Lifestyle, Nutrition and Glaucoma

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Abstract

The only proven strategy to prevent primary open-angle glaucoma (POAG) is the use of ocular hypotensive therapy among people diagnosed with ocular hypertension. In this review, various modifiable lifestyle factors, such as exercise, diet and cigarette smoking, that may influence intraocular pressure and that have been studied in relation to the risk of developing POAG are discussed. Epidemiologic studies on lifestyle factors are few, and the current evidence suggests that there are no environmental factors that are clearly associated with POAG; however, a few factors merit further study. This review also outlines future directions for research into the primary prevention of POAG.

Keywords

primary open-angle glaucoma; lifestyle factors; diet; semiquantitative food frequency questionnaire

Introduction

Primary open-angle glaucoma (POAG) is a common condition that is encountered daily in ophthalmic practice. Descriptive epidemiology studies reveal that the crude prevalence of POAG around the world varies by about 2 orders of magnitude with the lowest estimates found among Eskimos residing in Alaska (0.06%) and the highest found among African-derived people living in the Caribbean (7.1–8.8%). Analytical epidemiologic studies and clinical research are needed to determine whether the differing rates of disease are related to genes, environment or some combination of the two. This review will address environmental risk factors for POAG. The underlying hypothesis regarding candidate environmental factors for POAG is that they operate either by altering intraocular pressure (IOP), modifying optic nerve blood flow or by varying the rate of retinal ganglion apoptosis.

There are some compelling reasons to search for environmental risk factors associated with POAG. A positive family history is an important risk factor for POAG suggesting that there is a strong genetic predisposition to the disease but the identified genes to date account for < 5% of all POAG in the general population. The exploration for genes associated with POAG continues but it is imperative to also evaluate potential environmental factors as contributing causes of this complex disease. The discovery of novel environmental factors that modify the risk of POAG may provide new insights into disease pathogenesis. Second, the discovery of
lifestyle factors that could serve as primary preventive measures might diminish the economic consequences of glaucoma. Effective inexpensive lifestyle measures that would favorably alter the risk of developing glaucoma would certainly be welcome since the healthcare costs attributable to POAG escalate as the disease progresses to later stages. Primary preventive measures may also reduce the burden of visual disability incurred by POAG which is projected to be considerable by the year 2020.

The relation between intraocular pressure and primary open angle glaucoma

In the Baltimore Eye Survey, the risk of developing POAG for patients with an IOP of 35 mm Hg or more was 39-fold when compared to a reference group with IOP of less than 17 mm Hg. The strong positive relation between IOP and POAG has also been seen in incident POAG cases identified in the Barbados Eye Study. Furthermore, lowering IOP with conventional glaucoma treatment reduced the conversion from ocular hypertension to POAG and slowed disease progression among open-angle glaucoma patients with a range of baseline IOP. Thus lifestyle factors altering IOP could potentially also modify the risk of POAG.

Lifestyles factors known to modify IOP

Activities that elevate IOP

The level of IOP appears to be a quantitatively linked trait under genetic control. Yet certain lifestyle activities increase IOP including playing high wind instruments, drinking coffee, engaging in certain yoga positions, wearing tight neckties, and lifting weights. In assessing the clinical impact of these lifestyle-related changes on IOP, it is important to recognize the magnitude and duration of IOP alteration associated with these activities. When playing high wind instruments such as the oboe, the IOP can more than double in approximately 20 seconds with immediate return to baseline when playing ceases. A typical cup of coffee, the primary dietary source of caffeine, causes a 1–4 mm Hg rise in IOP that lasts for at least 90 minutes. Yoga positions that place the heart above the eye such as the headstand posture cause IOP to increase by 2-fold. IOP returns to baseline promptly within 5 minute in a normal position. Tight neckties cause a modest elevation of IOP (2 mm Hg) that is not sustained with continued wear. Weight lifting can cause a modest and transient increase in IOP of approximately 4 mm Hg (or a 22% increase from baseline) that is followed by a nominal IOP decrease of approximately 1 mm Hg after completion of exercise.

