

The Role of Diet in Glaucoma: A Review of the Current Evidence

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ABSTRACT

Intraocular pressure (IOP) reduction by medications, laser, or surgery remains the mainstay of treatment in glaucoma. However, the role of complementary and alternative medicine (CAM) in glaucoma has received great interest from both patients and ophthalmologists. Previous evidence suggests that diet, a major domain of CAM, can influence an individual's IOP level. Furthermore, certain dietary components have been linked to the incidence and progression of glaucoma. In this review, we aim to provide a summary of the current evidence regarding the role of obesity, certain dietary components, and dietary supplements in glaucoma.

Keywords: Alcohol; Antioxidants; Caffeine; Diet; Dietary supplements; Glaucoma; Intraocular pressure; Nutrition; Obesity

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INTRODUCTION

Glaucoma is a major cause of irreversible blindness worldwide. Globally, it is estimated that 5.7 million people are visually impaired as a result of glaucoma [1]. Increased intraocular pressure (IOP) is the most significant risk factor in glaucoma [2]; however, recent research on the pathogenesis of glaucoma suggests that non-IOP-dependent mechanisms also play a role. Vascular dysregulation [3], oxidative stress [4], autoimmunity [5], and excitotoxicity [6] are all mechanisms that can explain why glaucomatous optic neuropathy may occur despite normal IOP.

IOP reduction is currently the mainstay of glaucoma treatment. It has been shown that IOP reduction significantly delays glaucoma progression by means of optic disc damage and visual field loss [7]. This is usually achieved by anti-glaucoma medications, laser therapy, or surgical intervention. Recently, a considerable amount of glaucoma research has been directed towards therapeutic approaches targeting non-IOP-dependent mechanisms. The effect of novel therapeutic agents [8–10] and complementary medications [11–13] targeting such pathways is a subject of attention.

The use of complementary and alternative medicine (CAM), targeting both IOP-dependent and non-IOP-dependent mechanisms, in glaucoma has received interest from some ophthalmologists [14] and glaucoma patients [15]. A report from Canada showed that one in every

nine patients with glaucoma uses CAM in the treatment of his condition [16]. This encompasses a wide range of CAM categories, e.g. herbs, dietary interventions, exercise, and body-based practices.

A major domain of CAM in glaucoma is the utilization of dietary interventions. A considerable amount of research suggests that an individual's diet may have an effect on IOP [17], the incidence of glaucoma [18], and progression of the disease [19]. Furthermore, glaucoma patients commonly inquire about what to eat and drink in order to help in the treatment of their disease, and whether or not their dietary habits will affect the progression of their condition. Although it seems simple, an answer to such question is yet to be determined by ongoing research in this arena.

The objective of this review was to provide a summary of the current evidence regarding the effect of obesity and diet on IOP, incidence, and progression of glaucoma. The review outlines three major elements pertinent to diet: obesity and energy intake, individual dietary components, and dietary supplements.

METHODS

A literature review using the advanced search builder on PubMed was made in December 2017. The following search technique was implemented; "glaucoma" or "IOP" along with all of the following keywords: diet, nutrition, obesity, body mass index, alcohol, coffee, caffeine, tea, *Ginkgo biloba* extract, fruits, vegetables, chocolate, saffron, dietary supplements, and antioxidants. Search results were evaluated for relevance to our current review. Additional studies were added by manually reviewing bibliographies of articles obtained during the initial search. Results were limited to studies written in English, and published during the period from 1966 to 2017. In order to maintain clinical relevance, the main focus was on epidemiological and clinical studies conducted on human subjects.

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

OBESITY AND ENERGY INTAKE

Body mass index (BMI), a major anthropometric indicator of obesity, has been linked to elevated IOP in many cross-sectional [20–22] and longitudinal [23–25] studies on healthy subjects. The exact pathophysiology of elevated IOP in obesity remains unclear. Possible mechanisms that can explain such association include: obesity-related oxidative stress [26] leading to trabecular meshwork malfunctioning [27], increased orbital fat impeding aqueous outflow [28], and dysregulation of retrobulbar blood flow [29].

