. There was a 33% decreased risk of POAG in the highest quintile of Vitamin E intake compared to the lowest (RR = 0.67, 95% CI: 0.50, 0.90) [18]. In the multi-center Study of Osteoporotic Fractures including 1,155 women, we found that women who consumed at least one serving per month of green collards and kale, more than two servings per week of carrots per week, and at least one serving per week of canned or dried peaches, had a decreased likelihood of having glaucoma. In addition, a suggestive relationship existed between the greater intake of Vitamins B2 and A, obtained from natural food sources, and the decreased likelihood of glaucoma. The intake of dietary vitamin C increased the likelihood of having glaucoma [19]. These two studies presented preliminary evidence that there may be a relationship between nutritional intake and the presence of glaucoma.

Intake of Fats

Dietary fatty acids may influence the concentration of endogenous PG-F2α. Safflower oil supplementation was associated with a 13% decrease in IOP in rats at 40 weeks compared to safflower, flaxseed, and tuna oil supplementation [20]. Safflower, corn, and sunflower oils or meat contain N-6 polyunsaturated fatty acids (PUFAs). Flaxseed, canola and soy oils, leavy green vegetables, or fish oil, contain N-3 PUFAs.

The Nurses' Health Study and Health Professionals Follow-up Study involving the same 474 self-reported glaucoma cases above, found no relationship between the intake of major fats and POAG [21]. High-tension glaucoma was more likely in individuals consuming a higher ratio of n-3 to n-6 polyunsaturated fat.

Studies regarding dietary and fat intake relied on self-report of dietary consumption, which is subject to the recall bias. The Nurses' Health and Health Professionals Follow-up Study that investigated the role of the intake of fats and antioxidants, used self-reported glaucoma to identify individuals with the condition; the study did confirm the glaucoma cases. The Study of Osteoporotic Fractures, which found associations with the intake of fruits, vegetables and dietary antioxidants, included a relatively healthy cohort of older women and the results could not be generalized to males and less healthy females.

It is unknown why certain fruits/vegetables and antioxidants may be related to glaucoma, whether other constituents of fruits and vegetables besides antioxidants may be important, what the optimal dietary intake that decreases the prevalence of glaucoma may be, and what confounding factors play a role. Results regarding associations with dietary intake may be confounded by lifestyle factors. It is further unclear whether some antioxidants may do harm since the Study of Osteoporotic Fractures found that higher consumption of Vitamin C was related to a higher prevalence of glaucoma. Despite the limitations and unknowns related to the research regarding nutritional intake, the diet of individuals seems to affect glaucoma status. The associations should not be surprising since nutritional factors affect eye health [22].

Body Mass Index (BMI) and Obesity

Body mass index (BMI) and obesity which are also associated with nutritional intake, might be related to glaucoma status. Obesity may increase blood viscosity and episcleral venous pressure, and damage aqueous outflow facility [23-26]. Ocular hypertension is further related to hypertension [27-30], diabetes [31], and insulin resistance [31-33], which have been linked to obesity. A few studies examined the relationship of IOP or ocular hypertension to BMI or obesity. In the Beaver Dam Eye Study, having higher IOP was associated with higher BMI [34]. In another study, ocular hypertension and BMI of 30 or greater were related, when controlling for age and sex [35]. A study of 25,216 Japanese adolescents and adults aged 14-94, reporting both cross-sectional and longitudinal results; found that higher BMI was associated with elevated IOP, regardless of age, sex, and blood pressure [36]. Some studies suggest that the association between obesity and ocular hypertension may reflect an underlying association between insulin resistance and ocular hypertension since the association between obesity measures and IOP was not significant after adjustments for glucose and other confounders [31]. The relationship between obesity measures and IOP dissipated after adjusting for glucose in another study [31].

Other studies investigated a potential link between the presence of open-angle glaucoma and BMI or obesity. In the Barbados Eye Study, higher BMI tended to decrease the likelihood of open-angle glaucoma presence, after adjusting for age [37]. In contrast, another study found that higher

BMI was related to a greater likelihood of clinical diagnosis of glaucoma among individuals admitted to a hospital. The researchers only reviewed medical records to obtain the information for this study [38]. In another study of 288 control subjects and 186 glaucoma patients in Switzerland, individuals with glaucoma tended to have lower BMI than those without the condition [39]. In a case-control study, there was no difference in BMI status in individuals with and without glaucoma [39]. A recent literature review concluded that while evidence exists regarding the association between higher IOP and obesity (as defined by higher BMI), findings regarding the relationship between glaucomatous optic neuropathy and obesity are conflicting [40]. It is unclear whether higher BMI may increase or decrease the likelihood of having glaucoma and what confounding factors play a role.