Activities that lower IOP

Exercise lowers IOP but the exact mechanism is not completely understood. The magnitude of IOP reduction is related to the intensity of exercise performed. In a crossover study involving healthy subjects, the IOP reduction noted 5 minutes after 15 minutes of exercise at 40% maximum heart rate was 0.9 mm Hg vs. 4.7 mm Hg after exercise of similar duration but at 80% maximum heart rate. The ocular hypotensive effect of exercise is not limited to young healthy subjects. For example, in unconditioned subjects suspected of having glaucoma, mean IOP decreased by 4.6 mm Hg (P<0.001) after aerobic training. There is also data to suggest that people who are more physically fit have lower IOP. Qureshi et al. reported that among males employed in a steel factory, sedentary workers had applanation tensions that were 1.9 mm Hg higher than their co-workers who were engaged in strenuous labor (p<0.001). The same study used physiologic measures to confirm that the heavy laborers were more physically fit than their sedentary co-workers, although it did not control for other potential differences between the groups such as socioeconomic status and educational background. Nonetheless, the ocular hypotensive effects of exercise are short-lived in unconditioned individuals (< 1 hour) and last only for a few weeks in physically fit individuals who become deconditioned.
Alcohol promptly lowers IOP in a dose-dependent manner after acute ingestion. Nonetheless some studies suggest that daily alcohol consumption is associated with increased IOP.

The relation between lifestyle factors that modify IOP and POAG

Is there any evidence that lifestyle behaviors associated with transiently elevated IOP are linked to POAG? Overall, very few studies have been conducted on the relation between these lifestyle factors and the risk of developing POAG. A cross-sectional clinic-based study among 45 Boston-area musicians suggested that there was a positive relation between playing high wind instruments for longer duration and an abnormal HVF test. In the Blue Mountain Eye Study, open-angle glaucoma patients who consumed coffee regularly had higher IOP than their counterparts who abstained from coffee consumption (19.6 mm Hg vs. 16.8 mm Hg; p=0.03). Results from a large prospective, population-based sample of health professionals (N=121,172) suggests that consuming 5 or more cups of caffeinated coffee per day was associated with a 1.6-fold increased risk of POAG. Greater caffeine intake seemed more adversely related to high tension POAG among participants with a positive family history of glaucoma (p for trend = 0.0009).

To date, there have been no studies that have assessed whether weight lifting or certain yoga practices are related to the risk of developing glaucoma. While these latter activities produce elevated IOP, they may not necessarily predispose to glaucoma. The potential adverse effect of elevated IOP could be offset by compensatory changes in blood pressure and intracranial pressure that provide adequate perfusion pressure and trans-laminar pressure gradient within the optic nerve head.

Similarly, is there any evidence that lifestyle behaviors associated with reduced IOP are associated with a reduced risk of POAG? No study has evaluated the relation between exercise and the risk of developing POAG. Since the health benefits of exercise are myriad, more research is needed to determine whether a regular exercise routine could serve as a primary preventive measure for glaucoma. While exercise reproducibly lowers IOP, it may not necessarily prevent glaucoma. Exercise lowers blood pressure (which is positively correlated with IOP) and may reduce perfusion pressure (an important risk factor for glaucoma) possibly offsetting potential benefits of lower IOP.

Case-control and prevalence studies are mixed regarding the relation between alcohol use, which also lowers IOP and glaucoma with one showing an inverse relation, others showing no association and one actually showing a positive association. One prospective study found a statistically insignificant inverse association between consumption of 2 or more drinks daily and incident POAG. From a public health perspective, 1−2 drinks daily is associated with a decreased risk of coronary heart disease but the ophthalmic data is not compelling that this level of consumption is associated with a reduced risk of POAG.

Other lifestyle factors and glaucoma

Cigarette smoking

Direct inhalation of cigarette smoke exposes users to over 40 carcinogens, carbon monoxide and a host of other undesirable compounds. Cigarette smoking is linked to many systemic illnesses and ocular conditions such as cataract and age-related macular degeneration. On the other hand, nicotine (a major component of cigarette smoke) also increases blood flow in regions of the brain rich in nicotine receptors such as the thalamus. Nonetheless, the effects of nicotine on directly measured optic nerve blood flow and tissue oxygenation are unknown.
at this time. Currently, there is no strong evidence that IOP increases appreciably in the time immediately after smoking a cigarette.\textsuperscript{59}

Since smoking has a huge negative impact on health overall and smoking cessation has proven health benefits,\textsuperscript{60, 61} it is useful to investigate the effect of cigarette smoking on the risk of POAG. In the Blue Mountain Eye Study only a modestly elevated IOP was found among smokers (16.3 mm Hg) versus nonsmokers (16.04 mm Hg; \textit{p}=0.03 after adjustment for age and gender).\textsuperscript{62} Case-control and cross-sectional studies that evaluated the relation between cigarette smoking and POAG produced mixed, although mostly null results.\textsuperscript{49, 50, 63-68} The best evidence to date is from a large prospective study among 111,215 health professionals throughout the United States which assessed cigarette smoking exposure repeatedly over a decade and found that cigarette smoking did not increase the risk of developing POAG.\textsuperscript{69} Given the large number of noxious substances contained in cigarette smoke, more studies to help understand why smoking is not adversely related to glaucoma may yield insights into the pathophysiology of POAG.\textsuperscript{70}

