Dietary Intervention in Glaucoma

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Glaucoma is a multifactorial disorder caused by risk factors dependent on, as well as those independent of, intraocular pressure. Currently, the treatment of this condition is primarily lowering of intraocular pressure. However, despite achieving the apparent target pressure, some patients continue to deteriorate. As a result, other modalities such as complementary and alternative medicine are being increasingly used to manage patients with glaucoma. These approaches include modifications or supplementations in diet and lifestyle changes, such as exercise and cessation of smoking. The objective of this review is to assess how different diets can be useful or detrimental to the visual health of patients with glaucoma. It also aims to shed light on the effect of dietary intervention on the epidemiology of glaucoma.

Keywords

Glaucoma, intraocular pressure, diet, antioxidants, nutrition therapy

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Glaucoma is a chronic, disabling eye disease. It is characterized by the loss of retinal ganglion cells (RGC) and/or their axons, and tissue remodelling involving the optic nerve head and the retina.[1] Glaucoma has been known for millennia, and considerable money, time and effort have been spent finding an effective and universal cure. However, despite our best efforts, glaucoma remains one of the most common causes of visual impairment worldwide. Nearly 80 million people are suspected to have glaucoma, and almost six million are apparently blind from this disease.[2]

The current management of glaucoma is hampered by the lack of robust understanding of its aetiopathophysiology. It is generally accepted that glaucoma is caused by multiple factors; however, currently treatment of this condition is still largely limited to reducing intraocular pressure (IOP). Unfortunately, in many cases this IOP-dependent approach has failed to prevent blindness.[3] In at least two studies reported from the USA and Sweden, about 40% of patients with glaucoma were blind in one eye on long-term follow-up.[4,5]

There is growing evidence of metabolic deficiencies and defects playing a crucial role in causing glaucoma. Certain genes, such as ATP binding cassette subfamily A member 1 and phosphomannomutase 2, are involved in carbohydrate and lipid metabolism/anabolism. These genes are expressed in the retina and optic nerve, where functional disruptions to the RGCs and their networks have been identified in glaucoma. Variations in the aforementioned genes could contribute to development of glaucoma.[6] A genome-wide association study of normal-tension glaucoma (NTG) in Japan reported strong associations with elongase of very-long fatty acid 5 (*ELOVL5*), a gene involved in lipid metabolism pathways.[7] Davari et al.,[8] Dube et al.[9] and Pavlajasevic & Asceric[10] have found that serum cholesterol and triglycerides are closely associated with primary open-angle glaucoma (POAG). These researchers hypothesize the role of hypertriglyceridaemia in causing vascular dysfunction, ischaemia and RGC degeneration.[8–10] A case report supports this school of thought, pointing to the association of hypertriglyceridaemia and glaucoma.[11]

Complementary and alternative medicine (CAM) has been explored as a means to preserve or regain the visual health of patients with glaucoma. CAM is holistic in approach, and includes diet, exercise and general health measures. 'Complementary' interventions are those that are added to conventional therapy, while 'alternative' interventions are used in place of conventional treatment. 'Dietary supplements' provide nutrients, while 'food supplements' are concentrated sources providing nutrients.[12] In patients with glaucoma, CAM aims to address both IOP-dependent and IOP-independent factors in the development of glaucoma. A study from Canada revealed that nearly one in nine patients with glaucoma use some form of CAM treatment,[13] while a study from India reported that 5–10% of patients with glaucoma use CAM.[14]

Dietary agents that are useful in managing glaucoma include antioxidants, ginkgo biloba, saffron, peaches, egg plants and, possibly, tea. Conversely, certain foods are probably best avoided by patients with glaucoma, such as alcohol in large measures, coffee and foods that acutely increase blood pressure (BP). The role of these dietary interventions shall be elaborated further in this article.

The objective of this review is to assess how different diets can be useful or detrimental to the visual health of patients with glaucoma. It also aims to shed light on the effect of dietary intervention on the epidemiology of glaucoma.

Diets useful in glaucoma

Several diet-related substances are thought to promote better health of RGCs in glaucoma. This suggests some role for these agents in patients with this potentially blinding disorder.

