Dietary factors and the risk of glaucoma: a review

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Abstract: Glaucoma is an optic neuropathy characterized by a progressive typical pattern of optic neurodegeneration and visual field loss. A relatively high proportion of glaucomatous individuals admit to interest in dietary modification in an attempt to manage their disease. Heavy caffeine consumption appears to have a transient effect on increasing intraocular pressure (IOP). This effect may be clinically insignificant for nonglaucomatous individuals, but the association warrants clinical consideration in those with the disease. Studies investigating the relationship between self-reported antioxidant intake and risk of glaucomatous disease have reported conflicting results. Preliminary studies investigating the relationship between self-reported glaucoma diagnosis and consumption of the oxidants calcium and iron suggest a possible relationship indicating increased risk of the disease with increased consumption of these dietary factors. Initial reports in the literature suggest a potential role for dietary modification in the treatment of glaucomatous optic neuropathy. Further study, with randomized controlled trials, may be necessary to further characterize these relationships.

Keywords: antioxidants, caffeine, dietary supplements, glaucoma, intraocular pressure, nutrition, oxidants, risk factors

Introduction

Glaucoma is a group of eye diseases characterized by a multifactorial progressive optic neuropathy that can result in irreversible vision loss and blindness [Weinreb and Khaw, 2004]. The biological basis of glaucoma includes the degeneration of retinal ganglion cells resulting in characteristic cupping of the optic nerve with an accompanying pattern of visual field loss. While several factors have been identified that contribute to glaucomatous neurodegeneration, intraocular pressure (IOP) is currently the only established treatable risk factor. Population-based surveys have shown that 30–40% of patients diagnosed with glaucoma have IOP within the normal range [Dielemans *et al.* 1994; Klein *et al.* 1992]. Furthermore, the Baltimore Eye Survey evaluated the relationship between IOP and primary open-angle glaucoma (POAG) in white and black Americans and found that more than half of glaucomatous eyes had a screening IOP within the normal range regardless of treatment [Sommer *et al.* 1991]. A prospective multicenter study demonstrated that lowering IOP further in such patients offers a protective

benefit from glaucoma progression [Anderson, 2003].

The two main types of glaucoma are divided based on the appearance of the aqueous humor drainage angle between the cornea and the iris in the anterior chamber. POAG, the most common form of glaucoma, has a wide-open angle while angle closure glaucoma involves a degree of angle obstruction by iris tissue.

Secondary glaucomas may occur due to eye trauma, inflammation, tumor, diabetes, advanced cataract or steroid use. Pigmentary and exfoliative glaucoma are two specific secondary glaucomas relevant to this review. Pigment dispersion syndrome and pigmentary glaucoma represent a spectrum of disease characterized by excessive pigment release from the iris that is distributed throughout the anterior segment of the eye. These pigment granules flow throughout the aqueous drainage pathways and accumulate thus reducing the outflow facility of the eye. This results in elevation of IOP and optic nerve damage with

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associated visual field loss. Exfoliative syndrome and exfoliative glaucoma represent a spectrum of disease characterized by deposition of a proteinaceous dandruff-like exfoliation material within the anterior segment of the eye that is released from the outer layer of the lens. Similarly, this material obstructs aqueous outflow thus raising IOP and causing optic nerve damage with associated visual field loss.

Diagnosis and treatment

Glaucoma diagnosis is characterized by identifying progressive damage to the optic nerve that presents as structural changes in the optic disc and retinal nerve fiber layer or functional visual field deficit. Structural damage of the optic nerve is evaluated using clinical assessment *via* ophthalmoscopy, stereophotographs and/or *in vivo* imaging technology. Functional damage of the optic nerve is evaluated using computerized visual field testing to measure the loss of visual function. Glaucoma cannot be cured and glaucomatous damage is irreversible; however, if detected early, disease progression can be arrested or limited with medical and surgical treatment. Based on the Preferred Practice Patterns of the American Academy of Ophthalmology, the goals of glaucoma management are to achieve the following: controlled IOP in the target range; stable optic nerve/retinal nerve fiber layer status; and stable visual fields [Prum *et al.* 2010]. Since IOP is the only modifiable risk factor, treatment is primarily focused on achieving a lowered target IOP range. IOP reduction is initially attempted *via* medical management with medicated eye drops. When there is lack of medical therapy adherence or evidence of disease progression, surgical management is attempted. Surgical options include laser surgery, microinvasive glaucoma surgery, glaucoma drainage implants and traditional filtration surgery.

