Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/survophthal

Survey of Ophthalmology

Review article

Nutritional supplementation in the prevention and treatment of glaucoma

Sarah Chaudhry, BSc, MBBS[a,*], *Hamish Dunn, BLib Stud, MBBS(hons), FRANZCO*[a,b,d,e], *Nicole Carnt, BOptom (Hons) PhD, GradCertOcTher, FAAO, FBCLA*[a,c,d], *Andrew White, BMedSci(hons), MBBS, PhD, FRANZCO*[a,b,c,d,e]

[a] *Westmead Hospital, Westmead, Sydney, New South Wales, Australia*
[b] *Westmead and Central Clinical Schools, Discipline of Clinical Ophthalmology and Eye Health, The University of Sydney, Sydney, New South Wales, Australia*
[c] *Westmead Institute of Medical Research, Westmead, New South Wales, Australia*
[d] *The University of New South Wales, Sydney, New South Wales, Australia*
[e] *Save Sight Institute, Sydney Medical School, University of Sydney, New South Wales, Australia*

ARTICLE INFO

Article history:
Received 1 July 2021
Revised 4 December 2021
Accepted 6 December 2021
Available online 8 December 2021

Keywords:
Vitamins
Nutrients
Glaucoma
Supplements
Reactive Oxygen Species
Open Angle Glaucoma
Trabecular Meshwork
Retinal Ganglion Cells
Oxidative Stress

ABSTRACT

Glaucoma is a chronic optic neuropathy that creates a significant burden on public health. Oxidative stress is hypothesized to play a role to glaucoma progression, and its reduction is being analyzed as a therapeutic target. Dietary antioxidants play a crucial role in helping provide insight into this hypothesis. We reviewed 71 trials, interventional, *in-vivo* and *Iin vitro*, including 11 randomized controlled trials, to determine if adjunctive nutritional supplementation could lead to a reduction in oxidative stress and prevent glaucomatous progression. Many laboratory findings show that vitamins and natural compounds contain an abundance of intrinsic antioxidative, neuroprotective and vasoprotective properties that show promise in the treatment and prevention of glaucoma. Although there is encouraging early evidence, most clinical findings are inconclusive. The group of B vitamins appear to have the greatest amount of evidence. Other compounds such as flavonoids, carotenoids, curcumin, saffron, CoQ10, gingko biloba, and resveratrol however warrant further investigation in glaucoma patients. Studies of these antioxidants and other nutrients could create adjunctive or alternative preventative and treatment modalities for glaucoma to those currently available.

Abbreviations: POAG, Primary open angle Glaucoma; PEXG, Exfoliation Glaucoma; NTG, Normal Tension Glaucoma; IOP, Intraocular pressure; GON, Glaucomatous Optic Neuropathy; RGC, Retinal Ganglion Cells; PVD, Primary vascular dysregulation; TM, Trabecular Meshwork; SC, Schlemm's Canal; ROS, Reactive Oxygen Species; NO, Nitric Oxide; AA, Ascorbic acid; CoQ10, Coenzyme Q10; NOS, Nitric Oxide Synthase; Hcy, Homocysteine; ARMD, Age Related Macular Degeneration.

* Corresponding author: Sarah Chaudhry, BSc, MBBS, Department of Ophthalmology, Bankstown-Lidcombe Hospital, Corner Eldridge Road, Bankstown NSW, 2200 Australia.
E-mail address: sarah.ghaffar90@gmail.com (S. Chaudhry).

0039-6257/$ – see front matter
https://doi.org/10.1016/j.survophthal.2021.12.001

1. Introduction

Glaucoma is one of the most prevalent causes of irreversible blindness worldwide and evolves through a range of contributing factors.[5,109] It is often classified as primary or secondary glaucoma and provides an umbrella for a multitude of disease processes that result in optic neuropathy. Primary open-angle glaucoma (POAG), the most common type, is one such progressive optic neuropathy associated with both higher intraocular pressures or normal to low pressure levels.[124] Primary angle closure follows closely and in certain demographics is equally common.[122,151] Secondary glaucoma arises from various precipitating factors that range from pigment dispersion, pseudoexfoliation, post phacoemulsification, as well as trauma and tumors.

Ischemic and oxidative damage to the optic nerve head (ONH) has been hypothesized to damage to the retinal ganglion cells (RGC), which are characteristically affected in glaucomatous patients.[61,69,108,131,140,147] Although the current mainstay of treatment in glaucoma revolves around reducing raised intraocular pressure (IOP), antioxidative diets are an alternative avenue that could provide a minimally invasive effect in the progression of this disease. Studies such as the Nurses' Health Study highlighted the role of diet in relation to glaucoma prevention showing how increased nitrate and green vegetable were correlated intake slowed progression of POAG in patients.[54] These studies have helped facilitate many other similar projects.[54] We provide an updated review of the research defining the properties in various vitamins and nutrients and how these properties can influence ocular pathology with respect to glaucoma and will also review the current literature translating these properties to practical applications in glaucoma prevention and treatment.

2. Glaucoma risk factors and pathogenesis

Regardless of the classification of glaucoma, all patients exhibit optic nerve head changes such as retinal nerve fibre layer (RNFL) thinning and neuroretinal rim loss, that progress to visual field deficits. Although there is no consensus on the exact pathophysiology of glaucoma, the favored clinical dogma centers on IOP changes contributing to RGC death and damage to posterior structures such as the lamina cribosa, the range of risk factors associated with glaucoma is consistently growing.[66,67,102] Studies such as the Ocular Hypertension Treatment Study highlighted that elevated IOP is only associated with glaucomatous optic neuropathy in approximately 2% of patients per year with untreated ocular hypertension IOP >21 mmHg.[55]

Integrity of the trabecular meshwork (TM) and Schlemm canal (SC), the primary structures that facilitate aqueous humor drainage,[2] has been shown to be increasingly important in glaucoma. Increases in IOP, trauma, high cholesterol, oxidative damage, and advancing age have been hypothesized to contribute to outflow restriction by causing changes to the structure and integrity of these drainage tissues.[2,65-67] Structural changes within the TM include accumulation of fibrillar elements such as fibronectin and transglutaminase (TGM2), tissue stiffness, and cell loss.[2]

In patients with normal-tension glaucoma (NTG)–which accounts for 40% of Caucasian and up to 90% of Asian cases of glaucoma–the pathophysiology is considered to be multifactorial.[7,56] In these patients impaired ocular blood flow to the optic nerve head from both primary and secondary causes is thought to contribute to primary vascular dysregulation and subsequent damage.[21,83,90]

RGC's are rich in mitochondria and enable high levels of energy production required for nerve conduction.[50] Reactive oxygen species (ROS) are compounds that cause oxidative damage. Mitochondria in particular create the greatest amount of ROS as a byproduct in the electron transport chain in aerobic metabolism. This predominantly occurs through complex I and II of the oxidative phosphorylation processes.[9] As well as enabling energy metabolism, mitochondria are essential for regulating cell death, a process heavily dependent on ROS. Simultaneously an accumulation of calcium, free iron (thereby hydroxyl), and hydrogen peroxide free radical substrates damage cellular components and further increase ROS levels.[20,91] It is this increase in ROS that has been hypothesized to contribute to RGC loss and eventual RNFL and visual field changes noted in glaucoma.

Although the presence of ROS in the body is essential for normal physiological functioning, dysregulation of the normal ROS equilibrium in ocular mitochondria has been linked to DNA mutation, aging, and cell death.[9] The tipping of this fine balance in glaucoma could result in damage to ocular structures such as the RGCs. It has also been noted that reduced oxygen supply can induce a level of reperfusion injury, often in correlation with higher levels of endothelin-1 (ET-1), an important vasoconstrictive metabolite within the ocular tissues.[33,38] Glutamate excitotoxicity, disruption of axonal transport chains and activation of astrocytes have also been found to contribute to apoptotic processes.[61,95,135,139] This is in turn is hypothesized to increase production of ROS, which could damage crucial structures such as the optic nerve head, a pathophysiological process associated with vascular dysregulation and NTG.[84,90]

Identifying elements that can influence the aforementioned mechanisms of injury might create new avenues for developing treatments for glaucoma that address the multifactorial nature of the disease. The current mainstay of pharmacological glaucoma treatments revolves around lowering IOP, and although this is a significant modifiable risk factor, it does not encompass the entire pathogenesis of glaucoma.[24] Antioxidants work by neutralizing the damage caused by their oxidative counterparts through the donation of electrons (25). Given the potential hypotheses linking oxidative damage to RGC death, it is important to investigate this potential treatment modality.[77] The list of natural compounds that contain intrinsic sources of antioxidants is extensive, and therefore it is logical to investigate the effects of these compounds in glaucoma patients. Other nutritional compounds are thought to also provide various neuroprotective benefits that prevent inflammation, mitochondrial dysfunction, and vascular dysregulation in RGCs and retinal axons could be used as adjunctive treatments.[15,32,48,96,125,128,142] We shall examine the current literature on nutrient properties associated with im-

proved outcomes in ocular pathologies and to determine if there are any clinical correlations between human usage of nutritional compounds and glaucoma prevention and treatment.

3. Preclinical nutrient literature

3.1. *Vitamin B3*

Nicotinamide (NAM) is a specific amide form of vitamin B3 that is a nontoxic precursor to NAD+, a substrate in complex 1 of the electron transport chain responsible for ATP generation. This substrate has been associated with a reduction of oxidative damage secondary to protein oxidation and lipid peroxidation. It has also been found to contribute to axon neuroprotection and preventing neurodegenerative diseases.[80,126] The presence of NAD+ appears to decrease with age and has been linked specifically to RCG death.[126] Nicotinamide reduces the ischaemic and phototoxic injuries that occur in RGC's in rats, particularly those reperfusion injuries associated with poly-ADP-ribose polymerase (PARP) activation, a notable apoptotic mediator.[50,121]

In vivo NAM trials in mice have also shown protection of the retinal ganglion cells, giving preclinical support to trial nicotinamide supplements for glaucoma patients (32). In addition to PARP inhibition, the neuroprotective effects of nicotinamide have also been associated with its ability to stabilize blood flow, inhibit lipid peroxidation, and improve endothelial function.[40,50,144] Studies on DBA/2 mouse models illustrate that nicotinamide supplementation (orally and through gene therapy) inhibits mitochondrial dysfunction in mouse retinas, and even prevents RGC loss and optic nerve degeneration in 93% of mice.[143] Another *in vivo* study published by Ji and coworkers reinforced the positive effects of intravitreal nicotinamide in rats, showing that the vitamin attenuated the ischemic/reperfusion injuries caused by induced elevated IOP.[50]

3.2. *Vitamin B12, B6, and B1*

Metabolism of methionine to homocysteine (Hcy) and then to cysteine occurs via a pathway dependent on vitamins B12 and B6.[25] Hcy is the toxic molecule in this pathway, and elevated levels have been hypothesized to contribute to retinal vascular diseases such as vascular occlusion or optic neuropathies such as POAG and pseudoexfoliation glaucoma (PEXG).[6,12,110] Numerous studies have tested the presence of serum vitamin B12 and B6 in patients with NTG, POAG, and PEXG.[25,104,133,145] One prospective cohort study of 140 patients with PEXG demonstrated significantly lower levels of both serum B12 and B6 and elevated levels of Hcy when compared to controls.[115] Similarly, a prospective controlled trial of 120 patients by Turgut and coworkers reported increased serum levels of Hcy in PEXG when compared to controls.[133] Protective effects of B12 on neurons may prevent optic atrophy and visual field changes.[43,118] Although clinical evidence is limited, one small prospective study analyzed oral B12 supplementation in NTG glaucoma patients, and showed that patients did not experience a significant reduction in their visual fields at a 4 year follow up.[43,150]

Vitamin B1 or thiamine deficiency has been associated various neurodegenerative changes to microglia, astrocytes, endothelial cells and mast cells, all resulting in neuronal cell death.[84] The Rotterdam Study analyzed a prospective population of 3502 patients and noted that patients with lower serum thiamine were more likely to progress to developing POAG[110]; however, there are no other clinical trials to support this.