Nicotinamide adenine dinucleotide

Nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP+) are essential cellular metabolic factors. They are cofactors in various enzymatic oxidation–reduction reactions, especially glycolysis, the citric acid cycle and the electron transport chain. NAD is an electron carrier, helping convert energy between nutrients and adenosine triphosphate (ATP). Studies have found disrupted NAD homeostasis in several age-related neurodegenerative diseases, such as glaucoma, Alzheimer's disease and Parkinson's disease. This makes NAD a potential target for glaucoma management.[6,15]

Niacin refers broadly to nicotinic acid, nicotinamide (vitamin B3) and derivatives of nicotinamide. Both POAG and NTG are associated with lower niacin intake, and lower concentrations of nicotinamide have been detected in the sera of patients diagnosed with POAG.[16] Nicotinamide has been evaluated as a dietary supplement in patients with glaucoma.[17] Administration of nicotinamide up to 3 g/day prevented dysregulation of key metabolic pathways, loss of internal mitochondrial structure and size, and RGC loss.[18,19] However, the long-term effects of niacin administration are unknown.[6]

Nitrate-rich leafy vegetables

Vascular dysregulation in patients with POAG is mediated by nitric oxide (NO). Therefore, high consumption of dietary nitrates could have a protective effect.[20] The endogenous NO pathway is compromised in POAG and, therefore, dietary nitrates could offer an alternative pathway for NO synthesis.[21] A large prospective study found increasing intake of green leafy vegetables, which are rich in nitrates, was associated with a 20–30% lower risk of POAG.[22]

Pyruvate and lactate

Pyruvate and lactate are glycolysis end products that are important energy sources for various cells, including neurons. Pyruvate is converted to acetyl-coenzyme A and enters the citric acid cycle or is converted to lactate. The latter is a significant energy source for central nervous system neurons and Müller cells.[6] RGCs use glucose, lactate or pyruvate as energy sources.[23] Cell culture models have demonstrated the neuroprotective effect of pyruvate and lactate on RGCs. A study by Harder et al.[23] showed that long-term supplementation with oral pyruvate significantly reduced optic nerve degeneration and axon-transport disruption, protected against IOP-induced metabolic changes, and enhanced RGC survival. The effects on RGC survival were improved by adding low-dose nicotinamide to the above regimen.[23]

Ketogenic diets

Studies of ketogenic diets (or variants that increase circulating ketone bodies) have reported improved outcomes in some neurodegenerative conditions, such as Alzheimer's disease and Parkinson's disease.[24–26] The neuroprotective effects are proposed to act through reduced production of reactive oxygen species (ROS), modulation of oxidative stress, increased mitochondrial biogenesis, increased mitochondrial glutathione levels, bolstered energy reserves (including increased ATP and phosphocreatine) and altered expression of key metabolic enzymes, which disrupts metabolic processes.[6,27] Genes encoding bioenergetic enzymes are found to be upregulated by ketogenic diets.[28,29] Patients with glaucoma have ROS-induced RGC damage, mitochondrial loss and metabolic disruption.[30] Thus, a ketogenic diet could potentially have a protective role by suppressing formation of ROS.

An analysis of three cohort studies from the USA, namely, the Nurses' Health Study I and II and the Health Professionals Follow-up Study, showed that a low carbohydrate diet was not statistically significantly associated with the risk of developing POAG.[31] However, patients on diets containing low carbohydrates and higher fat and protein from vegetable sources had a lower risk of developing the POAG subtype characterized by initial paracentral visual loss, which is found in 10% of all patients with POAG.[31] Further studies are required to show any neuroprotective effect in glaucoma by adding or replacing traditional energy sources by ketones.[6]

Tea

A commonly used beverage worldwide, tea has many health benefits, often attributed to the complex mix of polyphenols/flavonoids, caffeine, vitamins and minerals.[6] In glaucoma, better outcomes are seen due to the high flavonoid content of tea, as flavonoids help in IOP and vascular regulation, and have antioxidant properties.[32] Based on an analysis of the National Health and Nutrition Examination Survey (NHANES), participants who consumed at least one cup of tea every day were less likely to have glaucoma compared with their non-consuming counterparts.[33] Green tea contains a flavonoid called epigallocatechin gallate. A study by Falsini et al., found that this agent, when given for 3 months, improved inner retinal function in patients with POAG, with early to moderately advanced glaucomatous degeneration. This effect was not seen in patients with ocular hypertension.[34]

However, further long-term research is required to assess the role of tea in neuroprotection.[6]

Antioxidants

During metabolism, ROS are continuously released by tissues. These ROS damage the RGCs, adversely affecting visual outcomes.[30] Antioxidants (such as vitamins A, C, E; omega-3 and -6; co-enzyme Q10; resveratrol; and green tea extract) are often prescribed to improve systemic and ocular health.[6,35] The Osteoporosis Fracture Cohort study found a reduced risk of POAG in women who consumed green leafy vegetables, carrots and canned peaches more than twice a week.[27–36]