### Postmenopausal hormone use

Menopause, which typically occurs in the early 50's, is an inevitable consequence of female reproductive aging characterized by dramatically lower levels of reproductive hormones such as estrogen. There is evidence that estrogen and estrogen analogs protect retinal ganglion cells from apoptosis via a mechanism that does not involve binding to estrogen receptors in the retinal ganglion cell layer.\textsuperscript{71, 72} Several studies report that postmenopausal hormone (PMH) use is associated with lower IOP and enhanced blood flow to the optic nerve.\textsuperscript{73-79} The age at which women enter menopause may be an important factor in influencing the risk of POAG and such an association would add support for a role of declining sex hormones in POAG pathogenesis. Among postmenopausal women in Rotterdam, entering menopause at age \textless{} 45 was associated with a 2.6-fold increased risk (95\% confidence interval: 1.5–4.0) of open-angle glaucoma compared with entering menopause at age \textgreater{} 50.\textsuperscript{80} Data from a subset of postmenopausal women participating in the Nurse Health Study supports this finding.\textsuperscript{81} Specifically, among postmenopausal women aged \textgreater{} 65, entering menopause at age \textgreater{} 54 years was associated with a reduced risk of POAG compared with entering menopause at ages 50 to 54 (relative risk = 0.53; 95\% confidence interval: 0.32–89).

On the issue of whether postmenopausal hormone (PMH) use may delay or prevent the onset of POAG, three population-based studies found only weak, non-significant inverse associations between PMH use and POAG overall.\textsuperscript{80-82} In the Nurses Health Study where 56,703 postmenopausal women were followed over a 22-year period, estrogen plus progesterone use (but not estrogen use alone) was associated with a 42\% reduced risk of high tension POAG (relative risk = 0.58; 95\% confidence interval: 0.36–0.94).\textsuperscript{81} Furthermore, there was a trend with longer duration of this type of PMH use and reduced risk of POAG associated with IOP > 21 mm Hg but this trend was not statistically significant (\textit{p}=0.07). The role of PMH use in women’s health maintenance is a controversial topic and more work is needed to understand how women might reduce their risk of POAG after menopause.

### Diet and glaucoma

#### Antioxidant intake

Many studies suggest that oxidative stress may play a role in glaucoma (see Kumar and Agarwal for a review).\textsuperscript{83} Oxidative damage to DNA in the trabecular meshwork may compromise outflow and increase IOP. Free radicals generated in the anterior chamber may escape the antioxidant buffer system and spill into the posterior segment where they interact with incident light to damage retinal ganglion cells. Yet little is known about whether antioxidant intake

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might prevent POAG, with only one prospective study published to date on the subject. Kang et al. used a semiquantitative food frequency questionnaire (SFFQ) to assess the relation between the intake of a variety of antioxidants derived from food and dietary supplements and their relation to POAG.84 The principle of using food frequency questionnaires to assess diet intake is that they reflect eating habits over a period of months or years and long-term dietary habits may be most important for impacting a slowly developing disease like glaucoma. In the SFFQ, a unit is specified for each food, and the participants are asked how often (“never” to “six or more times per day”), on average over the past year, they had consumed that unit of each food. The SFFQ has been validated using diet records and biomarkers for a large number of nutrients.85 In this study dietary assessments were repeated multiple times prior to a diagnosis of POAG in a large population. Antioxidant intake varied considerably in the population under analysis but no significant relation was found between consumption of carotenoids, vitamin C, and vitamin E and the risk of developing POAG. Also consumption of specific fruits and vegetables high in antioxidants did not appear to materially alter the risk of POAG. These data do not completely rule out a modest effect for antioxidants in preventing POAG and specific foods or antioxidants not yet studied may also modify the risk of POAG. Clearly, more research is needed to evaluate whether antioxidants may protect against the development of POAG.

Fat intake

The essential fatty acids (linoleic acid of the omega-6 (ω-6) series and linolenic acid of the omega-3 (ω-3) series) serve as competitive substrates for the endogenous ophthalmic enzymes that generate arachadonic acid, the precursor of prostaglandin F2 alpha. It is well established that analogs of prostaglandin F2 alpha are potent ocular hypotensive agents. Only one study has evaluated the relation between dietary fat intake and POAG.86 Dietary fat intake might modulate the availability of intraocular prostaglandins, altering IOP in a way that would influence the risk of POAG.86 Although total dietary intake of fats was not related to POAG risk, a diet characterized by a higher ω-6:ω-3 ratio was inversely associated with a risk of POAG, particularly among the high-tension subtype. On the other hand, there have been studies to indirectly suggest that high intake of ω-3 fat may be beneficial for reducing the risk of glaucoma. For example, an animal study suggested that high ω-3 fat diet is associated with a lower IOP,87 and another biomarker study found that patients with POAG might have lower circulating ω-3 fat levels than their unaffected siblings.88 Omega-3 fat is important for systemic health (e.g. in lowering risks of stroke and sudden cardiac death89) and is essential for the health of neurological tissues including the retina.90 Thus, although these findings suggest that dietary fats might modify IOP, it is unclear what dietary fat consumption recommendations can be made that are consistent with overall systemic and ocular health.