3.3. *Vitamin C*

Vitamin C, composed of the substrate ascorbic acid, is predominantly found in citrus or red peppers and is known for its non-enzymatic antioxidant effects.[14] Studies *in vitro* have shown that ascorbate acts as a potent osmotic agent and synthesizes a less viscous hyaluronic acid in the trabecular meshwork.[43] There is evidence supporting ascorbic acid in the reduction of IOP, prevention of retinal damage, and slowing cataract development and maculopathies.[1,15,19,129] An *in vitro* study by Xu and coworkers noted that reduced ascorbic acid levels in aqueous humor compromised lysosomal degradation of the outflow cells.[148] *In vivo* animal trials suggest that ascorbic acid reduced the loss of rhodopsin and photoreceptor cell nuclei, protecting the retina.[94] Small prospective human studies with samples of 18 and 40 patients highlighted that patients with exfoliation syndrome, a precursor to secondary glaucoma, had significantly lower levels of ascorbic acid within their aqueous humour.[59,63]

Nitric oxide (NO) is a molecule that works to increase blood flow, induce vasodilation, and reduce vascular resistance in the ocular circulation when released from the endothelium. Lower quantities of NO can reduce IOP by decreasing resistance in the outflow pathway through the trabecular meshwork.[16] At least one randomized control trial (RCT) of 24 patients and another trial have established the effectivity of NO donating prostanoid receptor agonist (latanoprostene bunod) in reducing IOP.[8,141] Recent studies have harnessed these properties of NO to create potential treatment modalities in the ongoing management of these patients.[5,16] Vitamin C has long been known to increase nitric oxide synthase activity (NOS), and it is possible that this stimulation of NOS decreases the resistance through the TM outflow tract resulting in positive impacts on glaucoma progression.[27,59,63,117]

3.4. *Vitamin E*

Vitamin E is a strong antioxidant, and one of its 8 active substrate's alpha-tocopherol has been associated with improving ocular pathology.[88,112] Current reviews on the tocopherol components have recognized the antioxidant effect vitamin E exhibits as a combined group of tocopherols in comparison to an isolated substrate.[46] Tocopherols additionally act to protect cell membranes of photoreceptor cells, inhibit fibroblast proliferation, prolong endothelial cell survival time in rabbits and serve as neuroprotective agents and vasoregulators.[29,30,112,114] A more recent cross sectional *in vitro* study used tissue culture reagents of vitamin E to examine its effects directly on trabecular meshwork mitochondria.[42] It showed that vitamin E reduced the levels of ROS in the TM cells of glaucomatous patients, a finding mirrored by other studies.[20,42,103]

Increased alpha tocopherol in ocular smooth muscles *in vitro* has also been shown to exhibit anti-proliferative effects through the inhibition of protein kinase c (PKC).[30] Retinal vascular dysfunction secondary to hyperglycemia is also modulated through the inhibitory effect of alpha-tocopherol on this diachylglycerol-PKC pathway.[29] Similarly another animal study illustrated a greater RGC death rates in rats supplemented with oral vitamin E against controls.[58] This preclinical data makes illustrates the inconclusive nature of the benefits of vitamin E in glaucomatous pathology.

3.5. *Vitamin A*

Vitamin A, sourced mostly from vegetables, is comprised of compounds such as carotenoids and retinol.[87] A small prospective study of eight animals from 2003 shows that carotenoids can create an intraocular antioxidant effect.[89] Similarly, a cross sectional study of 379 patients analyzed levels of serum carotenoids and vitamin C and noted an inverse relationship to the levels of serum CRP and leukocytes indicating another link between antioxidants in reduced inflammation.[134] Contrarily, there is also some *in vitro* research that has shown that the retinol component increases fibroblast growth, causing poor outflow filtration in turn increasing IOP.[57]

4. Other compounds

4.1. *Flavonoids*

Flavonoids are naturally occurring polyphenols that are harnessed for their neuroprotective and antioxidative properties.[101] Their main effects are exerted at the mitochondrial level, encouraging increased levels of ocular blood flow in rabbit retinas.[82,100] Interestingly, a randomized study on 30 glaucoma patients illustrated the venous vasodilatory effects on control patients after dark chocolate consumption, but not on glaucoma patients, which they hypothesize to be secondary to the underlying endothelial function in this group.[130] An *in vitro* study by Nakayama and coworkers examined the effects of flavonoids on RGC survival after exposure to oxidative and hypoxic damage.[86] Flavonoids appeared to exhibit neuroprotective effects in cells exposed to them by extending RGC survival rates despite stress exposure.[77,86]

Gingko biloba contains multiple flavonoid compounds which have been investigated in their association to glaucoma. Early literature shows that extracts from the fruit exhibit potent antioxidant as well as neuroprotective and vasoprotective effects successful in treating cognitive impairment, hypoxia, and other vascular diseases.[43] Currently there is literature suggesting gingko biloba can increase central and peripheral blood flow, reduce vasospasms and inhibit apoptosis.[26,90,111] Some studies have also illustrated an overall neuroprotectant effect of gingko biloba in rat models.[44] A study by Park and coworkers also showed that gingko biloba improved the peripapillary blood flow in patients with NTG.[99]

4.2. *Ubiquinone/Coenzyme Q10*

Ubiquinone or coenzyme Q10 (CoQ10) has been established as a specific mitochondrial targeting antioxidant that exhibits neuroprotective properties demonstrated by preventing lipid peroxidation and DNA damage through gene expression modulation.[23,84,116] Specifically, CoQ10 augments complex I in the electron transport chain, inhibits the action of the inflammatory transcription factor NF-kB, and also prevents the opening of the mitochondrial transition pore.[17] It's been shown that by inhibiting oxidative stress coenzyme Q10 can improve bioenergetic function at the optic nerve head in rat astrocytes.[116]

Neuroprotection through CoQ10 is now being acknowledged in the multifaceted treatment of glaucoma and is undergoing clinical trials to assess its practicality.[17,68] An *in vivo* study by Nucci and coworkers, showed that intraocular administration of CoQ10 reduces synaptic glutamate, a precursor to oxidative stress, and delays the apoptosis of RGC after ischemic/reperfusion injuries.[92] It has been noted that retinal CoQ10 levels decrease by up to 40% with age, which may be relevant for the treatment of ocular pathology.[106] Early research in mice shows that topical application of CoQ10 can improve levels of ocular hypertension. In a recent prospective clinical study of 43 patients with OAG, combination CoQ10 and vitamin E eye drop administration elicited benefits in retinal function.[97]

4.3. *Lutein, zeaxanthin, resveratrol and magnesium*

Lutein and zeaxanthin are from the family of carotenoids, and are often found in high concentrations in the macular lutea.[113] There appears to be a direct relationship between the level of lutein and zeaxanthin and levels of macular pigment, and their notable properties include their function as antioxidants and filters for high energy light wavelengths at the macula.[113] The Age-related Eye Disease Studies (AREDS) illustrated the relationship between these carotenoids and their anatomic distribution with resulting positive impact on disease processes in age-related macular degeneration (AMD).[62] A small experimental prospective animal study (n = 8) has shown a reduction in retinal ganglion cell loss in retinas supplemented with lutein and zeaxanthin indicating a potential role in glaucoma treatment.[89] Another *in vivo* study has demonstrated the neuroprotective effects of lutein. By examining rat retinal cells they found that lutein protects against inner retinal reperfusion/ischemic injury and creates anti-apoptotic effects through its antioxidative properties.[70]

In preclinical data, resveratrol has neuroprotective effects such as neurogenic stimulation, and inhibiting neuroinflammation.[116] *In vivo* studies have shown that resveratrol protects rat RGC's against retinal ischemia/reperfusion injuries induced secondary to increased intraocular pressures.[75] There is also evidence that resveratrol is responsible for inhibiting the formation of endothelin-1, which in turn creates vasoprotective effects.[84]

Magnesium (Mg) is an intracellular cation used in various enzymatic reactions, including inhibition of glutamate release and serving as a non-competitive antagonist for NMDA receptor activators.[28] Magnesium has been known for its neuroprotective effects and its deficiency has shown necrosis of the retinal pigment epithelium in rats.[28] In these animal studies, Mg appears to improve endothelial function, and ocular blood flow, and protect RGCs through the inhibition of glutatmate release, and endothelin 1 (ET-1).[28]

5. Saffron and curcumin (tumeric)

Saffron is another alternative compound composed of crocin and crocetin carotenoid derivatives, both of which are powerful radical scavenging compounds as well as proangiogenic and antiapoptotic.[11,49] A study by Maccarone and coworkers has also illustrated that dietary saffron supplementation *in-vivo* protects rat photoreceptors against photooxidative damage.[76] Animal studies *in vivo* have established the ability of crocin to improve retinal and choroidal blood flow, and other studies have shown its effects in preventing RGC apoptosis through the P13K/AKT pathway.[105,149]

The active compound in curcumin exhibits ketoenoltautomerism, an antioxidant property that serves as a neuroprotective agent in animal models *in vivo*.[152] A 2014 *in vivo* study showed that curcumin is also associated with neuroprotection of retinal ganglion cells despite high intraocular pressures.[152] Curcumin has also been shown to prevent mitochondrial dysfunction by maintaining levels of mitofusin 2 (mfn2) proteins and increasing levels of nuclear factor erythroid 2 related protein (Nrf2).[74] Mfn2 has been shown to be reduced in raised intraocular pressures and reperfusion injury. Nrf2 has been shown to increase as it exhibits a protective effect in oxidative stress.[137,152] These protective effects in ocular pathology have been shown in mouse models, but not in ophthalmic human trials.