Vitamin B12 is required for DNA synthesis, and fatty acid and amino acid metabolism.[37] Levels of vitamin B12 decrease with age, and are especially low in the sera of patients with POAG.[6] Long-term methylcobalamin (a vitamin B12 homologue) delayed visual-field loss in patients with NTG.[38] Low levels of vitamin B12 also correlate with hyperhomocysteinaemia, which has been reported in pseudo-exfoliative glaucoma.[39] Analysis of the Rotterdam Study, showed that those with a higher retinol intake had half the risk of POAG compared with those with the lowest intakes. Conversely, higher magnesium intake was associated with an increased risk of developing the disease. (retinol: p=0.019; vitamin B1: p=0.047; magnesium: p=0.014) compared with those with the lowest intake.[40]

Antioxidants have been broadly divided into carotenoids (α- and β-carotene, lutein, zeaxanthin, β-cryptoxanthin and lycopene), certain vitamins (retinol equivalents, vitamin B1, B6, B12, E and C), flavonoids and substances that improve ocular blood flow (omega-3

FA, eicosapentaenoic acid, docosahexaenoic acid).[40] Dietary sources having high retinol equivalents are dairy products (milk, cheese, butter) and liver. Similarly, grain products (bread, rice) and potatoes are good sources of vitamin B1. According to Ramdas et al., the clinical benefits of antioxidants only occur when sourced from food intake, whereas supplemental antioxidant vitamins do not appear to be beneficial.[40]

A cross-sectional analysis of NHANES investigated the possible association between supplemental intake and serum levels of vitamin A, C and E.[41] The investigators reported that neither supplement consumption nor serum levels of vitamin A and E were associated with glaucoma prevalence. However, supplemental consumption of vitamin C was associated with decreased odds of glaucoma (odds ratio [OR] 0.47; 95% confidence interval [CI] 0.23–0.97). Incidentally, serum levels of vitamin C did not correlate with glaucoma prevalence (OR 0.94; 95% CI 0.42–2.11).[41]

The use of antioxidants could have positive outcomes in terms of primary prevention of glaucoma. These agents also have apparent low risk/benefit ratio, making them attractive options for widespread use. However, some controlled studies and meta-analyses did find risk of harm on high-dose, long-term use of these agents. These incongruous results highlight the limitations of self-reported diagnosis and nutrient intake compared with objective measurements.[42]

Magnesium

Magnesium is a naturally occurring calcium-channel blocker and improves blood flow, while decreasing vascular resistance in various vascular beds.[43] It also reduces cytokine and free radical production and prevention of intracellular calcium entry, which minimizes injury to the RGCs and neuronal loss. Magnesium inhibits the release of glutamate, which plays a role in the biochemical degradation of RGCs. It has intrinsic antioxidant activity by modulating superoxide dismutase. The neuroprotective activity of magnesium is attributable to its regulation of glutathione synthesis, lipid peroxidation, and regulation of many metabolic enzymatic reactions.[44]

A study conducted by Gaspar et al. reported improved visual field parameters in NTG patients following 4 weeks of magnesium supplementation.[43] Yet, as mentioned previously, the analysis of the Rotterdam Study found higher magnesium intake was associated with a higher risk of developing POAG.[40] The recommended daily allowance of magnesium in adults (300–400 mg) can be obtained by eating adequate amounts of green leafy vegetables, bananas, avocados, nuts, seeds and whole grains.[45]

Ginkgo biloba

Ginkgo biloba is a tree, which has been described in Chinese traditional medicine texts dating to around 3,000 BC. Gingko biloba extract (GBE) has various roles that could prove beneficial in glaucoma. It has antioxidative properties due to its ability to scavenge ROS directly, and inhibit their generation by stabilizing the mitochondria.[46,47] Unlike other antioxidants, GBE can penetrate the inner mitochondrial membrane and act on the mitochondria more effectively.[1,46]

Gingkolid-B has an antagonistic action on platelet activating factor, which increases during trauma and hypoxia. Regulation of platelet activating factor may slow apoptosis and modulate post-ischaemic injury. GBE increases erythrocyte deformability, thereby improving blood viscosity and visco-elasticity, and facilitating blood perfusion. Endothelium-dependent vasodilation by GBE could also promote blood perfusion.[47,48]