Interestingly, epidemiological studies looking at the relationship between BMI and primary open-angle glaucoma (POAG) have yielded inconsistent results [30–35]. The Gangnam Eye Study [30] found a positive association between BMI and the incidence of POAG, while others reported a negative association [33–35]. Furthermore, after adjustment for possible confounding variables, some studies did not find any association [31, 32]. A possible explanation of such difference is the presence of a racial variation between the studied populations.

Although BMI is a commonly used indicator of obesity, it has some limitations. A major drawback is that it does not differentiate between fat and muscle, such that it does not reflect the actual amount of fat tissue. In an attempt to overcome this, some studies have looked into the influence of other obesity markers on IOP [20, 36, 37]. The Korea National Health and Nutrition Examination Survey [36] found a positive linear relationship between different obesity markers (i.e. waist circumference, total body fat mass, and fat percentage) and IOP. Other reports have also found similar results on variable markers [20, 37].

In addition to obesity, other components of metabolic syndrome (MetS) have also been linked to elevated IOP and glaucoma. In a retrospective review of 12,747 subjects, Wynnanski-Jaffe et al. [38] found that MetS was more prevalent in subjects with high IOP. Moreover, other reports have found that the IOP rises linearly as the number of MetS components increases [39]. Newman-Casey et al. [40] looked at the association between POAG development

and various components of MetS in a large cohort of patients. They found that those with diabetes mellitus (DM) or hypertension (HTN), alone or combined, had an increased risk of developing POAG. On the other hand, hyperlipidemia was found to decrease the risk of POAG, and reduce the effect of DM and HTN if it occurs with any of them.

INDIVIDUAL DIETARY COMPONENTS

Alcohol

It has been shown that alcohol lowers IOP following acute ingestion in both glaucoma patients and healthy subjects [41, 42]. The exact mechanism leading to such finding is poorly understood; however, it is thought to be secondary to variable physiological changes such as a hyperosmotic effect exerted by alcohol, reduction of net water movement into the eye through vasopressin suppression [43], and inhibition of secretory cells in the ciliary processes [44]. Moreover, alcohol was shown to increase blood flow to the optic nerve head, a mechanism that is thought to offer a protective effect against the development of POAG [45].

With this in mind, various epidemiological studies were conducted to investigate the relation between alcohol consumption and glaucoma. Contrary to what is expected, the majority of those studies did not report any association [33, 46–48]. On the other hand, data from the Framingham Eye Study [49] suggests that there is a positive association between high alcohol consumption and glaucoma. Finally, a subset of case-control studies conducted on small numbers of patients found that alcohol consumption offers a protective effect against the development of POAG [50] and ocular HTN [51].

Coffee

Coffee is a rich source of caffeine, a biologically active compound that exerts numerous physiological effects on the human body. A transient

elevation in IOP has been noted following caffeine ingestion in patients with different types of glaucoma [52–54] and, to a lesser extent, in healthy individuals [17, 55]. Furthermore, the Blue Mountains Eye Study [56] found a higher mean IOP among POAG patients that reported regular caffeine consumption. Caffeine acts as a phosphodiesterase inhibitor which leads to an increase in intracellular cyclic adenosine monophosphate dehydrogenase, thereby stimulating aqueous humor production [57, 58].

Although elevated IOP is a well-established risk factor in POAG, studies looking into the connection between caffeine consumption and the incidence of POAG did not establish any association [59, 60]. However, Pasquale et al. [61] reported a positive association between caffeine consumption and the likelihood of developing pseudoexfoliative glaucoma in a large cohort of patients. Such association is assumed to be secondary to a caffeine-induced elevation in homocysteine levels [62, 63], which is thought to be a trigger stimulating the formation of basement membrane material [64].