Body mass index

The body mass index (“BMI” calculated as weight in kilograms divided by height in meters squared) represents a balance between nutrient intake from all sources and energy expenditure and is a good measure of body fat adjusted for height in middle-aged adults. Elevated BMI is known to be a risk factor for type 2 diabetes mellitus, hypertension, coronary artery disease, stroke, and gout just to name a few conditions (see Ogden et al. for a review91). Furthermore, a review by Chueng and Wong92 concluded that there were several population-based studies showing that higher BMI was associated with age related cataract and macular degeneration although the biologic links between obesity and these diseases remains elusive. Many studies document a positive association between BMI and IOP.37, 93-95 In sharp contrast, few studies have directly studied the relation between BMI and POAG, and these studies suggest there may be an inverse association between BMI and POAG.51, 96 More study of the relation between various measures of body size and POAG are needed to determine if there are certain anthropometric features associated with POAG.
The quest to find environmental risk factors for POAG

In 1995, WC Stewart stated that, "In the future, modifiable risk factors for chronic open-angle glaucoma may become known." Yet, studies to date have not identified an established modifiable risk factor for POAG other than IOP. There may be several explanations for this. First, some exposures are complex (e.g. diet) and do not represent a single biologic agent. These complex exposures may exhibit what we would coin ‘environmental antagonistic pleiotropism’, that is they simultaneously generate biologic responses that offset one another. In one hypothetical example, “perceived stress” may increase epinephrine and lower IOP while also increasing endogenous steroid levels which could raise IOP. Second, environmental exposures may be modified by genetic factors. For example, while moderate-to-high alcohol consumption may only marginally alter the risk of POAG, slow metabolizers of alcohol may enjoy a protective effect from lower alcohol consumption. There are common polymorphisms in the genes that metabolize alcohol and slow its metabolism; interaction between these polymorphisms, alcohol consumption and POAG should be explored. Third, POAG exhibits considerable phenotypic heterogeneity, thus it would be very informative to conduct analyses where cases with specific patterns of visual field loss, cases with different levels of IOP associated with initial signs of disease or cases with family history are examined separately. Finally, the absence of environmental risk factors for POAG may be related to methodological issues such as small sample size of studies, short follow-up periods and the paucity of studies, especially those with prospective study designs. Furthermore, biomarker studies may yield more significant associations with POAG since the biologic response to an exposure may be more important than the exposure itself in triggering disease.

Only randomized clinical trials can demonstrate whether lifestyle factors, behaviors or diet will modify the risk of POAG. However, randomized trials cannot be conducted on all exposures (e.g. cigarette smoking or alcohol) and thus the results from epidemiologic studies would provide the best evidence to date.

In this review, we have examined the evidence on whether environmental factors are related to developing glaucoma. How do we answer the questions from newly diagnosed glaucoma patients on lifestyle behaviors and their relation to POAG? There is even scarcer data on lifestyle factors and their influence on disease progression. However, rather than default to the view that patients should simply comply with medical therapy and follow-up recommendations (which of course is true), we also suggest advocating for activities consistent with overall good health such as avoidance of smoking, moderate exercise and a diet high in fruits and vegetables. The weight of the current medical is not sufficiently strong to make broad recommendations regarding activities that glaucoma patients should avoid because they elevate IOP such as certain yoga positions, playing high wind instruments for long periods of time, and drinking large amounts of caffeinated coffee.

We suspect that advances in the fields of glaucoma genetics and neuroprotection will assist the discovery of environmental risk factors for POAG. Specifically, we hypothesize that the identification and characterization of POAG susceptibility genes or factors that favorably alter the rate of retinal ganglion cell apoptosis will reveal important biochemical pathways operative during the pre-clinical phase of the disease as well as novel environmental factors that modify these pathways. Ultimately such work could lead to the discovery of environmental factors that contribute to disease in certain genetic settings. The identification of these gene-environment interaction terms related to POAG could lead to genotype-specific lifestyle modification strategies that reduce the burden of glaucomatous visual loss.
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