A study has shown GBE significantly increased end-diastolic velocity in the ophthalmic artery and in all retrobulbar blood vessels. Optic-nerve-head blood flow also increased, although the effect was not significant compared with placebo.[47–49] In another study, GBE supplementation in patients with NTG statistically improved visual-field indices compared with placebo.[50] A study from Korea found visual-field progression slowed on GBE administration.[51] However, no significant changes were observed between GBE and placebo in Chinese patients with NTG.[52] GBE also reduces active cells (e.g. glial cells) in low-grade inflammation and thus, prevents apoptosis of surrounding RGCs.[47]

Gingko biloba has been found to be very safe. Rare cases of allergic reactions, headache or gastrointestinal upset have been reported. A few cases of retinal haemorrhages, spontaneous hyphema, subarachnoid haemorrhage and subdural haematoma have been noted, but it is not clear whether the bleeding was due to GBE or other causes.[46–48]

Chocolate

Dark chocolate, like many other sources discussed elsewhere, is a rich source of flavonoids. Evaluation of various cocoa and chocolate products found extra dark chocolate to be the best in terms of total polyphenol content as well as antioxidant capacity. Some authors are of the opinion that the antioxidant potential of dark chocolate is higher than that available through commercially available supplements.[53]

Glaucoma is characterized by an imbalance between endothelin-1 (ET-1) and NO, with decreased availability of the latter. A few studies have been performed to assess the possible association of chocolate and glaucoma. Flammer et al. is of the opinion that dark chocolate might have therapeutic benefits by acting through the above mentioned NO pathway and also due to its antioxidative effect.[54]

An analysis of NHANES to determine the association of chocolate consumption with glaucoma prevalence found that in the unadjusted model, there is a trend for reduced glaucoma prevalence as the chocolate consumption increases from less than six times a year to more than once per week. However, this trend weakened in the fully adjusted model. A statistically significant association between glaucoma and chocolate candy was found only in the non-Hispanic black subgroup.[55]

In another study, optometry students were given chocolate bars containing 40 g of sugar. A reduction of average IOP was recorded from 12.92 mmHg at baseline to 10.84 mmHg at 40 minutes after ingestion. Differences between the means were found to be statistically significant. ($F=46.82$, $p<0.001$).[56]

A study to compare the effects of dietary inclusion of dark or white chocolate showed that in the non-glaucoma control group the mean dilatation of the venules increased from 3.2 ± 0.9% (prior to dark chocolate ingestion) to 4.2 ± 1.4% after dark chocolate intake, which was statistically significant ($p=0.01$). The mean dilatation of the arterioles in the same group (control) had a trend to statistical significance ($p=0.14$) but did not reach statistical significant level. Mean diameter changes in the glaucoma group did not show any significant difference after dark chocolate consumption. The changes in the venules were attributed to the increased bioavailability of NO and improved endothelial function of the retinal venules following chocolate intake. However, in the glaucoma group the effects were not significant, possibly due to the already compromised endothelial function.[57] Based on these observations, it seems that while chocolate may be useful due to the flavonoid content and possible effect on IOP,

it may not affect the glaucoma prevalence or act as a neurovascular protective agent.

Saffron

Derived from the pistils of *Crocus sativus*, saffron has high concentrations of crocin and crocetin (carotenoid derivatives). Saffron is a powerful radical scavenging, antioxidant and antitumour agent.[58] These biochemical properties of saffron could have implications in glaucoma management.

In a study from Iran, oral saffron extract (30 mg/day) was given to patients with POAG.[59] Mean baseline IOP was 12.9 ± 3.7 mmHg in the saffron group and 14.0 ± 2.5 mmHg in the control group. After 1 week of saffron consumption, mean IOP fell to 12.0 ± 3.3 mmHg in the saffron group and 13.6 ± 2.6 mmHg in the control group. At four weeks, the mean IOP was 10.6 ± 3.0 mmHg in the saffron group and 13.8 ± 2.2 mmHg in the control group. At 1 month after stopping saffron, IOP rose to 12.9 ± 3.0 mmHg in the saffron group and 14.2 ± 2.0 mmHg in the control group.[59] These results demonstrate the ocular hypotensive effect of saffron following 3 weeks of high-dose consumption.

However, consumption of such high doses of saffron is not feasible over a long period of time. Doses of saffron above 10 g can induce abortions and above 20 g can be lethal. Other side effects include icteric-like staining of the sclera and skin, nausea, vomiting, diarrhoea and bleeding.[59]

Eggplant / Aubergine

Eggplant (aubergine) is a common vegetable belonging to the angiosperm family. It contains a number of chemicals, especially α-chaconine, which have anticholinesterase activity. This causes miosis in the eye, affecting the pupillary diameter and near point of convergence. Pupillary constriction stimulates the longitudinal muscles of the ciliary body and opens up the pores of the trabecular meshwork. This increases aqueous outflow from the eye.[60]

In one study, bolus consumption of 10 g of *Solanum melongena* (aubergine) was associated with a 25% reduction in IOP in healthy male volunteers.[60] However, this effect lasted only 120 minutes. Whether this hypotensive effect of aubergine consumption extends to patients with glaucoma needs to be studied, as does its therapeutic potential.