Glaucoma patient surveys have demonstrated that participants use supplements and diet modification in an attempt to manage their disease [Rhee *et al.* 2002; Wan *et al.* 2012]. There is a growing interest in the role of dietary factors in glaucoma because modification would be possible by changing eating habits or by supplementation [Pasquale and Kang, 2009]. The discovery of dietary factors that modify the risk of glaucoma may provide insight into glaucoma pathogenesis and serve as a primary preventive measure. Recent studies have suggested a link

between dietary factors and glaucoma risk. These findings may lead to the identification of IOP dependent or independent modifiable risk factors for the development and progression of glaucoma. In this review, we examine and summarize the evidence pertaining to caffeine, antioxidant and oxidant dietary factors, and their respective potential associations with glaucoma risk and/or progression.

Caffeine

Caffeine is widely consumed throughout the world [Barone and Roberts, 1996]. The majority of older adults in the age group at risk for POAG consume caffeine daily [Massey, 1998]. There have been conflicting reports about the effects of caffeine on IOP; however, most studies indicate a transient increase in IOP of 2 mmHg for a 2-hour period [Ajayi and Ukwade, 2001; Avisar *et al.* 2002; Higginbotham *et al.* 1989; Okimi *et al.* 1991; Peczon and Grant, 1964; Ricklefs, 1968; Ricklefs and Pohls, 1969]. Caffeine may transiently elevate IOP by either promoting aqueous production or inhibiting outflow facility, though the specific mechanism has yet to be determined. Caffeine-induced elevated IOP fluctuations in susceptible eyes may portend a pathophysiological connection for increased risk of developing glaucoma.

Kang and colleagues conducted the first prospective study to examine the relationship between caffeine consumption and risk of developing POAG [Kang *et al.* 2008]. The investigators utilized existing data from 79,120 women from the Nurse's Health Study (NHS) and 42,052 men from the Health Professionals Follow-up Study (HPFS) with repeated lifestyle risk factor assessment over 18 years of follow up and reported that overall caffeine intake was not significantly associated with risk of developing POAG. However, secondary analysis revealed an increased risk of developing POAG among caffeine users with a self-reported family history of glaucoma in relation to POAG with increased IOP (p -trend = 0.0009, p -interaction = 0.04). In an alternate prospective study using the same two cohorts with similar sample size and follow up, Pasquale and colleagues examined the association between caffeine and coffee consumption in relation to risk of exfoliation glaucoma (EG) or exfoliation glaucoma suspect (EGS) [Pasquale *et al.* 2012]. Investigators observed a positive association between heavier coffee consumption and the risk

of developing EG or EGS. Participants who consumed ≥ 500 mg of caffeine per day had a nonsignificant increased trend toward risk of EG/EGS compared with participants who consumed < 125 mg of caffeine per day [relative risk (RR) = 1.43; 95% confidence interval (CI) 0.98–2.08; p -trend = 0.06]. However, participants who drank ≥ 3 cups of caffeinated coffee daily were at increased risk of EG/EGS compared with abstainers (RR = 1.66; 95% CI, 1.09–2.54; p -trend = 0.02). In addition, there was a stronger association among women with a family history of glaucoma (p -interaction = 0.06 for coffee; p -interaction = 0.03 for caffeine).