Deficiencies in zinc have also been linked to a greater level of oxidative stress and with low levels predisposing an increased risk of glaucoma.[4,78] Although prominent research papers highlight the benefits of zinc given as a combination treatment of patients with ocular pathologies such as AMD, to our knowledge there is little research on glaucoma and zinc.[3,37,78] It appears that a homeostasis must be achieved as too much zinc contributes to neuronal death.[4,71] A recent *in vitro* study examined the effects of zinc chelation on the retinal ganglion cells and the optic nerve after intravitreal injections into mice. Researchers imply that by facilitating the chelation of zinc released post oxidative stress through intravitreal injections they can stimulate the regeneration of RGCs and axons.[71]

6. Clinical applicability for nutrients in glaucoma

We assessed 43 human studies that highlighted how properties of complementary nutrients and vitamins have the potential to impact the treatment and progression of glaucoma.[35,138]. This has been highlighted in Table 1. Firstly, there are a number of research papers that have assessed the link between deficiencies in various nutritional components and risk of developing glaucomatous diseases. One cross sectional study of 662 patients in the USA assessed general dietary intake and correlated this to their incidence of developing glaucoma. Interestingly, patients with higher intakes of foods rich in Vitamin A, C, and carotenoids had a reduced incidence of developing glaucoma.[34,35] This finding is at odds with another cross sectional study of 2912 patients from the National Health and Nutritional Survey that showed that there was no correlation between glaucoma prevalence and serum vitamin A, C, and E levels.[138]

A large Korean survey of 16,770 people showed that increased consumption of niacin (B3) and riboflavin (B2) were directly linked to lower risks of glaucoma[51] Similarly, a prospective study of 34 POAG patients revealed lower serum nicotinamide levels in patients with POAG over controls.[60] One prospective cross sectional study of 345 patients noted lower serum retinol levels in patients with NTG and POAG as compared to controls.[97] A recent paper by Li and coworkers revealed that aqueous humor zinc levels in 72 glaucoma patients was greater than in 66 control patients.[72] Similarly, a prospective trial of 33 patients suggests that higher zinc levels are seen in patients with glaucomatous disease when compared to control groups.[45] A case control study of approximately 226 patients in New Zealand explored the correlation between oral dietary intake and glaucoma risk. Increased intake of fruits, vegetables and diets rich in vitamin C and beta-carotene was associated with a reduced risk of developing oxidative stress related diseases, including glaucoma. Similarly higher intakes of meats and nuts were proportionally harmful.[13]

Using data from the Nurses' Health Study and the Health Professionals follow up study, one paper analyzed the dietary intake of 474 glaucoma patients and found a notable inverse relationship between the intake of lutein and zeaxanthin and POAG risk over a 4 year period.[53] Another paper sampled 399 cases from the Nurses' Health Study population and found that greater folate intake was associated with a reduced risk of developing exfoliation glaucoma.[52] Elevated Serum Hcy levels have also been associated with increased risks of POAG, a correlation hypothesized to be associated with the increased risk of RGC death, and oxidative stress reactions seen with Hcy.[12,25,115,133,146]

A larger cross-sectional study conducted by Giaconi and coworkers examined the effect of dietary intake in 584 African American women over 65 and found that dietary intakes of fruits and vegetables, particularly those higher in levels of vitamin A and C, exhibited a statistically significant lower risk of developing glaucoma.[35] After analysis of optic discs and visual fields over a year, they noticed a lower odds ratio incidence of developing glaucoma if greater levels of fruit and vegetables (>2 servings) were incorporated into the diet. The demographic of these women also fell into standard representations with regards to co-morbidities such as diabetes and hypertension. This paper also compared this evidence to another study of theirs that looked at a predominantly Caucasian population of women from a similar sample and highlighted similar findings in reference to vitamin B2 and vitamin A.[22] They thought that differences in the findings with reference to specific vitamin intakes not correlating to changes in glaucoma risk between the two groups could be attributed to the differences in food preparation, metabolism, and hormones or genes. The important conclusion this study draws attention to is the multifaceted considerations involved in tackling this pathology and the complexity in creating treatments for individuals.

A recently published Australian article referenced a retrospective sample of 1483 subjects within the Nurses' Health Study that found that a diet rich in nitrates and green leafy

Table 1 – Vitamins and Nutrients: evidence for effects.

Class of Studies	Reference	Year and Location	Vitamin/Nutrient Examined	Type of study	Sample size	Treatment duration	Outcome Measures	Key Findings
Animal	Neacşu et al	2003, Romania	Lutein and Zeaxanthin	Experimental animal prospective study	8	3 months	Lutein/zeaxanthin serum levels correlated with RGC loss and	Lutein and zeaxanthin additions to guinea pig diet reduced the retinal ganglion cell loss.
Animal	Ji et al	2007, UK	Nicotinamide	Experimental prospective study	N/A	5 days	ERG function post ischemia and post nicotinamide	Nicotinamide significantly blunted effects of ischemia/reperfusion injury in rat retina.
Animal	Williams et al	2018, USA	Nicotinamide	Experimental prospective animal study	N/A	Not mentioned	Rates of glaucoma in DBA/2J mice administered nicotinamide orally	Mice given nicotinamide had less likelihood of developing glaucoma.
Animal	Organisciak et al	1990, USA	Ascorbic acid.	Experimental prospective animal study	N/A	Two weeks	Rhodopsin, retinal light damage and retinal DNA levels after ascorbate oral supplementation.	Ascorbic acid protects photoreceptors and RPE against oxidative damage.
Animal	Ko et al	2009, Taiwan	Vitamin E	Experimental prospective study	N/A	Five weeks	RGC death rates in rats after oral supplementation with vitamin E versus controls	Rats with vitamin E deficient diets had increased levels of RGC death compared to controls.
Animal	Robison et al	1979, USA	Vitamin E	Experimental prospective study	N/A	8 months	Retinal photoreceptor changes after supplementation with vitamin E	Vitamin E protect photoreceptor membrane from oxidative damage.
Animal	Kawai et al	2002, USA	Nitric Oxide Synthase	Experimental prospective study	N/A	7 months	Retinal ganglion cell loss after supplementation with oral nitric oxide synthase.	Nitric oxide synthase supplementation prevented RGC loss in eyes with elevated IOP although it didn't effect intraocular pressure.
Animal	Mills et al	2016, USA	Nicotinamide	Experimental prospective animal study	N/A	12 months	Oral administered Nicotinomide mononucleotide in mice effects on energy metabolism, insulin sensitivity, eye function, and lipid profile.	Nicotinomide mononucleotide minimises age associated physiological decline. Improves insulin sensitivity, plasma lipid profile, and increases physical activity and energy metabolism.
Animal	Park et al	2004, Korea	Flavonoids	Experimental prospective animal study	N/A	N/A	Determine ocular blood flow in rabbit eyes after flavonoid addition	Flavonoids increased ocular blood flow
Animal	Liu et al	2013, China	Resveratrol	Experimental Prospective study	N/A	60 mins	ERG and real time PCR findings after resveratrol administration in rats	Resveratrol can reduce oxidative damage after retinal ischaemic insult.
Animal	Xuan et al	1999, USA	Crocin	Experimental animal study	N/A	120 mins	ERG assess retinal function after retinal ischaemia in rats given oral Crocin	Crocin analogues increase retinal blood flow in rat retina and could be used to treat ischaemic retinopathy and or ARMD.

(*continued on next page*)

Table 1 (*continued*)

Class of Studies	Reference	Year and Location	Vitamin/Nutrient Examined	Type of study	Sample size	Treatment duration	Outcome Measures	Key Findings
Animal	Qi et al	2013, China	Crocin	Experimental prospective animal study	N/A	24 hours	Effect on RGC loss and retinal injury after intravitreal crocin injection.	PI3KT/AKT pathway activated by crocin in ganglion cell layer after retinal injury. Crocin prevents retinal ischaemic/reperfusion apoptosis of RGCs by activating PI3k/AKT pathway.
Animal Cell Based	Li et al	2017, USA	Zinc	Cell culture study	N/A	60mins	Assess RGC survival rates after intravitreal zinc chelator	Intravitreal injections with zinc chelators allow prolonged RGC lifespan.
Cell Based	Wang et al	2011, China	Curcumin	Experimental cell culture study	N/A	60mins	Assess inhibition in neuronal ischemia reperfusion injury after curcumin administered orally	Dietary Curcumin inhibited degeneration of retinal neurons and capillaries and apoptotic cell death in ganglion cell layer.
Cell Based	Hirooka et al	2004, Japan	Ginkgo Biloba	Experimental cell culture study	N/A	5 months	RGC loss in eyes treated with ginkgo biloba oral supplementation against controls	Ginkgo Biloba supplementation serves as a neuroprotective agent in RGCs of rats.
Cell Based	Nucci et al	2007, Italy	CoEnzyme Q10	Experimental primary cell culture	N/A	24 hours	Intraocular administration of CoQ10 effects on retinal ischaemia/reperfusion injury.	CoQ10 facilitates neuroprotection, delays apoptosis, and prevents oxidative mechanisms that contribute to RGC death.
Cell Based	Maccarone et al	2008, Italy	Saffron	Experimental Cell culture	N/A	1 week	Assess retinal protein levels, fibroblast growth factors and photoreceptor analysis after oral saffron in rats	Saffron protects photoreceptors from retinal stress.
Cell Based	Yue et al	2014, China	Curcumin	Experimental Cell culture	N/A	6 weeks	RGC loss quantification after intragastric administration of curcumin	Cell viability of RGC increases and apoptosis decreases after curcumin administration intragastric.
Cell Based	Xu et al	2014, USA	Ascorbic Acid	Primary cell culture study	N/A	10 days	Monitor cell viability after ascorbic acid supplementation in porcine trabecular meshwork cells	Reduced ascorbic acid in plasma and aqueous humour compromises outflow pathway and lysosomal degradation.
Cell Based	Nakayama et al	2011, Japan	Flavonoids	Primary cell culture study	N/A	3 hours	Assess RGC survival rates after administration of hree flavonoids in hypoxic stress	Flavonoids increase RGC survival rate in hypoxic conditions and enhance neuroprotective activity.
Cell Based	Suk-Yee Li et al	2010, Hong Kong	Lutein	Primary cell culture study	N/A	N/A	Lutein effect on retinal ischemia and oxidative stress in retinal rat cells	Higher levels of RGC cells were present in cells supplemented with lutein.
Cell Based	Kamat et al	1999, India	Nicotinamide, ascorbic acid, alpha tocopherol.	Primary Cell culture Study	N/A	30mins	Assess oxidative changes in rat brain mitochondria after exposure to nicotinamide, ascorbate and alpha tocopherol	Nicotinamide inhibits oxidative damage, protects against protein oxidation and lipid peroxidation in rat brain mitochondria.