Salt

Ocular perfusion pressure (OPP) is the difference between BP and IOP; therefore, high BP and low IOP improves OPP.[61] Excessive salt intake can increase BP and indirectly affect IOP.

In the Thessaloniki Eye Study patients with hypertension who consumed salt frequently had a higher prevalence of POAG. This association was not seen in patients with pseudoexfoliative glaucoma or those individuals who were not on antihypertensive medications.[62]

Conversely, in patients with significant fluctuations in their BP, especially nocturnal hypotension, the periods of low BP can affect aqueous humour formation and ocular blood flow.[1] Mozaffarieh and Flammer recommended patients with low BP to increase their salt intake (1–5 g/day). In severe cases, addition of a fludrocortisone (0.1 mg twice weekly) increases BP and also improves blood flow regulation.[1]

Long-chain, polyunsaturated fatty acids

Long-chain, polyunsaturated fatty acids (PUFAs) have been mentioned in the previous section on antioxidants; however, their role is controversial and requires further discussion. An imbalance between omega-3 and omega-6 FAs increases the risk of developing POAG, and its progression.[63,64] In a rat model of glaucoma, omega-3 supplementation reduced IOP, which was attributed to the production of prostaglandins that possess IOP-lowering effects.[65] A clinical study involving normotensive adults showed that oral omega-3 supplementation for 3 months significantly reduced IOP.[66] However, a further study did not find any benefit of omega-3 supplementation in patients with POAG.[67]

Borage tea

Borage is a flowering herb, found in Mediterranean countries and especially commonly consumed in Iran.[68] Flowers of Borage have cardiodepressant effects, which is probably mediated though a calcium antagonising mechanism similar to that seen with verapamil.[69] This calcium antagonizing activity of borage could potentially be channelled into treatment of glaucoma.

These flowers are also rich sources of vitamins A and C as well as carotenoids and polyphenols. Seeds of borage contain high levels of gamma linolenic acid, which is converted into prostaglandin E-1. This is an endogenous vasodilator, which improves blood flow.[70]

Individuals suffering from Flammer syndrome have profound vascular dysregulation, with high retinal venous pressure (RVP) and ET-1 levels.[71] In a study conducted in Iran, daily borage tea consumption for 21 days significantly reduced RVP from a mean of 38.91 ± 8.56 to 32.50 ± 8.[55] mmHg (p=0.003) in Flammer syndrome positive patients, without a significant change seen in IOP. It also reduced the ET-1 levels in such patients. Borage has strong antioxidant activities, which are attributed to its diverse polyphenolic content, improving blood flow and enhancing vascular dysregulation. The pharmaceutical action to reduce RVP could prove beneficial in patients suffering from Flammer syndrome.[71]

The calcium antagonizing property, antioxidant activity, regulation of blood flow, and stabilizing of RVP and ET-1, as well as prostaglandin formation could be beneficial in the dietary treatment of glaucoma.

Resveratrol

Resveratrol, a naturally occurring polyphenol found in various organic sources, is being investigated for a possible role in the dietary modification of glaucoma. This agent is present in red wine, berries, grapes, tomatoes, peanuts, plums and dark chocolate.[72] There is experimental evidence supporting its anti-apoptotic, antioxidant, anti-inflammatory, neuroprotective and life-enhancing properties.[73,74]

A study by Shamsher et al., showed treatment with resveratrol nanoparticles in a rat model of ocular hypertension led to a significant reduction in RGC loss, compared with vehicle-treated eyes (1.02 ± 0.05 vs 0.70 ± 0.11 RGC density ratio, p<0.05).[73] Pirhan et al, used a rat model of glaucoma to inject intraperitoneal resveratrol and riluzole. At the end of the study period the mean RGC counts, in mm^2, were 404 ± 65 in the vehicle-treated group, 714 ± 25 in the riluzole group and 667 ± 20 in the resveratrol group. Thus, both resveratrol and riluzole were able to significantly delay RGC loss.[75]