These findings suggest that caffeine may have a possible adverse effect on subjects with an inherent susceptibility to glaucoma. Li and colleagues conducted a systematic review and meta-analysis of six randomized controlled studies that measured IOP in 103 normal individuals and 41 patients with glaucoma or ocular hypertension at 30, 60 and 90 minutes after caffeine consumption [Li *et al.* 2011]. The investigators reported that caffeine had different effects on IOP in normal, ocular hypertensive and glaucomatous participants. In normal subjects, caffeine had no significant effect on IOP but there was a significant effect in subjects with ocular hypertension and glaucoma at all measured time points (weighted mean difference, 95% CI: 0.347, 0.078–0.616; 2.395, 1.741–3.049; 1.998, 1.522–2.474). Similarly, these findings suggest a potential IOP-mediated adverse effect due to caffeine intake in subjects susceptible to glaucomatous optic neuropathy. However, the results of this meta-analysis are limited in their implications because the included studies were not uniform in their design, patient sample, follow-up time or IOP measurement methodology.

Jiwani and colleagues conducted the first and largest prospective, double-masked, crossover, randomized controlled trial to examine the effect of caffeinated coffee consumption on IOP, ocular perfusion pressure (OPP) and ocular pulse amplitude (OPA) at 60 and 90 minutes after ingestion in those with or at risk for POAG who were at least 40 years of age [Jiwani *et al.* 2012]. The investigators reported that caffeine intake statistically significantly increases IOP (0.99 ± 1.52 , $p < 0.0001$ at 60 minutes; 1.06 ± 1.67 , $p < 0.0001$ at 90 minutes) and OPP (1.57 ± 6.40 , $p = 0.01$ at 60 minutes, 1.26 ± 6.23 , $p = 0.04$). Given the variability of IOP measurements and diurnal

fluctuations in IOP, these findings are clinically insignificant for the majority of participants and are unlikely to impact the risk of development and/or progression of glaucoma. It is possible to argue that caffeine-induced transient rises in IOP may cause or worsen glaucomatous damage in those with an inherent susceptibility. While early evidence supported this association, the most appropriately designed and well-controlled study by Jiwani and colleagues makes this claim suspect.

In summary, caffeine has a transient effect on increasing IOP; however, this is likely to be of no clinical relevance with moderate intake. Further research may be warranted to investigate the risk of conversion to, or progression of, glaucoma in subjects with sustained heavy caffeine intake. In regard to clinical practice, physicians should consider advising glaucoma patients to moderate caffeine consumption and avoid caffeine intake prior to visits requiring IOP evaluation.

Antioxidants

Nutrition and the respective antioxidant constituents may be important in the development of eye disease. Antioxidants have been suggested to protect retinal ganglion cells, the specific cell type damaged by glaucomatous optic neuropathy [Hanneken *et al.* 2006; Lucius and Sievers, 1996; Ritch, 2000; Veach, 2004; West *et al.* 2006]. Fruits and vegetables are rich in antioxidants and several studies have evaluated fruit and vegetable consumption along with the constituent antioxidants in relation to glaucoma risk. In a prospective study of 116,484 participants combined from NHS and HPFS cohorts followed for at least 10 years, investigators reported no association between dietary antioxidant intake and the risk of POAG [Kang *et al.* 2003]. This study assessed dietary antioxidant intake from fruit and vegetable consumption as well as supplement use. However, Coleman and colleagues conducted a cross-sectional cohort study of 1155 women and reported that a higher intake of certain fruits and vegetables may be associated with a decreased risk of glaucoma in predominantly older white women [Coleman *et al.* 2008]. Women with greater intake of carrots [odds ratio (OR) = 0.36; 95% CI, 0.17–0.77], collard greens or kale (OR = 0.31, 95% CI, 0.11–0.91), and canned or dried peaches (OR = 0.53; 95% CI, 0.29–0.97) had reduced odds of glaucoma risk compared with those who consumed less than one serving per

month. These specific fruits and vegetables are rich in vitamin A, C, B2 and carotenoids. In subgroup analysis, the strongest association was between green leafy vegetables (collard greens and kale) and glaucoma in African American women but this was based on a limited sample size. The same group of investigators reported that higher intake of certain fruits and green leafy vegetables high in vitamin A and C and carotenoids may be associated with a decreased likelihood of glaucoma in 662 older African-American women based on a cross-sectional analysis of the same cohort [Giaconi *et al.* 2012].