(*continued on next page*)

Table 1 (*continued*)

Class of Studies	Reference	Year and Location	Vitamin/Nutrient Examined	Type of study	Sample size	Treatment duration	Outcome Measures	Key Findings
Cell Based	Williams et al	2017, USA	Nicotinamide	Primary Cell culture Study	N/A	12 months	Assess glaucomatous neurodegeneration after oral nicotinamide administration. Assess retinal Nicotinamide expressed from the WLD^S gene.	Nicotinamide prevents axonal degeneration, prevents mitochondrial changes, and reduces synaptic degeneration WLD^S increases Retinal Nicotinamide levels also.
Cell Based	Song et al	2005, USA	Statins	Primary Cell culture Study	N/A	24 hours	Cellular changes in porcine trabecular meshwork and ciliary body	Lovastatin and compactin induce cellular and tissue relation and create ocular hypotension in Porcine trabecular meshwork and ciliary body after 24 hrs
Cell Based	Maher et al	2005, USA	Flavonoids	Primary cell culture study	N/A	7 days	Assess effect of flavonoids on retinal ganglion cell death rates	Flavonoids protected RGC death despite exposure to oxidative stress.
Human Study	Mutolo et al	2015, Italy	Forskolin, Homotaurine, Carnosine, Folic Acid	Randomised case-control prospective study	22	12 months	Assess PERG changes, foveal sensitivity and IOP changes in POAG patients after oral supplementation	Patients given supplementation showed improved PERG amplitudes, foveal sensitivity and reduced IOP in POAG patients compared to controls.
Human Study	Goldblum et al	2009, Switzer-land	Tocopherol	Double Blind RCT	39	2 months	Assess effect of oral tocopherol supplementation on IOP in patients post phaco-trabeculectomy	Success rates and IOP reduction were comparable between the two groups. No significant difference was found.
Human Study	Kang et al	2014, USA	Folate, B6, Vitamin B12	Prospective Cohort study	399	30 years	Assess Exfoliation glaucoma incidence in patients with various levels of oral folate, B12, and B6 consumption	Higher folate levels were associated with a lower risk of exfoliation glaucoma and vitamin B6 and B12 intakes were not associated with exfolation glaucoma.
Human Study	Li et al	2020, China	Zinc	Prospective Case-Control Study	138	N/A	Assess aqueous humor levels of zinc in glaucoma patients versus age-matched controls	Patients with glaucoma had 3.75-fold greater numbers of aqueous humor zinc compared to controls.
Human Study	Kang et al	2003, USA	Dietary alpha carotene, beta cryptoxanthin, lutein/zeaxanthin, vitamin C, E, A.	Cohort study	474	40 years	Assess risk of POAG in context of dietary consumption of various antioxidants	No significant associations between antioxidant consumption and the risk of POAG.
Human Study	Jabbarpoor et al	2014, Iran	Saffron	Prospective Comparative Randomized Interventional Study	34	4 weeks	Assess IOP in POAG patients after oral aqueous saffron administration versus placebo.	Oral saffron extract creates an antihypertensive effect in patients with POAG.
Human Study	Stark et al	1985, Germany	Vitamin A+ E	Prospective cohort study	114	5 months	Assessment of visual field changes after supplementation of vitamin A+E	Reduction of visual field changes in patients with POAG after oral supplementation with Vitamin A+E.
Human Study	Jung et al	2018, Korea	Niacin	Population cross sectional survey	16 770	N/A	Assessment of dietary niacin intake in relation of POAG diagnosis	Lower intake of foods with niacin was linked to a greater risk of developing POAG and NTG in patients.

(*continued on next page*)

Table 1 (*continued*)

Class of Studies	Reference	Year and Location	Vitamin/Nutrient Examined	Type of study	Sample size	Treatment duration	Outcome Measures	Key Findings
Human Study	Kouassi et al	2019, France	Nicotinamide	Semiquantitative case-control prospective study	64	N/A	Plasma levels of nicotinamide were measured between controls and patients with diagnosed POAG	Plasma nicotinamide was significantly lower in POAG patients compared to control.
Human Study	Braakhuis et al	2017, New Zealand	Dietary antioxidants	Case-Control study	226	18 months	Association between intakes of nutrients and risk of developing glaucoma	High intake of fruits and vegetables reduces risk of glaucoma. Higher intakes of meats and nuts increases risk of oxidative stress related eye diseases.
Human Study	Wang et al	2012, USA	Calcium and Iron	Cross Sectional Study	3833	2 years	Incidence of being diagnosed with glaucoma after Calcium and iron oral supplementation.	In higher doses Calcium and iron intake may increase risk of glaucoma.
Human Study	Park et al	2011, Korea	Ginkgo Biloba	Prospective Case-Control study	30	4 Weeks	Assess otpic nerve blood flow and neuroretinal rim changes after supplementation with oral Ginkgo Biloba or placebo.	Ginkgo biloba patients had statistically significant increase in blood flow with good supply to the neuroretinal rim compared to controls.
Human Study	Garcia-Medina et al	2015, Spain	Oral antioxidant supplement	Open label randomized controlled trial.	117	2 years	Assessment of visual field changes, and OCT changes after 2 years of supplementation with tablet	Oral supplementation of antioxidants did not show any differences in visual fields or retinal nerve fibre changes between control and POAG patients
Human Study	Kang et al	2016, USA	Dietary nitrate	Prospective cohort study	63 893	2 years	Incidence of POAG	Higher dietary nitrate intake was associated with lower risks of POAG.
Human Study	Hui et al	2020, Australia	Nicotinamide	Crossover, double masked Randomised clinical trial	57	6 weeks	Change in inner retinal function assessed after placebo or nicotinamide administered orally.	Photopic parameters improved after nicotinamide compared to placebo. A trend for improved visual field mean deviation was seen in patients supplemented with nicotinamide.
Human Study	Cumurcu et al	2006, Turkey	Homocysteine, B12, Folic acid.	Prospective cohort study.	61	N/A	Serum homocysteine, B12 and folic acid levels measured in patients with POAG, PEXG, NTG and control patients	There were elevated levels of plasma homocysteine in patients with PEXG. No significant elevation seen in B12 or folic acid.
Human Study	Bleich et al	2002, Germany	Homocysteine	Prospective Case control study	37	N/A	Plasma homocysteine levels in patients with POAG and PEXG	Homocysteine levels are increased in patients with POAG.
Human Study	Ramdas et al	2011, Nether-lands	Carotenoids, vitamins E, C, B12, B1, flavonoids, omega acids, magnesium	Prospective population cohort study	3502	9.7 years	Assess if dietary intake of nutrients is associated with incidence of POAG	Low vitamin B1 and retinol intake and high magnesium intake appears to increase the risk of POAG.
Human Study	Puustjärvi et al	2004, Finland	Homocysteine, B6 and B12	Cross sectional study	72	N/A	Plasma homocysteine levels in patients with pseudoexfolation syndrome versus control group	High plasma homocysteine in patients with psuedoexfoliation syndrome patients than controls.

(*continued on next page*)

Table 1 (*continued*)

Class of Studies	Reference	Year and Location	Vitamin/Nutrient Examined	Type of study	Sample size	Treatment duration	Outcome Measures	Key Findings
Human Study	Turgut et al	2010, Turkey	Homocysteine, B6, B12	Prospective controlled trial	120	N/A	Serum homocysteine, vitamin B6, B12 and folic acid were measured in patients with PEXG, POAG and NTG.	Plasma homocysteine higher in PEXG patients and plasma B6 was higher in patients with NTG and POAG.
Human Study	Roedl et al	2007, Germany	Homocysteine, B12 and B6	Prospective Case-Control	140	N/A	Assess Serum B12, folate, B6 levels and association with homocysteine in patients with PEXG versus control	PEXG patients had reduced levels of folate, B12 and B6 which was associated with increased levels of homocysteine.
Human Study	Teikari et al	1998, Finland	Alpha tocopherol and beta carotene	Prospective controlled clinical cohort trial	941	9 years	Long term supplementation with beta-carotene or alpha-tocopherol in risk of developing ARM	No link between alpha tocopherol and beta carotene intake in preventing ARMD
Human Study	Christen et al	2014, USA	Multivitamin, Vitamin E and Vitamin C	Randomized double blinded Placebo controlled trial	14 641	11.2 years	Incident cataract and visually significant AMD after multivitamin or placebo.	Long term vitamin use reduces risk of cataracts, no significant effect on ARMD.
Human Study	Koliakos et al	2002, Greece	Ascorbic Acid	Prospective Case control study	80	N/A	Ascorbic acid concentration in patients with PEXG and controls	Reduced levels of ascorbic acid in aqueous humour of PEXG patients.
Human Study	Leite et al	2009, Brazil	Ascorbic Acid	Prospective case control study	45	N/A	Ascorbic acid levels in patients with POAG and controls.	Aqueous humour in post-surgical glaucoma patients has lower levels of ascorbic acid compared to cataract patients.
Human Study	Wang et al	2013, USA	Vitamin A, C and E	Cross sectional study	2912	12 months	Correlation of vitamin supplementation to increased odds of developing glaucoma	Neither supplementary or serum levels of vitamin A and E were associated with glaucoma. Vitamin C in supplementation gave reduced odds of glaucoma + serum vitamin C had no correlation also.
Human Study	Sitorus et al	2017, India	Vitamin C and E	Pre-post experimental study	26	30 days	Free radical level post administration of vitamin C or E	Reduction of free radicals noted in serum after administration of oral vitamin C and E
Human Study	Engin et al	2007, Turkey	Alpha-tocopherol	Prospective experimental study	60	12 months	Blood tocopherol levels were monitored alongside Visual field changes and doppler flow of ophthalmic artery in glaucomatous patients	Patients supplemented with alpha tocopherol has better vascular supply to the posterior ciliary + ophthalmic artery.
Human Study	Van Herpen-broekmans et al	2004, Nether-lands	Carotenoids and vitamins	Prospective cross sectional study	379	N/A	Serum carotenoids and alpha tocopherol concentration in relation of inflammatory markers – CRP and fibrinogen	Inverse relationship between serum carotenoids, vitamin C and CRP and leukocytes.
Human Study	Terai et al	2014, Germany	Flavonoid	Prospective randomised study	30	2 hours	Effect of flavonoids in chocolate on retinal vessel analysis, blood pressure.	Venous vasodilation improved after 2 hours of intake in control group but not in the glaucoma group.

(*continued on next page*)

Table 1 (*continued*)

Class of Studies	Reference	Year and Location	Vitamin/Nutrient Examined	Type of study	Sample size	Treatment duration	Outcome Measures	Key Findings
Human Study	Harris et al	2018, USA	Oral Gingko Biloba supplement	Randomized, double blinded placebo-controlled cross over study	45	4 weeks	Assess intraocular pressure, ocular perfusion pressure, retrobulbar blood flow and retinal capillary flow with supplementation or placebo	One month oral administration of antioxidants increases ocular blood flow in retinal + retrobulbar vascular beds.
Human Study	Quaranta et al	2003, Italy	Gingko biloba	Prospective randomized placebo-controlled double masked cross over trial.	27	4 weeks	Assess visual field changes in NTG patients after oral supplementation with gingko biloba versus placebo.	Ginkgo orally improves visual field damage in patients with NTG.
Human Study	Parisi et al	2014, Italy	CoenzymeQ10 and vitamin E	Prospective case control study.	43	12 months	IOP, PERG and VEP changes after oral CoQ10 and vitamin E topical eye drops given to POAG patients	CoenzymeQ10 and vitamin E in POAG improved inner retinal functioning and consequent visual cortical enhancement on VEP.
Human study	Modrzejewska et al	2015, Poland	Cholesterol LDL, HDL	Prospective case-control study	110	N/A	LDL and HDL levels in POAG patients. Correlation between these levels and blood flow velocity and vascular risk factors	POAG patient had lower blood velocity and ocular perfusion than controls. This is also associated with higher levels of HDL and LDL in these patients.
Human Study	Nagaoka et al	2006, Japan	Simvastatin	Prospective placebo-controlled double-masked trial	12	7 days	Assess retinal blood flow, IOP and plasma nitrate levels after simvastatin administration.	After 7 days of simvastatin there was a significant increase in retinal blood flow velocity, reduction in IOP and increase in plasma nitrate levels.
Human Study	Akyol et al	1990, Turkey	Zinc and Copper	Cross sectional Study	44	N/A	Serum aqueous humour zinc and copper concentrations in patients with POAG.	Serum levels of zinc and copper seen in aqueous humour samples of glaucoma patients were within normal range, however levels of copper were higher in patients with glaucoma.
Human Study	Giaconi et al	2013, USA	Fruits and vegetables	Cross sectional study	662	N/A	Rates of glaucoma prevalence in correlation to survey of fruit and veg intake in African American women	Higher intake of vitamin A, C and carotenoids may be associated with reduced incidence of glaucoma in African American Women.
Human Study	Coleman et al	2008, USA	Fruits and vegetables	Cross sectional cohort study	1155	N/A	Assess risk of glaucoma diagnosis in reference to nutrient consumption	Higher intake of fruits and vegetables reduces risk of glaucoma.
Human Study	Moise et al	2012, DRC	Carotenoids, Vitamin C and E and selenium	Prospective cros-sectional study	500	N/A	Risks of developing glaucoma, cataract in patients with Mediterranean diet	No individual substance has statistically significant protective effects. Combined diet has statistically significant effects in reducing risk of cataract and glaucoma development.