Luna et al. subjected trabecular meshwork cells to chronic stress. When these cells were treated with resveratrol, there was significant reduction in the production of intracellular reactive oxygen species and inflammatory markers (IL1α, IL6, IL8 and ELAM-1). There was also reduced expression of senescence markers sa-β-gal, lipofuscin and carbonylated proteins. The study demonstrated the effectiveness of resveratrol in preventing tissue abnormalities that develop in glaucoma patients.[74]

Resveratrol is extensively metabolized and inactivated in the liver. This makes oral administration of this compound pharmacologically unfeasible.[76] The chemical structure of resveratrol resembles oestrogen. Thus, it may alter oestrogen metabolism and is theoretically contraindicated in women suffering from carcinomas of the breast, ovaries or uterus, as well as conditions such as endometriosis and uterine fibroids.[77,78] Resveratrol may cause bleeding in patients on anti-coagulants, due to its antiplatelet activity.[79] It lowers blood sugar by increasing the sensitivity to insulin and oral hypoglycaemic agents and could trigger hypoglycaemic episodes. The compound also lowers blood pressure and should be used with caution in patients who are well controlled with antihypertensive agents.[80]

Anthocyanins

Anthocyans or anthocyanins are water-soluble vacuolar pigments. Their colour varies from red to purple to blue to black. Several plants are rich in these compounds, including bilberry, blackcurrant, blueberry, raspberry, coloured rice, soya bean and others. Anthocyanidins are flavylium carbon derivatives and their water-soluble glycosides are the anthocyanins. These molecules have antioxidant and free-radical scavenging properties.[81]

The *Vaccinium myrtillus* (bilberry) anthocyanoside and its anthocyanidin constituents (cyanidin, delphinidin and malvidin) protect RGCs against N-methyl-D-aspartate induced retinal damage.[82]

In one study, patients with NTG were treated with anthocyanins over 6–53 months.[83] The mean best-corrected visual acuity improved from 0.16 (± 0.34) to 0.11 (± 0.18) logMAR units (p=0.008). The Humphrey Visual Field mean deviation also improved from -6.44 (± 7.05) to -5.34 (± 6.42) (p=0.001).[83]

In another study, patients with NTG who received 50 mg oral anthocyanin once daily for 6 months had increased plasma concentrations of ET-1 (3.27 ± 1.67 pg/mL improved to 4.10 ± 2.14 pg/mL).[84] The blood flow in the superior and inferior temporal neuroretinal rim also significantly increased (p<0.05–0.01) at the end of treatment period.[84]

Yoshida et al. reported lower serum levels of ET-1 in patients diagnosed with POAG (3.18 ± 1.06 pg/mL vs 4.38 ± 1.03 pg/mL in healthy volunteers). Treatment with anthocyanin elevated the ET-1 concentration in these glaucoma patients to 4.59 ± 1.84 pg/mL; comparable to the levels seen in healthy individuals, suggesting some neuroprotective potential for anthocyanins.[85] A study corroborated the elevated retinal blood flow and reduced degradation of the visual fields in patients with POAG who were treated with anthocyanins over 24 months.[86]

These studies demonstrate improved visual function in both POAG and NTG patients following anthocyanin treatment.

Diets harmful in glaucoma

As the RGCs are susceptible to a variety of insults, including through vascular and biochemical mechanisms, it is imperative to protect the eyes from agents that could potentially damage these cells further. In this aspect, a few substances have been found to be detrimental and play some part in the development and progression of glaucoma.

Caffeine

Several drinks and foods contain caffeine. The commonly used beverages coffee and tea have variable amounts of caffeine. Coffee modulates glaucomatous degeneration through multiple mechanisms. It acts as a phosphodiesterase inhibitor, thus, stimulating aqueous humour production.[22,87,88] It is also found to cause ultrastructural changes in the nonpigmented ciliary epithelium, which increases aqueous transport.[88] Caffeine decreases the tone of the ciliary smooth muscles in the angle, leading to the closure of trabecular pores.[87,88] Caffeine also has a detrimental effect in glaucoma patients by causing transient rise in BP and through reduced blood supply to the optic nerve, choroid and macula.[42,87–89]

Coffee is found to transiently elevate IOP in different glaucoma subgroups by around 2 mmHg for about 90 minutes. This effect is also seen in normotensive healthy individuals but to a lesser extent.[6,42,90] In a study from Malaysia, coffee drinking was associated with an 8-fold increased risk of glaucoma progression.[87]