Tea

The nutritional value of tea is derived from its major constituents (i.e. polyphenols, caffeine, and minerals) [65]. Flavonoids, a major polyphenol in tea, are thought to play a role in glaucoma [13, 66] owing to their various physiological actions that are proposed to affect non-IOP-dependent mechanisms. Studies have shown that flavonoids demonstrate their protective effect by reducing oxidative stress [67] and improving blood flow [68].

The available evidence on the relation between tea consumption, outside the context of caffeine intake, and the incidence of glaucoma is scarce. Wu et al. [60] recently published a cross-sectional report from the National Health and Nutrition Examination Survey in the USA on the association between glaucoma and commonly consumed beverages. Their results have demonstrated that participants consuming at least one cup of hot tea daily are less likely to have glaucoma compared to their non-consuming counterparts.

***Ginkgo biloba* Extract**

Ginkgo biloba extract (GBE) has been tested in the treatment of various medical conditions [69], including glaucoma [70, 71]. GBE exhibits a myriad of pharmacological properties making it relevant to the pathogenesis of glaucoma. The current evidence suggests that GBE increases ocular blood flow [72], improves retinal ganglion cell survival [73], and protects against oxidative stress [74].

Based on the fact that reduced ocular blood flow is thought to be a major player in the pathogenesis of normal tension glaucoma (NTG) [75], multiple studies have looked into the effect of GBE on patients with NTG. Park JW, et al. [76] proved that GBE intake improves retinal blood flow in the peri-papillary region among patients with NTG. Moreover, multiple reports agree that GBE improves visual function [77, 78], and slows the progression of visual field damage [19] in NTG. Conversely, a clinical trial from China found no effect on newly diagnosed patients with mild visual field loss [79].

Fruits and Vegetables

Being rich in antioxidants, it is speculated that a diet rich in fruits and vegetables can decrease the risk of developing glaucoma. However, the nutrient composition of different fruits and vegetables varies, making it difficult to link the presumed protective effect to a single source. Nonetheless, multiple cross-sectional studies were conducted using food frequency questionnaires in an attempt to link certain fruits and vegetables to glaucoma. Coleman et al. [80] found a decreased glaucoma risk in women who consumed fruits and vegetables rich in vitamin A and carotenes, namely collard greens, kale, carrots, and peaches. Another study by Giaconi et al. [18] also concluded that there is a decreased likelihood of glaucoma among women that reported a greater intake of fruits and vegetables rich in vitamins A and C, and carotenes.

Moreover, nitric oxide (NO) is thought to be a major contributor to vascular dysregulation in patients with POAG [81]. Therefore, it is

hypothesized that high consumption of dietary nitrates might have a protective effect against the development of POAG. In a prospective cohort, Kang et al. [82] found that a diet rich in nitrates and green leafy vegetables was associated with a lower risk of developing POAG.

Chocolate

Dark chocolate is a rich dietary source of polyphenol compounds, specifically flavonoids [83]. Acute consumption of dark chocolate has been shown to reverse vascular endothelial dysfunction by decreasing oxidative stress and increasing the bioavailability of NO [84]. Therefore, it is proven beneficial in patients with certain cardiovascular diseases such as HTN [85] and peripheral artery disease [86].

In glaucoma, the only trial looking into the effect of dark chocolate was published by Terai et al. [87]. Their study showed that acute consumption of dark chocolate increased retinal vessel diameter in healthy subjects, but not in glaucoma patients. A possible explanation of such finding is a compromised ability of the vascular endothelium to produce NO in patients with glaucoma. In spite of that, further research is still required to properly outline the role of dark chocolate in glaucoma.

Saffron

The only published study on the relation between IOP and saffron comes from Iran, the world's largest saffron exporter. Jabbarpoor Bonyadi et al. [88] studied the effect of a daily oral saffron capsule on IOP in patients with POAG. After a period of 3 weeks, a statistically significant decline in IOP was noted among the study group. They suggested that this hypotensive action is secondary to the antioxidative effect of saffron [89] on dysfunctional trabecular meshwork. However, due to limited experimental data, the exact mechanism remains unclear.