(*continued on next page*)

Table 1 (*continued*)

Class of Studies	Reference	Year and Location	Vitamin/Nutrient Examined	Type of study	Sample size	Treatment duration	Outcome Measures	Key Findings
Human Study	Altintaş et al	2005, Turkey	Homocysteine, Nitric Oxide (NO)	Cross Sectional Prospective Study	79	N/A	Plasma levels of Homocysteine and NO and risk factor for developing POAG/PXG	Plasma Homocysteine and NO was elevated in Psuedoexfoliation syndrome and PXG patients.
Human Study	Kang et al	2014, USA	Folate, vitamin B6, B12	Cross sectional study	399	N/A	Association between nutrient intake and risk of PEXG	High folate intake gave lower risk for PEXG. Intake of vitamin b6 and B12 not associated with PEXG risk.
Human Study	Davari et al	2014, Iran	Serum Cholesterol	Cross sectional study	80	N/A	Association between serum cholesterol and rates of glaucoma	Higher serum cholesterol and triglyceride levels were seen in POAG patients compared to controls.
Human Study	Ohguro et al	2012, Japan	Flavanoids – Black currant acanthcyanins	Randomised placebo controlled double masked trial	38	24 months	Change in HVF, IOP and ocular blood flow in POAG patients given black currant supplement versus placebo	Patients receiving supplement had better HVF outcomes and ocular blood flow compared to placebo patients. There was no change in IOP.
Human Study	Falsini et al	2009, Italy	Epigallocatechin-gallate	Randomised placebo controlled double masked trial	18	3 months	Assess ERG changes and IOP changes in POAG patients with supplementation versus placebo	Patients receiving supplementation had improved PERG compared to patients receiving placebo.
Human Study	Guo et al	2014, China	Ginkgo Biloba	Randomised placebo controlled crossover trial	35	8 weeks	Assess change in HVF in patients with NTG after oral supplementation with ginkgo biloba versus placebo	Treatment with ginkgo biloba didn't reveal any changes in HVF in patient's with NTG.
Human Study	Pang et al	2021	Retinol	Prospective Cross Sectional study	345	N/A	Assess serum retinol concentrations in NTG, POAG and controls	Lower Serum retinol noted in patients with NTG. Serum retinol positively correlated to optic nerve sheath diameter in glaucoma patients.

vegetables is associated with a 20-30% reduction in POAG risk.[54,123] The study also noted that levels of paracentral visual field loss was reduced by up to 40% in patients who were consuming greater levels of dietary nitrates, as well as green vegetables.[54] Another cross-sectional study of 500 patients examined the effects of a Mediterranean diet in preventing glaucoma in diabetic African patients.

Daily intake of three specific Mediterranean vegetables high in antioxidants was found to reduce significantly the risk of glaucoma and cataracts.[81] Although there were no specific nutrients and vitamins being investigated, the study highlighted the effects of overall increased antioxidant consumption. Studies such as these provide the basis for considering oral supplementation of these nutrients in patients to assess if there is a change in their risk of developing glaucoma if they are nutrient deficient. They also highlight the potential need for individualized management based on the type of glaucoma.

There are various papers analyzing direct nutrient supplementation. Wang and coworkers performed a cross sectional study of 2912 patients that revealed that supplementation with Vitamin C was associated with decreased odds of glaucoma prevalence.[138] Similarly, a non-randomized trial of 60 glaucomatous patients illustrated a statistically significant improvement in ocular blood flow, as well as subsequent prevention of visual field changes, in patients supplemented with oral tocopherol [29] A recent pilot study of 48 patients by Jabbarpoor and coworkers showed that saffron supplementation reduced intraocular pressures in patients with POAG.[49] On a larger scale, a prospective population based cohort study of 3502 patients assessed retinol equivalent intake and found a lower risk of developing POAG in patients with higher retinol equivalent consumption.[110]

There are a number of RCTs that look at the effect of targeted nutrient supplementation in glaucoma patients. One randomized double-masked trial of 38 POAG patients supplemented them with black currant anthocyanins, rich in flavonoids, over a 24-month period. It showed an improvement in ocular blood flow and visual field testing in the POAG patients supplemented with the nutrients over patients receiving placebo.[93] Another RCT tested the flavonoid epigallocatechin-gallate in 18 POAG patients, and observed a slight improvement in electroretinograms after 3 months in patients receiving supplementation over placebo.[31] Other RCTs provide inconclusive results; for example, Goldblum and coworkers found that 39 POAG and PXF patients post trabeculetomy supplemented with oral tocophereol over 2 months revealed no significant difference in IOP between treatment and control groups.[36]

Similarly, in a recent prospective double-masked randomized crossover human trial in Melbourne,[47] Hui and coworkers examined 57 POAG participants supplemented with either NAM orally or a placebo and noted positive inner retinal function improvement and also a trend in visual field improvement in patients supplemented with nicotinamide over placebo.[47]

Other flavonoid supplementation assessed in RCTs include ginkgo biloba that has been associated with an improvement in visual field function, oxidative stress markers, and some retinal nerve fibre layer changes after supplementation in POAG and NTG patients.[39,107,119]

Supplementation of antioxidants and nutrients in a combined formulation has also been trialed in a few pharmaceutical company funded articles. A prospective study of 114 glaucoma patients taking a specific combined oral supplement of vitamin A, E, and nicotinic acid illustrated reduced visual field defects after 5 months of treatment compared to controls.[127] Similarly, a randomized control trial of 22 glaucoma patients treated with another formulated supplement containing forskolin, homotaurine, carnosine, folic acid, vitamins B1, B2, B6, and magnesium in POAG patients illustrated a reduction in IOP and improvement in foveal sensitivity over a period of 12 months.[85]

Similarly, at least one RCT of 24 patients and another trial have established the effectiveness of a NO-donating prostanoid receptor agonist (latanoprostene bunod) in reducing IOP.[8,141] Another pharmaceutical company funded trial of 45 patients from the US found a reduction in vascular resistance within the eye, as well as improving blood flow, in patients with POAG after oral gingko biloba supplementation.[41] This was supported by a randomized placebo-controlled double masked cross-over trial of 27 patients showing visual field improvements in patients with normal tension glaucoma after 4 weeks of oral supplementation.[107] In a recent prospective clinical study of 43 patients with OAG, combination CoQ10 and vitamin E eye drop administration elicited benefits in retinal function.[79,98,120]

Another important consideration when research into nutritional supplementation is being undertaken is the safety of these complementary medications. The AREDS 1 trial provided the cautionary tale of a higher risk of lung cancer, particularly amongst smoking patients, consuming the levels of beta-carotene and zinc in their supplementation.[18] Similarly, excess doses of alpha tocopherol are associated with increased subarachnoid bleeding risks, ascorbic acid is associated with kidney stones, and retinol can be associated with raised intracranial pressure.[10,64,73,132] Higher quantities of certain nutrient compounds or anti-oxidants may have inadvertent consequences on systemic health that we are yet to fully understand. This caveat is one that could have potentially substantial implications on the systemic wellbeing of patients, and without definitive evidence to indicate a potential benefit in glaucoma management clinicians should consider the advice provided carefully of the advice they provide.

These papers highlight the benefits of dietary intake of vitamins, although evidence of clinical implementation is still in early stages. There are promising findings for certain groups such as the B vitamins; however, we cannot validate supplemental use in affecting glaucomatous outcomes. All the Randomized control trials analyzed were limited by both their sample sizes and also their duration of follow up. Given the chronicity of glaucomatous damage, it is difficult to draw conclusions from such early interventional data. Similarly, bioavailability of supplementation and biomarker assessments are difficult to quantify, and so correlating findings could be a stretch. Although there is current research yielding potentially significant findings in the treatment of glaucoma, there are still a large number that leave inconclusive results. Other reviews in the literature also appear to reach a similar

conclusion… Moving forward, it will be invaluable for future research to target those compounds in clinical settings that will address the existing insufficiency.

7. Conclusion

Glaucoma is a multifactorial disease that continues to burden health systems across the globe. In order to abate the ongoing consequences of this disease, it is important to examine what treatment and prevention potentials are available. Currently the mainstay treatment target in glaucoma is IOP reduction. Through the use of nutrients, treatments can directly target oxidative damage, RGC survival, axonal growth and vasoregulation and mitochondrial protection. Many of the natural compounds analyzed appear to facilitate at least one of the aforementioned properties both *in vivo, in vitro* and clinically. Simple compounds such as nicotinamide, carotenoids, flavonoids, curcumin, saffron, CoQ10, gingko biloba, folic acid, and resveratrol appear to show promise and deserve further investigation; however, the data to translate these findings into clinical treatments and support their clinical applicability remains inconclusive.

Wholesome dietary vitamin intake has been supported by multiple studies in reducing the risk of POAG. Similarly, although theoretical links have been made between nutrient intake and other types of glaucoma such as NTG or PEXG, there have been no definitive findings to help guide clinical decision making. Owing to the complexity and variation seen in pathophysiology under the umbrella of glaucoma it may be worthwhile to assess each subset of glaucoma with different potential treatments. The complex nature of the disease process emphasizes the importance of a multifaceted approach in both treatment and prevention. Furthermore, the process of researching glaucoma relies on time and sample sizes, aspects that require thorough study designs and strategic analyses to overcome.

Nutritional supplements and vitamins are an adjunct in glaucoma intervention that is easily accessible, has minimal costs associated, and has a relatively good safety profile. Although the evidence at this stage is inconclusive, recommendations by clinicians for their patients may not be unacceptable. In fact, a cross-sectional survey of over 1500 patients revealed that 1 in 9 patients were already using nutritional supplementation alongside their glaucoma treatment.[136] Further research into the underlying inflammatory processes associated with neurodegeneration in glaucoma may also provide vital clues in determining effective regulatory processes or treatment targets. Harnessing the use of nutritional supplementation will provide important adjuncts in the treatment and prevention of glaucoma and warrant ongoing research.

8. Method of literature search

A thorough electronic MEDLINE and PubMed search revealed 71 English print articles that were used for analysis. Search terms used included “vitamins AND Glaucoma OR Open Angle Glaucoma OR Pseudoexfoliation OR Normal Tension Glaucoma” and “Nutrient supplementation AND Glaucoma OR Open Angle Glaucoma OR Pseudoexfoliation OR Normal Tension Glaucoma” and “Anti-oxidants supplementation AND Glaucoma OR Open Angle Glaucoma OR Pseudoexfoliation OR Normal Tension Glaucoma”. Although trials published since 1970 were included, the paper was based predominantly on articles written ideally in the last decade. We included all forms of literature including cell based, animal and human studies. No minimal sample size was required for inclusion, however case reports were excluded. The reference lists of each publication were also examined to find other articles not found in the original searches.

Financial Support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors of this paper have no conflicts of interest to declare.