Pasquale et al. performed a study to examine the association of caffeine consumption with respect to the risk of exfoliative glaucoma or exfoliation glaucoma suspect (EG/EGS). The authors reported that significantly high consumption of caffeinated coffee adversely increased the risk of EG/EGS. Subjects who drank three or more cups of caffeinated coffee had 1.66-fold higher risk (95% CI: 1.09–2.54) compared with those who did not drink a similar beverage. Significantly higher association between coffee drinking and occurrence of EG/EGS was found in females with a positive history of glaucoma (P interaction=0.06 for coffee; P interaction=0.03 for caffeine). There was no significant association between intake of decaffeinated coffee or other caffeinated beverages such as caffeinated soda, tea or chocolate with the occurrence of EG/EGS.[91]

Li et al. conducted a systematic review and meta-analysis of six randomized controlled studies that measured IOP at 30, 60 and 90 minutes after consuming caffeine in 103 healthy individuals and 41 patients with glaucoma or ocular hypertension.[88] The investigators reported that caffeine had variable effects on IOP in healthy individuals, patients with ocular hypertension and patients with glaucoma. In healthy individuals, caffeine had no significant effect on IOP; however, there was a significant effect in patients 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], respectively). These findings suggest caffeine produces a potential IOP-mediated adverse effect in subjects susceptible to glaucomatous optic neuropathy.[88]

Jiwani et al. conducted the first and largest prospective, double-masked, crossover, randomized controlled trial comparing the effect of caffeinated versus decaffeinated coffee on IOP, OPP and ocular pulse amplitude at 60 and 90 minutes after ingestion. The authors reported statistically significant increased levels of IOP following caffeinated coffee consumption compared with decaffeinated coffee in the order of ~1 mmHg (p<0.0001); OPP by ~1.25–1.50 mmHg, and ocular pulse amplitude by ~0.2 mmHg. However, in the majority of patients the IOP elevations were modest, transient and unlikely to influence conversion or progression to glaucoma. A small minority of the subjects did have larger and potentially clinically significant elevations in IOP or decreased OPP after consuming caffeinated, but not decaffeinated coffee.[89]

Alcohol

The association between alcohol and glaucoma is controversial. Red wine is a source of flavonoids, and a meta-analysis has shown

that flavonoids play a promising role in improving visual function in patients with glaucoma and ocular hypertension.[92] Consumption of red wine is found to both improve and slow down the progression of visual-field loss.[92]

Ethanol intake acutely lowers IOP by 3–4 mmHg for approximately 1 hour.[93] Historically, alcohol was used as an osmotic agent in managing acute angle closure.[94] Acetaldehyde, which is a byproduct of ethanol, decreases blood-vessel resistance and increases blood flow in the optic nerve head, thus providing some protective effect.[95] A study from China to investigate the link between genetic and environmental factors with the risk of developing POAG, found that the risk of developing POAG decreased by more than 97% in regular drinkers.[96]

On the other hand, a large number of studies have found a positive correlation between alcohol consumption and the risk of developing glaucoma. Alcohol consumption was associated with significantly higher IOP in the Long Island Glaucoma Case-control Study.[97] Barbados Eye Study,[98] Framingham Eye Study[99] and in studies conducted across Japan[100] and China.[101]

Excessive alcohol drinking increases the risk of other diseases such as diabetes and obesity, which have potentially adverse associations with glaucoma. Alcohol use may be associated with other unhealthy lifestyle factors such as cigarette smoking or poor nutrition, which may also impact the physiological functions of the eye.[102–104]

While it has been shown that mild alcohol consumption has some health benefits, moderate use of alcohol increases the risk of liver disease.[105] Some practitioners are of the opinion that in view of the conflicting reports regarding alcohol use and its effect on glaucoma, it is risky to advise patients to consume alcohol.[106]

Trans-fatty acid

Trans-FAs are commonly known as trans-fats. These are unsaturated FAs produced from either natural or industrial sources. The natural sources of trans-fats are ruminants (cows and sheep), while synthetic trans-fats are produced by adding hydrogen to vegetable oil, converting the liquid into a solid, the 'partially hydrogenated' oil.[107]

PUFAs are fundamental molecules in our physiology. They are integral parts of cell membranes, precursors of prostaglandins, steroids and other molecules, and they also regulate gene expression.[108] FAs can be involved in the pathogenesis of glaucoma through the following mechanisms. FAs prevent RGC apoptosis by their anti-inflammatory effects and regulation of glial cells. Being components of cell membranes they play a key role in the rheology of red blood cells. Thus, an imbalance in FAs can cause decreased ocular blood flow and impair optic nerve perfusion. Being precursors of prostaglandins they affect IOP by regulating aqueous transport.[108]