The major limitation of these epidemiological studies is their reliance on surveys without objective measurement of antioxidants and nutrients. Studies that evaluated the relationship of glaucoma with serum vitamin levels were case-control studies with limited sample sizes [Engin *et al.* 2010; Yuki *et al.* 2010]. Wang and colleagues conducted a cross-sectional analysis of 2912 participants from the prospective National Health and Nutrition Examination Survey (NHANES) to investigate the association between supplemental intake as well as serum levels of vitamin A, C and E. The investigators reported that neither supplement consumption nor serum levels of vitamin A and E were associated with glaucoma prevalence [Wang *et al.* 2013a]. Furthermore, while supplement consumption of vitamin C was associated with decreased odds of glaucoma (OR = 0.47; 95% CI, 0.23–0.97), serum levels were not associated with glaucoma prevalence (OR = 0.94; 95% CI, 0.42–2.11). These incongruous results highlight the limitation of self-reported diagnosis and nutrient intake compared with objective measurements.

Based on the available data to date, there is no compelling evidence that antioxidant and vitamin intake have a beneficial effect on glaucoma outcomes. Supplements have traditionally been considered low risk/possible benefit interventions; however, these agents may have harmful effects and clear evidence of benefit is required before their recommendation is made for glaucoma therapy. Furthermore, demonstrated risk of harm has been documented in properly designed and controlled trials as well as meta-analysis and systematic reviews. Intake of supplemental antioxidants with vitamin A, B, C, E and β -carotene have been implicated to increase morbidity and mortality in healthy and disease patients [Bjelakovic *et al.* 2004, 2008; Heinonen

and Demetrius, 1994; Omenn *et al.* 1996; Schurks *et al.* 2010].

In regard to clinical practice, physicians should continue to promote an evidence-based healthy balanced diet because consumption of fruits and vegetables have been consistently reported to have very minimal risks and demonstrable benefits.

Oxidants

Oxidative stress has been suggested to play a role in glaucoma pathogenesis [Izzotti *et al.* 2006; Kumar and Agarwal, 2007]. As oxidants, calcium and iron have been implicated to impact the function of trabecular meshwork and retinal ganglion cells in glaucoma subjects [Farkas *et al.* 2004; He *et al.* 2008; Lin *et al.* 2010].

Building on animal and preliminary human studies, Wang and colleagues conducted a cross-sectional analysis of 3833 participants in the NHANES study to evaluate the association between a previous self-reported glaucoma diagnosis and supplementation with oxidants calcium and iron [Wang *et al.* 2012]. After adjusting for confounding factors, the investigators reported that participants who consumed >800 mg/day of supplementary calcium or >18 mg/day supplementary iron had significantly greater odds of being diagnosed with glaucoma (OR 2.44, 95% CI 1.25–4.76 for calcium; OR 3.80, 95% CI 1.79–8.06 for iron). Furthermore, concurrent consumption of calcium and iron was associated with greater odds of glaucoma (OR 7.24, 95% CI 2.42–21.62). The authors posit that there may be a threshold intake of calcium and iron above which there is an increased risk of developing glaucoma. Using the NHANES database, the same investigators evaluated the association between self-reported glaucoma diagnosis and total and dietary oxidant calcium and iron consumption in 6316 subjects [Wang *et al.* 2013b]. The investigators reported increased odds of glaucoma with higher total consumption of calcium (p -trend < 0.0001) and iron (p -trend < 0.0001); however, there was also a contrasting trend of decreased odds of glaucoma with increasing dietary calcium (p -trend < 0.0008) and iron intake (p -trend < 0.0022).