REFERENCES

1. Antioxidant status and neovascular age-related macular degeneration. Arch Ophthalmol. 1993;111(1):104–9.
2. Abu-Hassan DW, Acott TS, Kelley MJ. The trabecular meshwork: a basic review of form and function. J Ocul Biol. 2014;2(1).
3. Kassoff A, Kassoff J, Beuhler J, Eglow M, Kaufman F, Mehu M, et al. Age-Related Eye Disease Study Research G. A Randomized, Placebo-Controlled, Clinical Trial of High-Dose Supplementation With Vitamins C and E, Beta Carotene, and Zinc for Age-Related Macular Degeneration and Vision Loss: AREDS Report No. 8. Arch of Ophthalmol. 2001;119(10):1417–36.
4. Akyol N, Değer O, Keha E, Kiliç S. Aqueous humour and serum zinc and copper concentrations of patients with glaucoma and cataract. Br J Ophthalmol. 1990;74(11):661–2.
5. Aliancy J, Stamer WD, Wirostko B. A Review of Nitric Oxide for the Treatment of Glaucomatous Disease. Ophthalmol Ther. 2017;6(2):221–32.
6. Altintaş Ö, Maral H, Yüksel N, Karabaş VL, Dillioğlugil MÖ, Çağlar Y. Homocysteine and nitric oxide levels in plasma of patients with pseudoexfoliation syndrome, pseudoexfoliation glaucoma, and primary open-angle glaucoma. Graefes Arch Clin Exp Ophthalmol. 2005;243(7):677–83.
7. Anderson DR. Collaborative normal tension glaucoma study. Curr Opin Ophthalmol. 2003;14(2):86–90.
8. Ashworth A, Bescos R. Dietary nitrate and blood pressure: evolution of a new nutrient? Nutr Res Rev. 2017;30(2):208–19.
9. Babizhayev MA. Generation of reactive oxygen species in the anterior eye segment. Synergistic codrugs of N-acetylcarnosine lubricant eye drops and mitochondria-targeted antioxidant act as a powerful therapeutic platform for the treatment of cataracts and primary open-angle glaucoma. BBA Clin. 2016;6:49–68.
10. Bartlett H, Eperjesi F. Possible contraindications and adverse reactions associated with the use of ocular nutritional supplements. Ophthalmol Physiol Opt. 2005;25(3):179–94.

11. Bie X, Chen Y, Zheng X, Dai H. The role of crocetin in protection following cerebral contusion and in the enhancement of angiogenesis in rats. Fitoterapia. 2011;82(7):997–1002.
12. Bleich S, Jünemann A, Von Ahsen N, Lausen B, Ritter K, Beck G, et al. Homocysteine and risk of open-angle glaucoma. J Neural Transm. 2002;109(12):1499–504.
13. Braakhuis A, Raman R, Vaghefi E. The Association between Dietary Intake of Antioxidants and Ocular Disease. Diseases. 2017;5(1):3.
14. Buettner G, Q Schafer, F. Albert Szent-Györgyi: Vitamin C Identified 2006.
15. Burdon KP, Macgregor S, Hewitt AW, Sharma S, Chidlow G, Mills RA, et al. Genome-wide association study identifies susceptibility loci for open angle glaucoma at TMCO1 and CDKN2B-AS1. Nat Genet. 2011;43:574.
16. Chandrawati R, Chang Jason YH, Reina-Torres E, Jumeaux C, Sherwood Joseph M, Stamer WD, et al. Localized and controlled delivery of nitric oxide to the conventional outflow pathway via enzyme biocatalysis: toward therapy for glaucoma. Adv Mater. 2017;29(16):1604932.
17. Cheung W, Guo LI, Cordeiro MF. Neuroprotection in Glaucoma: Drug-Based Approaches. Optometry and vision Sci. 2008;85(6):406–16.
18. Chew EY, Clemons TE, SanGiovanni JP, Danis R, Ferris FL, Elman M, et al. Lutein+ zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. JAMA. 2013;309(19):2005–15.
19. Christen WG, Glynn RJ, Manson JE, MacFadyen J, Bubes V, Schvartz M, et al. A multivitamin supplement and cataract and age-related macular degeneration in a randomized trial of male physicians. Ophthalmol. 2014;121(2):525–34.
20. Chrysostomou V, Rezania F, Trounce IA, Crowston JG. Oxidative stress and mitochondrial dysfunction in glaucoma. Curr Opin Pharmacol. 2013;13(1):12–15.
21. Chung HS, Harris A, Kagemann L, Martin B. Peripapillary retinal blood flow in normal tension glaucoma. Br J Ophthalmol. 1999;83(4):466–9.
22. Coleman AL, Stone KL, Kodjebacheva G, Yu F, Pedula KL, Ensrud KE, et al. Glaucoma Risk and the Consumption of Fruits and Vegetables Among Older Women in the Study of Osteoporotic Fractures. Am J Ophthalmol. 2008;145(6):1081–9.
23. Crane FL. Biochemical functions of coenzyme Q10. J Am Coll Nutr. 2001;20(6):591–8.
24. Crawley L, Zamir SM, Cordeiro MF, Guo L. Clinical options for the reduction of elevated intraocular pressure. Ophthalmol Eye Dis. 2012;4:S4909 OED.
25. Cumurcu T, Sahin S, Aydin E. Serum homocysteine, vitamin B 12 and folic acid levels in different types of glaucoma. BMC Ophthalmol. 2006;6:6.
26. Cybulska-Heinrich AK, Mozaffarieh M, Flammer J. Ginkgo biloba: An adjuvant therapy for progressive normal and high tension glaucoma. Mol Vis. 2012;18:390–402.
27. d'Uscio LV, Milstien S, Richardson D, Smith L, Katusic ZS. Long-term vitamin C treatment increases vascular tetrahydrobiopterin levels and nitric oxide synthase activity. Circ Res. 2003;92(1):88–95.
28. Ekici F, Korkmaz Ş, Karaca EE, Sül S, Tufan HA, Aydın B, et al. The role of magnesium in the pathogenesis and treatment of glaucoma. Int Sch Res Notices. 2014;2014:1–7 745439.
29. Engin K, Engin G, Kucuksahin H, Oncu M, Engin G, Guvener B. Clinical evaluation of the neuroprotective effect of α-tocopherol against glaucomatous damage. Eur J Ophthalmol. 2007;17(4):528–33.
30. Engin KN. Alpha-tocopherol: looking beyond an antioxidant. Mol Vis. 2009;15:855.
31. Falsini B, Marangoni D, Salgarello T, Stifano G, Montrone L, Di Landro S, et al. Effect of epigallocatechin-gallate on inner retinal function in ocular hypertension and glaucoma: a short-term study by pattern electroretinogram. Graefes Arch Clin Exp Ophthalmol. 2009;247(9):1223–33.
32. Fingert JH, Robin AL, Stone JL, Roos BR, Davis LK, Scheetz TE, et al. Copy number variations on chromosome 12q14 in patients with normal tension glaucoma. Hum Mol Genet. 2011;20(12):2482–94.
33. Flammer J, Konieczka K, Flammer AJ. The primary vascular dysregulation syndrome: implications for eye diseases. EPMA J. 2013;4(1):14.
34. Garcia-Medina Jose J, Garcia-Medina M, Garrido-Fernandez P, Galvan-Espinosa J, Garcia-Maturana C, Zanon-Moreno V, et al. A two-year follow-up of oral antioxidant supplementation in primary open-angle glaucoma: an open-label, randomized, controlled trial. Acta Ophthalmol. 2014;93(6):546–54.
35. Giaconi JA, Yu F, Stone KL, Pedula KL, Ensrud KE, Cauley JA, et al. The Association of Consumption of Fruits/Vegetables with Decreased Risk of Glaucoma among Older African American Women in the Study of Osteoporotic Fractures. Am J Ophthalmol. 2012;154(4):635–44.
36. Goldblum D, Meyenberg A, Mojon D, Tappeiner C, Frueh BE. Dietary tocopherol supplementation after trabeculectomy and phacotrabeculectomy: double-blind randomized placebo-controlled trial. Ophthalmol. 2009;223(4):228–32.
37. Gorin M, Chew E, Clemons E. Long-Term Effects of Vitamins C, E, Beta-Carotene and Zinc on Age-Related Macular Degeneration. AREDS Report No. 35 2017.
38. Grieshaber MC, Mozaffarieh M, Flammer J. What is the link between vascular dysregulation and glaucoma? Surv Ophthalmol. 2007;52(6):S144–SS54.
39. Guo X, Kong X, Huang R, Jin L, Ding X, He M, et al. Effect of Ginkgo biloba on visual field and contrast sensitivity in Chinese patients with normal tension glaucoma: a randomized, crossover clinical trial. Invest Ophthalmol Vis Sci. 2014;55(1):110–16.
40. Guymer C, Wood JP, Chidlow G, Casson RJ. Neuroprotection in glaucoma: recent advances and clinical translation. Clin Exp Ophthalmol. 2019;47(1):88–105.
41. Harris A, Gross J, Moore N, Do T, Huang A, Gama W, et al. The effects of antioxidants on ocular blood flow in patients with glaucoma. Acta Ophthalmol. 2017;96(2):e237–ee41.
42. He Y, Leung KW, Zhang Y-H, Duan S, Zhong X-F, Jiang R-Z, et al. Mitochondrial Complex I Defect Induces ROS release and degeneration in trabecular meshwork cells of POAG Patients: protection by antioxidants. Invest Ophthalmol Vis Sci. 2008;49(4):1447–58.
43. Head K. Natural therapies for ocular disorders part two: cataracts and glaucoma. Altern Med Rev. 2001;6(2):141–66.
44. Hirooka K, Tokuda M, Miyamoto O, Itano T, Baba T, Shiraga F. The Ginkgo biloba extract (EGb 761) provides a neuroprotective effect on retinal ganglion cells in a rat model of chronic glaucoma. Curr Eye Res. 2004;28(3):153–7.
45. Hohberger B, Chaudhri MA, Michalke B, Lucio M, Nowomiejska K, Schlötzer-Schrehardt U, et al. Levels of aqueous humor trace elements in patients with open-angle glaucoma. J Trace Elem Med Biol. 2018;45:150–5.
46. Howard AC, McNeil AK, McNeil PL. Promotion of plasma membrane repair by vitamin E. Nat Commun. 2011;2:597.
47. Hui F, Tang J, Williams PA, McGuinness MB, Hadoux X, Casson RJ, et al. Improvement in inner retinal function in glaucoma with nicotinamide (vitamin B3) supplementation: A crossover randomized clinical trial. Clin Exp Ophthalmol. 2020;48(7):903–14.
48. Hysi PG, Cheng C-Y, Springelkamp H, Macgregor S, Bailey JNC, Wojciechowski R, et al. Genome-wide analysis of