Table 1 summarizes key findings from all the cited studies providing evidence regarding the effect of individual dietary components on IOP and glaucoma.

Table 1 Summary of included studies providing evidence on the effect of individual dietary components on IOP and glaucoma

Component	Study	Design	Sample	Key finding
Alcohol	Ramdas et al. [33]	Prospective cohort	3939 healthy subjects	Incidence of POAG was not associated with alcohol consumption
	Giurlani et al. [41]	Non-randomized trial	73 healthy subjects	Acute ingestion of alcohol results in a statistically significant reduction in IOP
	Buckingham et al. [42]	Non-randomized trial	6 healthy subjects	On average, the IOP decreased by 3.7 mmHg following acute ingestion of alcohol, and normal values were restored after 65 min
	Klein et al. [46]	Cross-sectional	4926 subjects	Alcohol consumption was not related to the prevalence of POAG
	Kang et al. [47]	Prospective cohort	120,379 healthy subjects	Alcohol consumption did not influence the risk of developing POAG
	Xu et al. [48]	Cross-sectional	4141 subjects	Alcohol consumption was not related to the prevalence of POAG
	Kahn et al. [49]	Cross-sectional	2433 subjects	Alcohol consumption was directly related to glaucoma
	Fan et al. [50]	Case-control	32 POAG patients, 96 controls	Alcohol consumption offers a protective effect against POAG
	Seddon et al. [51]	Case-control	100 OHT patients, 100 controls	Absence of alcohol intake was significantly associated with OHT

Table 1 continued

Component	Study	Design	Sample	Key finding
Coffee	Ajayi et al. [17]	Randomized controlled trial	40 healthy subjects	A statistically significant elevation in IOP was noted following acute ingestion of caffeinated coffee
	Jiwani et al. [52]	Randomized controlled trial	22 POAG, 18 NTG, 20 OHT, 21 POAG suspect, and 25 healthy individuals	A statistically significant elevation in IOP was noted following acute ingestion of caffeinated coffee when pooling all groups together
	Avisar et al. [53]	Randomized controlled trial	6 NTG patients and 22 OHT patients	A statistically significant elevation in IOP was noted following acute ingestion of regular caffeinated coffee in both groups
	Higginbotham et al. [54]	Randomized controlled trial	13 POAG or POAG suspects randomized into two groups	A higher IOP was noted upon acute ingestion of coffee, compared to tea. The difference between both interventions was statistically significant at 90 min
	Chandrasekaran et al. [56]	Cross-sectional	3654 subjects	POAG patients reporting a high intake of caffeine had a significantly higher IOP compared to those reporting no intake
	Kang et al. [59]	Prospective cohort	124,172 healthy subjects	Caffeine intake did not influence POAG risk
	Wu et al. [60]	Cross-sectional	1678 subjects	No association was found between coffee consumption and glaucoma risk
	Pasquale et al. [61]	Prospective cohort	120,179 subjects	A positive association between heavy coffee consumption and EG/EGS was noted
Tea	Wu et al. [60]	Cross-sectional	1678 subjects	Daily consumers of hot tea are less likely to have glaucoma compared to non-consumers