Exercise

Obesity is related to exercise; exercise has been related to glaucoma presence. Exercise may alter episcleral venous pressure [41], increase blood lactate and decreases blood ph [42], change plasma osmolarity by increasing serum osmolarity [43], and increase the facility of eye channels outflow stopping obstruction of the aqueous outflow pathways [44]. Exercise temporarily reduced IOP in individuals without glaucoma [45] and with glaucoma [45, 46]. The variations in the percentage reduction in IOP may be due to duration and type of exercise, timing of IOP assessment, demographic characteristics, and seasonal differences [45]. In one study that included 7 subjects with and 7 subjects without glaucoma, the IOP in all subjects dropped between 56 and 61%, following five minutes of walking and jogging [45]. The effect of exercise may dissipate once subjects stop exercising. In a study of 9 sedentary glaucoma suspects who underwent 3 months of aerobic training, IOP levels returned to their original measurements three weeks after exercise cessation [46].

Overall, exercise seems to have a beneficial effect on IOP. Studies regarding the benefits of exercise, however, included small non-probability samples of subjects. It is arguable what the optimal level, type, and duration of exercise may be, whether the initial level of fitness and degree of exhaustion make a difference, what the benefits of exercise in sedentary subjects and older adults may be, and if a combined effect of exercise and intake of glaucoma medications exists.

Smoking

Cigarette smoking increases the risk of vascular disease [47]. Primary open angle glaucoma interferes with the blood flow to the optic nerve head and thus may have a vascular origin [48]. A case-control study found that current cigarette smoking was related to glaucoma presence in multiple logistic regression analysis [49]. Other studies failed to find an association between smoking and glaucoma. Specifically, smoking was not related to open-angle glaucoma in a population-based cross-sectional study of Hispanics aged older than 40 years residing in Arizona [50]. Previous or current smoking was not associated with the presence of glaucoma in the population-based study conducted in Beaver Dam, Wisconsin, in individuals ages 43 to 84 [51]. In two case-control studies, one conducted in Congo [52], and another in France [53], researchers found smoking was not related to glaucoma status. In a recent meta-analysis of existing studies, an association existed between having primary open-angle glaucoma and current smoking; no relationship with former smoking was present [54]. Smoking status has a strong association with eye health, especially age-related macular degeneration [55], but population-based studies found no association in the area of glaucoma.

Sleep Apnea

The sleep apnea syndrome (OSAS) is described as the repetitive, complete, or partial collapse of the pharyngeal airway during sleep [56]. Each episode (lasting 10 seconds to 1 minute) is terminated by arousal that causes sleep disturbance [57]. OSAS is associated with daytime sleep problems including sleepiness, chronic fatigue, and compromised cognitive function. Potential risk factors for sleep apnea include obesity, being a male, alcohol use, smoking, and snoring [58, 59]. OSAS may result in abnormal blood coagulation, systemic hypertension, cerebrovascular disease, vasospastic disease, and optic nerve vascular dysregulation [60]. In 212 patients in an eye clinic, there was an association between open-angle glaucoma and sleep-disturbed breathing, which was assessed by a questionnaire [61]. In 114 patients evaluated for OSAS, 7% of patients with OSAS had open-angle glaucoma, which was higher than that expected in the general population [62]. In 51 subjects with OSAS, there was a higher likelihood of normal-tension glaucoma compared to normal white controls of the same age [60]. The prevalence of OAG in 228 patients with OSAS, however, was 2%, which is similar to the rate of 1.5-3% in the general population [63].

One limitation of existing studies is the use of subjective information to determine the presence of sleep apnea. A study with a larger sample size (n=212) that found an association between open angle glaucoma and sleep-disturbed breathing (SDB), assessed SDB by a questionnaire instead of objective measurement [61]. The reciprocal relationship between sleep apnea and glaucoma is not clear. In addition, as with other potential modifiable risk factors, it is unknown what the influence of sleep apnea is in the prevalence, incidence, and development of the disease.

CONCLUSION

Although current research tentatively supports that modifiable factors other than IOP may be related to the presence of glaucoma, these studies have significant limitations. Few case-control or population-based studies investigated the associations. Promising areas for future case-control studies are related to the role of nutritional factors, exercise, and sleep apnea.

Individuals with low SES are involved in more unhealthy behaviors and may be more likely to be members of minority groups [64]. They consume less fruits and vegetables, are more likely to be obese, have less time to exercise [65], and are more likely to smoke [15]. In the broader context, since differences in knowledge about glaucoma are greatest between individuals with low and high SES but not as significant in people within middle and high groups of SES [9], steps to decrease socioeconomic inequalities are essential. SES is a societal issue and ophthalmologists have a

limited ability to interfere. If we hope to decrease the burden of glaucoma, future research needs to incorporate the broader behavioral and social factors that may affect glaucoma.

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