In summary, epidemiological studies suggest that supplementary and total consumption of calcium and iron are associated with increased odds of

Table 1. Summary of studies reporting on the effect of dietary factors on risk of glaucoma.

Dietary factor	Study	Type	Number of participants	Conclusion
Caffeine	Kang <i>et al.</i> [2008]	Prospective	121,172	Overall caffeine intake was not associated with increased risk of POAG.
	Pasquale <i>et al.</i> [2012]	Prospective	120,179	Positive association between heavier coffee consumption with risk of EG/EGS.
	Li <i>et al.</i> [2011]	Systematic review and meta-analysis	144	Caffeine did not have an effect on IOP in normal individuals but caffeine did increase IOP in patients with glaucoma or OHT.
	Jiwani <i>et al.</i> [2012]	Prospective, double-masked, cross-over, randomized controlled trial	106	Consuming one cup of caffeinated coffee (182 mg caffeine) statistically increases, but likely does not clinically impact, IOP and OPP in those with or at risk for POAG.
Antioxidants	Kang <i>et al.</i> [2003]	Prospective	116,484	No association between antioxidant consumption and risk of POAG.
	Coleman <i>et al.</i> [2008]	Cross-sectional	1155	A higher intake of certain fruits and vegetables may be associated with a decreased risk of glaucoma.
	Giaconi <i>et al.</i> [2012]	Cross-sectional	662	Higher intake of certain fruits and vegetables high in vitamin A and C and carotenoids may be associated with a decreased likelihood of glaucoma in older African-American women.
	Wang <i>et al.</i> [2013a]	Cross-sectional	2912	Neither supplementary consumption with nor serum levels of vitamins A and E were found to be associated with glaucoma prevalence. While low- and high-dose supplementary consumption of vitamin C was found to be associated with decreased odds of glaucoma, serum levels of vitamin C did not correlate with glaucoma prevalence.
Oxidants	Wang <i>et al.</i> [2012]	Cross-sectional	3833	There may be a threshold intake of iron and calcium above which there is an increased risk of development of glaucoma.
	Wang <i>et al.</i> [2013b]	Cross-sectional	6316	While greater total consumption of calcium and iron may be associated with increased odds of glaucoma, dietary rather than supplemental consumption of these oxidants was found to be associated with lower odds of glaucoma.
EG, exfoliation glaucoma; EGS, exfoliation glaucoma suspect; IOP, intraocular pressure; OPP, ocular perfusion pressure; OHT, ocular hypertension; primary open-angle glaucoma, POAG.				

glaucoma but dietary consumption of calcium and iron is associated with decreased odds of glaucoma. These paradoxical results may potentially be attributed to the fact that NHANES participants self-report the glaucoma diagnosis and nutrient intake. Given that supplementation with calcium and iron is an established treatment for diseases caused by deficiencies, it would be very premature to suggest dietary changes given the available evidence.

In regard to clinical practice, physicians should continue to advise supplementation of calcium and iron to glaucoma patients with established deficiencies or related diseases.

Conclusion

Recent evidence suggests that caffeine, antioxidant and oxidant dietary factors may play a role in the risk of glaucoma. A summary of the relevant studies is displayed in Table 1. The associations reported in the epidemiological studies are based on self-reported databases and more rigorous prospectively designed trials are required to confirm these initial reports. Significant additional research is necessary before glaucoma patients should be advised to change their dietary and supplement habits for the purpose of reducing glaucoma risk. Based on the best available evidence to date, physicians should consider promoting activities consistent with overall health by

advising moderate caffeine intake and a healthy balanced diet rich in fruits and vegetables.

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Conflict of interest statement

A.A.A. has served as a paid speaker for Alcon Laboratories Inc. and Merck Sharp & Dohme, Inc. I.I.B. declares no conflict of interest in preparing this article.

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