Table 1 continued

Component	Study	Design	Sample	Key finding
GBE	Lee et al. [19]	Retrospective	42 NTG patients treated with GBE 80 mg three times daily	GBE slowed the visual field damage in patients with NTG
	Chung et al. [72]	Randomized controlled trial	11 healthy subjects	GBE significantly increased ocular blood flow in healthy subjects when compared to placebo
	Park et al. [76]	Randomized controlled trial	30 NTG patients	GBE significantly increased peripapillary blood flow in patients with NTG when compared to placebo
	Shim et al. [77]	Case-control	332 NTG patients: 132 received anthocyanins, 103 received GBE, and 97 were controls	Both anthocyanins and GBE were associated with improved visual function in patients with NTG
	Quaranta et al. [78]	Randomized controlled trial	27 NTG patients with pre-existing visual field damage	GBE improved pre-existing visual field damage in patients with NTG
	Guo et al. [79]	Randomized controlled trial	28 newly diagnosed NTG patients	GBE had no effect on visual field in newly diagnosed NTG patients
Fruits and vegetables	Giaconi et al. [18]	Cross-sectional	584 African American subjects	A decreased likelihood of glaucoma was noted among women that reported a higher intake of fruits and vegetables containing vitamins A and C, in addition to carotenes
	Coleman et al. [80]	Cross-sectional	1155 female subjects	Consumption of fruits and vegetables rich in vitamin A and carotenes was associated with decreased risk of glaucoma
	Kang et al. [82]	Prospective cohort	104,987 subjects	A higher intake of nitrates and green leafy vegetables was associated with a lower risk of POAG
Chocolate	Terai et al. [87]	Randomized controlled trial	30 glaucoma patients, 30 controls	An increase in retinal vessel diameter was noted 2 h after dark chocolate intake in healthy subjects, but not in glaucoma patients

Table 1 continued

Component	Study	Design	Sample	Key finding
Saffron	Jabbarpoor Bonyadi et al. [88]	Randomized controlled trial	34 POAG patients	A statistically significant ocular hypotensive effect was noted after 3 weeks of treatment with saffron extract

POAG primary open angle glaucoma, *IOP* intraocular pressure, *OHT* ocular hypertension, *NTG* normal tension glaucoma, *EG* exfoliation glaucoma, *EGS* exfoliation glaucoma suspect, *GBE* *Ginkgo biloba* extract

DIETARY SUPPLEMENTS

The benefit of dietary supplements is well-established in the management of patients with age-related macular degeneration [90, 91]; however, in glaucoma, we still lack supporting evidence. A considerable amount of research suggests that levels of oxidative markers are altered in the plasma [92–97] and aqueous [98, 99] of patients with POAG [95, 99], as well as different types of glaucoma [92–94]. Therefore, it is hypothesized that the use of dietary supplements rich in antioxidants might play a role in glaucoma.

Wang et al. [100] looked at the relation between the prevalence of glaucoma and the use of dietary supplements containing antioxidant vitamins (i.e. A, C, and E) among participants of the National Health and Nutrition Examination Survey. They also obtained measurements of serum vitamin levels to correlate them with the intake of supplements. No relation was found between reported glaucoma and supplemental use, or serum levels, of vitamins A and E. On the other hand, the supplemental intake of vitamin C was linked to a decreased chance of glaucoma; however, this did not correlate with serum vitamin C levels.

To date, the only prospective randomized clinical trial evaluating the possible effect of antioxidant supplements in glaucoma was published by Garcia-Medina et al. [101]. They studied the effect of the Age-Related Eye Disease Study (AREDS) formula on a small sample of patients with mild to moderate POAG. After 2 years of follow up, there was no difference in outcome between the studied groups.

Moreover, the possible role of long-chain polyunsaturated fatty acids has also been explored in the literature. A fatty acid imbalance between omega-3 and omega-6 is believed to contribute to the pathogenesis of POAG [102]. Furthermore, epidemiological studies assessing the dietary consumption of fatty acids have suggested that an imbalance in the omega-3-to-omega-6 ratio might be associated with an increased risk of developing glaucoma [103, 104]. However, in the trial conducted by Garcia-medina et al. [101], the addition of

omega-3 supplements to one of the arms in the study did not yield any benefit to POAG patients.

CONCLUSION

The current level of evidence suggests that an individual's diet might have an impact on IOP, incidence, and progression of glaucoma. Given that the majority of results are drawn from observational studies, well-designed, randomized, controlled, clinical trials are required to reinforce the current body of evidence.

A sound dietary advice to glaucoma patients would be to maintain a normal weight, avoid excessive coffee consumption, and increase the intake of fruits and vegetables. However, patients should be advised that nutritional management may complement, but would not substitute conventional glaucoma treatment.

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Data Availability. Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

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