multi-ancestry cohorts identifies new loci influencing intraocular pressure and susceptibility to glaucoma. Nat Genet. 2014;46:1126.
49. Jabbarpoor Bonyadi MH, Yazdani S, Saadat S. The ocular hypotensive effect of saffron extract in primary open angle glaucoma: a pilot study. BMC Complement Altern Med. 2014;14(1):399.
50. Ji D, Li G-Y, Osborne NN. Nicotinamide attenuates retinal ischemia and light insults to neurones. Neurochem Int. 2008;52(4):786–98.
51. Jung KI, Kim YC, Park CK. Dietary niacin and open-angle glaucoma: The Korean national health and nutrition examination survey. Nutr. 2018;10(4):387.
52. Kang JH, Loomis SJ, Wiggs JL, Willett WC, Pasquale LR. A prospective study of folate, vitamin B6, and vitamin B12 intake in relation to exfoliation glaucoma or suspected exfoliation glaucoma. JAMA Ophthalmol. 2014;132(5):549–59.
53. Kang JH, Pasquale LR, Willett W, Rosner B, Egan KM, Faberowski N, et al. Antioxidant Intake and Primary Open-Angle Glaucoma: A Prospective Study. Am J Epidemiol. 2003;158(4):337–46.
54. Kang JH, Willett WC, Rosner BA, Buys E, Wiggs JL, Pasquale LR. Association of dietary nitrate intake with primary open-angle glaucoma: A prospective analysis from the nurses' health study and health professionals follow-up study. JAMA Ophthalmol. 2016;134(3):294–303.
55. Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120(6):701–13.
56. Kim KE, Park K-H. Update on the prevalence, etiology, diagnosis, and monitoring of normal-tension glaucoma. Asia-Pac J Ophthalmol. 2016;5(1):23–31.
57. Kim RY, Stern WH. Retinoids and butyrate modulate fibroblast growth and contraction of collagen matrices. Invest Ophthalmol Vis Sci. 1990;31(6):1183–6.
58. Ko M-L, Peng P-H, Hsu S-Y, Chen C-F. Dietary deficiency of vitamin E aggravates retinal ganglion cell death in experimental glaucoma of rats. Curr Eye Res. 2010;35(9):842–9.
59. Koliakos GG, Konstas AGP, Schlötzer-Schrehardt U, Bufidis T, Georgiadis N, Ringvold A. Ascorbic acid concentration is reduced in the aqueous humor of patients with exfoliation syndrome. Am J Ophthalmol. 2002;134(6):879–83.
60. Kouassi Nzoughet J, Chao de la Barca JM, Guehlouz K, Leruez S, Coulbault L, Allouche S, et al. Nicotinamide deficiency in primary open-angle glaucoma. Invest Ophthalmol Vis Sci. 2019:2509–14.
61. Kumar DM, Agarwal N. Oxidative stress in glaucoma: a burden of evidence. J Glaucoma. 2007;16(3):334–43.
62. Landrum JT, Bone RA. Lutein, zeaxanthin, and the macular pigment. Arch Biochem Biophys. 2001;385(1):28–40.
63. Leite Mauro T, Prata Tiago S, Kera Clarissa Z, Miranda Denise V, De Moraes Barros Silvia B, Melo Luiz AS. Ascorbic acid concentration is reduced in the secondary aqueous humour of glaucomatous patients. Clin Exp Ophthalmol. 2009;37(4):402–6.
64. Leppälä JM, Virtamo J, Fogelholm R, Albanes D, Taylor PR, Heinonen OP. Vitamin E and beta carotene supplementation in high risk for stroke: a subgroup analysis of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Arch Neurol. 2000;57(10):1503–9.
65. Leske MC, Connell A, Wu S-Y, Hyman LG, Schachat AP. Risk factors for open-angle glaucoma: the Barbados Eye Study. Arch Ophthalmol. 1995;113(7):918–24.
66. Leske MC, Connell AM, Wu S-Y, Nemesure B, Li X, Schachat A, et al. Incidence of open-angle glaucoma: the Barbados Eye Studies. Arch Ophthalmol. 2001;119(1):89–95.
67. Leske MC, Wu S-Y, Hennis A, Honkanen R, Nemesure B, Group BS. Risk factors for incident open-angle glaucoma: the Barbados Eye Studies. Ophthalmol. 2008;115(1):85–93.
68. Levin LA, Crowe ME, Quigley HA. Neuroprotection for glaucoma: Requirements for clinical translation. Exp Eye Res. 2017;157:34–7.
69. Levkovitch–Verbin H, Harris–Cerruti C, Groner Y, Wheeler LA, Schwartz M, Yoles E. RGC death in mice after optic nerve crush injury: oxidative stress and neuroprotection. Invest Ophthalmol Vis Sci. 2000;41(13):4169–74.
70. Li S-Y, Lo AC. Lutein protects RGC-5 cells against hypoxia and oxidative stress. Int J Mol Sci. 2010;11(5):2109–17.
71. Li Y, Andereggen L, Yuki K, Omura K, Yin Y, Gilbert H-Y, et al. Mobile zinc increases rapidly in the retina after optic nerve injury and regulates ganglion cell survival and optic nerve regeneration. Proc Natl Acad Sci. 2017;114(2):E209.
72. Li Y, Li Y, Liang S, Zhuo Y. Abnormal Levels of Zinc in the Aqueous Humor: Implications of Primary Glaucoma. Invest Ophthalmol Vis Sci. 2020;61(7):3427.
73. Libien J, Blaner WS. Retinol and retinol-binding protein in cerebrospinal fluid: can vitamin A take the "idiopathic" out of idiopathic intracranial hypertension? J Neuro-Ophthalmol. 2007;27(4):253–7.
74. Liu X-F, Hao J-L, Xie T, Mukhtar NJ, Zhang W, Malik TH, et al. Curcumin, a potential therapeutic candidate for anterior segment eye diseases: a review. Front Pharmacol. 2017;8(66).
75. Liu X-Q, Wu B-J, Pan WHT, Zhang X-M, Liu J-H, Chen M-M, et al. Resveratrol mitigates rat retinal ischemic injury: the roles of matrix metalloproteinase-9, inducible nitric oxide, and heme oxygenase-1. J Ocul Pharmacol Ther. 2012;29(1):33–40.
76. Maccarone R, Di Marco S, Bisti S. Saffron Supplement Maintains Morphology and Function after Exposure to Damaging Light in Mammalian Retina. Invest Ophthalmol Vis Sci. 2008;49(3):1254–61.
77. Maher P, Hanneken A. Flavonoids protect retinal ganglion cells from oxidative stress–induced death. Invest Ophthalmol Vis Sci. 2005;46(12):4796–803.
78. Marreiro DD, Cruz KJ, Morais JB, Beserra JB, Severo JS, de Oliveira AR. Zinc and oxidative stress: current mechanisms. Antioxidants (Basel). 2017;6(2).
79. Milde J, Elstner EF, Graßmann J. Synergistic effects of phenolics and carotenoids on human low-density lipoprotein oxidation. Mol Nutr Food Res. 2007;51(8):956–61.
80. Mills KF, Yoshida S, Stein LR, Grozio A, Kubota S, Sasaki Y, et al. Long-term administration of nicotinamide mononucleotide mitigates age-associated physiological decline in mice. Cell Metab. 2016;24(6):795–806.
81. Moïse MM, Benjamin L-M, Doris TM, Dalida KN, NO Augustin. Role of Mediterranean diet, tropical vegetables rich in antioxidants, and sunlight exposure in blindness, cataract and glaucoma among African type 2 diabetics. Int J Ophthalmol. 2012;5(2):231–7.
82. Mozaffarieh M, Flammer J. Is there more to glaucoma treatment than lowering IOP? Surv Ophthalmol. 2007;52(6):S174–S1S9.
83. Mozaffarieh M, Flammer J. New insights in the pathogenesis and treatment of normal tension glaucoma. Curr Opin Pharmacol. 2013;13(1):43–9.
84. Mozaffarieh M, Grieshaber MC, Orgül S, Flammer J. The potential value of natural antioxidative treatment in glaucoma. Surv Ophthalmol. 2008;53(5):479–505.
85. Mutolo MG, Albanese G, Rusciano D, Pescosolido N. Oral administration of forskolin, homotaurine, carnosine, and folic acid in patients with primary open angle glaucoma:

changes in intraocular pressure, pattern electroretinogram amplitude, and foveal sensitivity. J Ocul Pharmacol Ther. 2016;32(3):178–83.
86. Nakayama M, Aihara M, Chen Y-N, Araie M, Tomita-Yokotani K, Iwashina T. Neuroprotective effects of flavonoids on hypoxia-, glutamate-, and oxidative stress–induced retinal ganglion cell death. Mol Vis. 2011;17:1784.
87. National Institutes of Health. Vitamin a: Fact sheet for health professionals. 2018 Available from: https://ods.od.nih.gov/factsheets/VitaminA-HealthProfessional/. Accessed 22/10/2020.
88. National Institutes of Health. Vitamin e: fact sheet for health professionals. 2018 Available from: https://ods.od.nih.gov/factsheets/VitaminE-HealthProfessional/. Accessed 22/10/2020.
89. Neacşu A, Oprean C, Curea M, Tuchilă G, Trifu M. [Neuroprotection with carotenoids in glaucoma]. Oftalmologia (Bucharest, Romania: 1990). 2003;59(4):70–5.
90. Nicolela MT. Clinical clues of vascular dysregulation and its association with glaucoma. Can J Ophthalmol. 2008;43(3):337–41.
91. #x142, gorzata Nita M, Grzybowski A. The role of the reactive oxygen species and oxidative stress in the pathomechanism of the age-related ocular diseases and other pathologies of the anterior and posterior eye segments in adults. Oxid Med Cell Longev. 2016;2016:23.
92. Nucci C, Tartaglione R, Cerulli A, Mancino R, Spanò A, Cavaliere F, et al. Retinal damage caused by high intraocular pressure–induced transient ischemia is prevented by coenzyme Q10 in rat. In: International Review of Neurobiology, 82. Academic Press; 2007. p. 397–406.
93. Ohguro H, Ohguro I, Katai M, Tanaka S. Two-year randomized, placebo-controlled study of black currant anthocyanins on visual field in glaucoma. Ophthalmol. 2012;228(1):26–35.
94. Organisciak DT, Jiang YL, Wang HM. Bicknell I. The protective effect of ascorbic acid in retinal light damage of rats exposed to intermittent light. Invest Ophthalmol Vis Sci. 1990;31(7):1195–202.
95. Osborne N, Ugarte M, Chao M, Chidlow G, Bae J, Wood J, et al. Neuroprotection in relation to retinal ischemia and relevance to glaucoma. Surv Ophthalmol. 1999;43:S102–SS28.
96. Osborne NN. Pathogenesis of ganglion “cell death” in glaucoma and neuroprotection: focus on ganglion cell axonal mitochondria. Prog Brain Res. 2008;173:339–52.
97. Pang R, Feng S, Cao K, Sun Y, Guo Y, Ma D, et al. Association of serum retinol concentration with normal-tension glaucoma. Eye. 2021:1–6.
98. Parisi V, Centofanti M, Gandolfi S, Marangoni D, Rossetti L, Tanga L, et al. Effects of Coenzyme Q10 in Conjunction With Vitamin E on Retinal-evoked and Cortical-evoked Responses in Patients With Open-angle Glaucoma. J Glaucoma. 2014;23(6):391–404.
99. Park JW, Kwon HJ, Chung WS, Kim CY, Seong GJ. Short-term effects of Ginkgo biloba extract on peripapillary retinal blood flow in normal tension glaucoma. Korean J Ophthalmol. 2011;25(5):323–8.
100. Park Y-H, Chiou GC. Structure–activity relationship (SAR) between some natural flavonoids and ocular blood flow in the rabbit. J Ocul Pharmacol Ther. 2004;20(1):34–41.
101. Patel S, Mathan JJ, Vaghefi E, Braakhuis AJ. The effect of flavonoids on visual function in patients with glaucoma or ocular hypertension: a systematic review and meta-analysis. Graefe’s Arch Clin Exp Ophthalmol. 2015;253(11):1841–50.
102. Pavljašević S, Aščerić M. Primary open-angle glaucoma and serum lipids. Bosn J Basic Med Sci. 2009;9(1):85.
103. Pinazo-Duran MD, Shoaie-Nia K, Zanon-Moreno V, Sanz-Gonzalez SM, Del Castillo JB, Garcia-Medina JJ, et al. Strategies to reduce oxidative stress in glaucoma patients. Curr Neuropharmacol. 2017;16:903–18.
104. Puustjärvi T, Blomster H, Kontkanen M, Punnonen K, Teräsvirta M. Plasma and aqueous humour levels of homocysteine in exfoliation syndrome. Graefe’s Archive for. Clin Exp Ophthalmol. 2004;242(9):749–54.
105. Qi Y, Chen L, Zhang L, Liu W-B, Chen X-Y, Yang X-G. Crocin prevents retinal ischaemia/reperfusion injury-induced apoptosis in retinal ganglion cells through the PI3K/AKT signalling pathway. Exp Eye Res. 2013;107:44–51.
106. Qu J, Kaufman Y, Washington I. Coenzyme Q10 in the Human Retina. Invest Ophthalmol Vis Sci. 2009;50(4):1814–18.
107. Quaranta L, Bettelli S, Uva MG, Semeraro F, Turano R, Gandolfo E. Effect of Ginkgo biloba extract on preexisting visual field damage in normal tension glaucoma. Ophthalmol. 2003;110(2):359–62.
108. Quigley HA. Glaucoma. Lancet. 2011;377(9774):1367–77.
109. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol. 2006;90(3):262–7.
110. Ramdas WD, Wolfs RC, Kiefte-de Jong JC, Hofman A, de Jong PT, Vingerling JR, et al. Nutrient intake and risk of open-angle glaucoma: the Rotterdam Study. Eur J Epidemiol. 2012;27(5):385–93.
111. Ritch R. Potential role for Ginkgo biloba extract in the treatment of glaucoma. Med Hypotheses. 2000;54(2):221–35.
112. Rizvi S, Raza ST, Ahmed F, Ahmad A, Abbas S, Mahdi F. The Role of Vitamin E in Human Health and Some Diseases. Sultan Qaboos Univ Med J. 2014;14(2):e157–ee65.
113. Roberts RL, Green J, Lewis B. Lutein and zeaxanthin in eye and skin health. Clin Dermatol. 2009;27(2):195–201.
114. Robison W, Kuwabara T, Bieri J. Vitamin E deficiency and the retina: photoreceptor and pigment epithelial changes. Invest Ophthalmol Vis Sci. 1979;18(7):683–90.
115. Roedl JB, Bleich S, Reulbach U, Rejdak R, Naumann GO, Kruse FE, et al. Vitamin deficiency and hyperhomocysteinemia in pseudoexfoliation glaucoma. J Neural Transm (Vienna). 2007;114(5):571–5.
116. Rusciano D, Pezzino S, Mutolo MG, Giannotti R, Librando A, Pescosolido N. Neuroprotection in Glaucoma: Old and New Promising Treatments. Adv Pharmacol Sci. 2017:19 2017.
117. Saccà SC, Izzotti A, Rossi P, Traverso C. Glaucomatous outflow pathway and oxidative stress. Exp Eye Res. 2007;84(3):389–99.
118. Sakai T. Effect of long-term treatment of glaucoma with vitamin B_< 12. Glaucoma. 1992;14:167–70.
119. Sari MD. Ginkgo Biloba Extract Effect on Oxidative Stress Marker Malonildialdehyde, Redox Enzyme Gluthation Peroxidase, Visual Field Damage, and Retinal Nerve Fiber Layer Thicknessin Primary Open Angle Glaucoma. 2016.
120. Schneider D, Elstner EF. Coenzyme Q10, Vitamin E, and Dihydrothioctic Acid Cooperatively Prevent Diene Conjugation in Isolated Low-Density Lipoprotein. Antioxid Redox Signal. 2000;2(2):327–33.
121. Schober MS, Chidlow G, Wood JP, Casson RJ. Bioenergetic-based neuroprotection and glaucoma. Clin Exp Ophthalmol. 2008;36(4):377–85.
122. Seah SK, Foster PJ, Chew PT, Jap A, Oen F, Fam HB, et al. Incidence of acute primary angle-closure glaucoma in Singapore: an island-wide survey. Arch Ophthalmol. 1997;115(11):1436–40.
123. Skalicky WDS, White A. The Many Facets of Glaucoma 2021.
124. Song J, Deng P-F, Stinnett SS, Epstein DL, Rao PV. Effects of cholesterol-lowering statins on the aqueous humor outflow pathway. Invest Ophthalmol Vis Sci. 2005;46(7):2424–32.

125. Springelkamp H, Iglesias AI, Mishra A, Höhn R, Wojciechowski R, Khawaja AP, et al. New insights into the genetics of primary open-angle glaucoma based on meta-analyses of intraocular pressure and optic disc characteristics. Hum Mol Genet. 2017;26(2):438–53.
126. Srivastava S. Emerging therapeutic roles for NAD+ metabolism in mitochondrial and age-related disorders. Clin Transl Med. 2016;5(1):1–11.
127. Stark H. Studies with the computer-guided perimeter "Peritest" on the effect of Cosaldon A+ E on glaucomatous visual field defects. Ophthalmol J Int Ophthalmol Int J Ophthalmol Zeitschrift fur Augenheilkunde. 1985;191(4):238–49.
128. Takamoto M, Kaburaki T, Mabuchi A, Araie M, Amano S, Aihara M, et al. Common variants on chromosome 9p21 are associated with normal tension glaucoma. PLoS One. 2012;7(7):e40107.
129. Teikari JM, Laatikainen L, Virtamo J, Haukka J, Rautalahti M, Liesto K, et al. Six-year supplementation with alpha-tocopherol and beta-carotene and age-related maculopathy. Acta Ophthalmol Scand. 1998;76(2):224–9.
130. Terai N, Gedenk A, Spoerl E, Pillunat LE, Stodtmeister R. The short-term effect of flavonoid-rich dark chocolate on retinal vessel diameter in glaucoma patients and age-matched controls. Acta Ophthalmol. 2014;92(5):e341–e3e5.
131. Tezel G. Oxidative stress in glaucomatous neurodegeneration: Mechanisms and consequences. Prog Retin Eye Res. 2006;25(5):490–513.
132. Thomas LD, Elinder C-G, Tiselius H-G, Wolk A, Åkesson A. Ascorbic acid supplements and kidney stone incidence among men: a prospective study. JAMA Intern Med. 2013;173(5):386–8.
133. Turgut B, Kaya M, Arslan S, Demir T, Güler M, Kaya MK. Levels of circulating homocysteine, vitamin B6, vitamin B12, and folate in different types of open-angle glaucoma. Clini Interv Aging. 2010;5:133–9.
134. van Herpen-broekmans W, Klöpping-ketelaars I, Michiel B, Cornelis K, Hans P, Hendriks F, et al. Serum carotenoids and vitamins in relation to markers of endothelial function and inflammation. Eur J Epidemiol. 2004;19(10):915–21.
135. Vrabec J, Levin L. The neurobiology of cell death in glaucoma. Eye. 2007;21(1):S11–SS4.
136. Wan MJ, Daniel S, Kassam F, Mutti G, Butty Z, Kasner O, et al. Survey of complementary and alternative medicine use in glaucoma patients. J Glaucoma. 2012;21(2):79–82.
137. Wang L, Li C, Guo H, Kern TS, Huang K, Zheng L. Curcumin inhibits neuronal and vascular degeneration in retina after ischemia and reperfusion injury. PLoS One. 2011;6(8):e23194.
138. Wang S, Singh K, Lin S. Glaucoma and vitamins A, C, and E supplement intake and serum levels in a population-based sample of the United States. Eye. 2013;27(4):487.
139. Wang SY, Singh K, Lin SC. The Association between Glaucoma Prevalence and Supplementation with the Oxidants Calcium and Iron. Invest Ophthalmol Vis Sci. 2012;53(2):725–31.
140. Wax MB, Tezel G. Neurobiology of glaucomatous optic neuropathy. Mol Neurobiol. 2002;26(1):45–55.
141. Weinreb RN, Scassellati Sforzolini B, Vittitow J, Liebmann J. Latanoprostene Bunod 0.024% versus Timolol Maleate 0.5% in Subjects with Open-Angle Glaucoma or Ocular Hypertension: The APOLLO Study. Ophthalmol. 2016;123(5):965–73.
142. Wiggs JL, Yaspan BL, Hauser MA, Kang JH, Allingham RR, Olson LM, et al. Common variants at 9p21 and 8q22 are associated with increased susceptibility to optic nerve degeneration in glaucoma. PLoS Genet. 2012;8(4):e1002654.
143. Williams PA, Harder JM, Foxworth NE, Cardozo BH, Cochran KE, John SW. Nicotinamide and WLDS act together to prevent neurodegeneration in glaucoma. Front Neurosci. 2017;11:232.
144. Williams PA, Harder JM, John SW. Glaucoma as a Metabolic Optic Neuropathy: Making the Case for Nicotinamide Treatment in Glaucoma. J Glaucoma. 2017;26(12):1161–8.
145. Xu F, Zhang L, Li M. Plasma homocysteine, serum folic acid, serum vitamin B12, serum vitamin B6, MTHFR and risk of pseudoexfoliation glaucoma: a meta-analysis. Graefes Arch. Clin Exp Ophthalmol. 2012;250(7):1067–74.
146. Xu F, Zhao X, Zeng S-M, Li L, Zhong H-B, Homocysteine Li M, Vitamins B. Methylenetetrahydrofolate Reductase Gene, and Risk of Primary Open-Angle Glaucoma: A Meta-analysis. Ophthalmol. 2012;119(12):2493–9.
147. Xu H, Chen M, Forrester JV. Para-inflammation in the aging retina. Prog Retin Eye Res. 2009;28(5):348–68.
148. Xu P, Lin Y, Porter K, Liton PB. Ascorbic acid modulation of iron homeostasis and lysosomal function in trabecular meshwork cells. J Ocul Pharmacol Ther. 2014;30(2-3):246–53.
149. Xuan BO, Zhou Y-H, Li NA, Min Z-D, Chiou GCY. Effects of Crocin Analogs on Ocular Blood Flow and Retinal Function. J Ocul Pharmacol Ther. 1999;15(2):143–52.
150. Yamazaki Y, Hayamizu F, Tanaka C. Effects of long-term methylcobalamin treatment on the progression of visual field defects in normal-tension glaucoma. Curr Ther Res. 2000;61(7):443–51.
151. Yip JL, Foster PJ. Ethnic differences in primary angle-closure glaucoma. Curr Opin Ophthalmol. 2006;17(2):175–80.
152. Yue YK, Mo B, Zhao J, Yu YJ, Liu L, Yue CL, et al. Neuroprotective effect of curcumin against oxidative damage in BV-2 microglia and high intraocular pressure animal model. J Ocul Pharmacol Ther. 2014;30(8):657–64.