The association of plasma levels and dietary intake of FAs to glaucoma have interested researchers for a long time. Gupta et al. used clofibrate (an antilipaemic agent) in experimental glaucoma to reduce serum lipoproteins. They reported lower IOP rise in rats with acute glaucoma when pretreated with clofibrate. The drug also lowered IOP when given after inducing acute experimental glaucoma.[109] A subanalysis of the Montrachet study was performed to compare plasma FAs among elderly POAG patients with normal controls and to investigate any specific patterns in the FA levels in glaucoma patients. The results showed no significant difference among the two groups on multivariable analysis (p=0.078). Univariate analysis revealed significantly lower level of eicosapentaenoic acid (p=0.032) among POAG participants. However, after adjusting for age, sex, axial length and lipid-lowering drug intakes, there was no significant association between eicosapentaenoic acid and POAG (p=0.058).[108]

Kang et al. analysed the hypothesis that dietary fat intake could modulate the availability of endogenous prostaglandins and the differences in their physiological concentrations could affect IOP. In this large, prospective study the authors did not find that intakes of specific types of fats (including trans-fats) could be independent risk factors in the development of POAG. However, the ratio of n-3 to n-6 fats was related to the development of POAG. A diet high in n-6 and low in n-3 PUFAs was associated with a lower prevalence of POAG.[110]

When a group of patients was put on 'fat-free' parenteral nutrition for 7 ± 1.2 weeks significant reduction in IOP was recorded in them. At the end of the study period, the mean IOP was lower by 3.53 ± 2.20 mmHg compared with the mean level measured when on fat supplemented diet (p=0.0001).[111]

Based on the above observations it seems controversial how exactly FAs affect glaucoma. It has been mentioned in literature that diets high in trans-FAs are detrimental to the health of the optic nerve. Suggestions for avoiding foods for patients with glaucoma include baked goods such as cookies, cakes and doughnuts or fried items such as French fries or stick margarine.[112]

Calcium and iron

Calcium plays a key role in the biochemical mechanisms which regulate the development of glaucoma. Increased influx of calcium ions (Ca++) into the RGCs leads to altered calcium homeostasis and can induce a cascade of metabolic reactions. Increased intracellular Ca++ causes increased generation of NO, which is released into the surrounding region causing further neuronal toxicity and death. Glutamate release and subsequent excitotoxicity is also dependent on intracellular calcium levels.[113] Glaucoma patients also demonstrate impaired calcium regulation and calcium overload in the trabecular meshwork and lamina cribrosa cells, pointing to further roles of calcium in glaucoma pathogenesis.[114]

Iron is a catalytic agent responsible for the creation of highly reactive hydroxyl radicals. These molecules cause oxidative damage to DNA, lipids and proteins. Increased expression of iron regulating genes and the effect of redox-active iron on trabecular meshwork cells also contributes to the development of glaucoma.[114]

A cross-sectional study involving 3833 participants of NHANES investigated the association of supplemental calcium and iron in the development of glaucoma.[114] The results of the study showed individuals consuming more than 800 mg of calcium per day or more than 18 mg of iron per day had significantly higher odds of developing glaucoma compared with those who did not take these supplements (OR: 2.44, 95% CI: 1.25– 4.76 for calcium; OR: 3.80, 95% CI: 1.79–8.06 for iron). Individuals who consumed calcium and iron concurrently had even greater odds of being diagnosed with glaucoma (OR 7.24, 95% CI 2.42–21.62). The investigators did not find a definite dose–response relationship between the quintiles of supplementary calcium or iron usage and glaucoma diagnosis. However, there appeared to be a

threshold level of oxidant consumption beyond which a substantially higher risk of glaucoma was seen.[114]

The same investigators cited above have reported that the adjusted odds of developing glaucoma increased with higher total consumption of calcium (p trend <0.0001) and iron (p trend <0.0001). However, when dietary, instead of supplemental calcium and iron were increased, there was a tendency for decreasing odds of developing glaucoma (calcium p-trend=0.0008; iron p-trend=0.0022). The increasing trend towards development of glaucoma with higher intake of total iron and calcium is attributed to the cellular damage induced by these oxidants.[115]

Conclusion

Glaucoma is a multifactorial disease with a complex interplay of IOP- and non-IOP-dependent factors that determine the course of the disease. Diets modify many systemic diseases, but what role dietary modification can play in managing glaucoma remains to be assessed on a broader scale. Based on our current understanding of the pathogenesis of glaucoma, as well as few clinical and animal studies, dietary modification could prove to be a viable therapeutic strategy. It appears worthwhile to recommend some diets and to avoid others to protect further damage to RGCs and the optic nerve in patients with glaucoma. ❑

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