EXPERT VIEW/REVIEW PAPER

Lifestyle Modification as Complementary Medicine in Glaucoma Management

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Abstract

Glaucoma, a multifactorial disease, currently leads the causes of irreversible blindness globally, with complex underlying pathophysiology. For a long time, decreasing intraocular pressure (IOP) has remained the desired primary outcome for each modality of glaucoma management—medical, laser, or surgical. However, the understanding of non-IOP-dependent mechanisms and the identification of additional risk factors affecting optic nerve health have extended the range of preventive and therapeutic options for tackling glaucoma in a more holistic manner. Adopting a healthy lifestyle has been the key to managing all chronic diseases, especially cardiovascular disorders and diabetes, with proven benefits in significantly reducing their incidence and severity. Glaucoma is recognized as a chronic degenerative ailment of the second cranial nerve, and lately, there has been a tremendous upsurge in the subject to evaluate the potential role of lifestyle factors like diet, nutrition, exercises, sleep postures, and smoking in relation to the health of the optic nerve. Existing evidence suggests that some modifications in lifestyle have positive impact in preventing development and retarding its progression, although some findings are conflicting. This write-up aims to furnish a comprehensive overview of the same by analyzing existing evidence and summarizing the repercussions of different lifestyle factors—namely diet and nutritional supplements or exercises—on IOP or the perfusion pressure of the eye, which ultimately leads to retinal ganglion cell loss and optic neuropathy. Knowledge of their putative role as preventive or supportive medicine in glaucoma management can empower both patients and glaucoma specialists in mitigating the agony of the disease affecting the quality of life.

Keywords: Caffeine, Exercise, Glaucoma, Lifestyle changes, Nutrition.

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Glaucoma, with a prevalence of 76 million people worldwide in 2020, leads the list of irreversible blindness globally.[1] The burden of the disease is trending high, and by the end of 2040, it is projected to reach 118.8 million.[2] Being a multifactorial chronic neurodegenerative disease, it causes irreversible optic damage with a typical pattern of defects in the visual field map.[3] The main pathology involves the accelerated programmed demise of ganglion cell bodies along with their axons in the retina through multiple mechanisms, including oxidative stress, dysregulated blood supply, immune-inflammatory response, excitotoxicity, and mitochondrial impairment.[4] To date, a range of risk factors have been identified, including increased intraocular pressure (IOP), aging, positive ancestral history, epigenetic factors, and environmental influences. All conventional treatment measures primarily aim to lower eye pressure through various combinations of topical antiglaucoma drops, laser procedures, and surgical interventions since IOP is the only determinant that can be modified. However, there are situations where, despite lowering IOP, glaucoma progression continues.[5] Recent insights into the complex pathophysiology of glaucoma suggest the role of non-IOP-dependent factors, one of which is reduced ocular perfusion pressure (OPP). Reduced OPP contributes to the death of retinal ganglion cells (RGCs), astrocytes, and oligodendrocytes by initiating a vicious cascade of apoptosis.[6] This information has driven interest in exploring factors that affect IOP or OPP to be utilized as additional modalities, either as alternatives or complements to traditional glaucoma management. These include the development of novel pharmacological agents and the investigation of nonpharmacological approaches. Lifestyle modification or the adoption of healthy living practices forms the cornerstone of management protocols for addressing various chronic ailments, such as diabetes, hypertension, and cardiorespiratory diseases, with proven benefits. Glaucoma, as a chronic neurodegenerative disease of the eye, is no exception. In fact, the famous series of cross-sectional surveys conducted to assess the health and nutritional status of individuals—including children and adults—in the United States, known as the National Health and Nutrition Examination Survey (NHANES), concluded that health-conscious living, as indicated by good cardiac status, was associated with a reduced risk of ocular diseases, especially diabetic eye diseases.[7] These results promote the belief that measures to prevent cardiovascular diseases might also play a role in preventing ocular diseases. At present, there is growing interest in evaluating the potential role of lifestyle factors, such as diet, nutrition, exercise, sleep postures, and smoking, on the health of the optic nerve.[8]

While some reports suggest that certain lifestyle modifications positively impact retarding glaucoma development and progression, other findings remain conflicting. This article aims to

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provide an extensive insight into the existing evidence regarding the effects of different lifestyle factors—namely dietary habits, nutritional supplements, and exercises—on IOP or OPP, which ultimately lead to retinal ganglion cell loss and optic neuropathy. Knowledge of their potential role as preventive or supportive medicine in glaucoma management can empower both patients and glaucoma specialists in actively mitigating the agony of the disease.

Methods

A thorough review of the literature was conducted using PubMed, Google Scholar, and Scopus to identify relevant articles published with keywords such as glaucoma and lifestyle, diet, nutritional supplements, fatty acids, herbals, vitamins, minerals, ginkgo biloba, exercise, body mass index (BMI), weight loss, bariatric surgery, smoking, cigarette, marijuana, alcohol, swimming, sleep position, sleep pattern, physical activity, exercise IOP, diabetes, and hypertension. Additionally, the reference lists in the reviewed literature were examined, and relevant articles were retrieved. Publication year was not restricted, and relevant epidemiological studies and clinical trials published in English were included.

Diet and Glaucoma

The possible impact of diet or food on ocular health is supported by the prevalence of the gut-eye axis. Gong et al. have reported differences in the gut microbiome and serum metabolic composition between healthy individuals and glaucoma patients.[9] However, certain population-based clinicoepidemiological studies evaluating the effect of food intake on the likelihood of developing glaucoma are limited and contradictory. A reduction in the risk of high-pressure glaucoma was found by Hanyuda and colleagues in three cohort studies conducted in the United States (US) when carbohydrates were substituted with fats or protein derived from vegetable sources. However, the theoretical risk was not at all mitigated by an isolated low-carbohydrate diet.[10] A prospective study by Kang et al., analyzing the health status of medical professionals, reported that edibles with high nitrate content, such as green leafy vegetables, have the potential to lower the risk of POAG.[11] Cross-sectional studies in 584 otherwise healthy females or 1,155 elderly females with osteoporotic fractures concluded that a higher intake of fresh fruits, particularly citrus fruits, and fresh green vegetables containing significant amounts of vitamins may be protective and decrease the probability of developing glaucoma.[12,13] Yoserizal et al. have reported that high iron intake poses a potential danger for glaucoma.[14] Another study by Mylona et al. reported that the intake of pure fruit juice, a low-salt diet, and low-fat-content meat can be beneficial for glaucoma suspects and POAG patients.[15]

Open-angle glaucoma patients have reduced levels of omega-3 fatty acids in their blood, which are primarily alpha-linolenic acid derivatives, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). An individual-based observational study on 3,865 subjects by Wang et al. explored the role of polyunsaturated fatty acids (PUFAs), particularly long-chain omega-3 and omega-6 fatty acids, in the pathogenesis of glaucoma.[16] It was observed that higher daily consumption of EPA and DHA was beneficial, whereas a higher intake of total PUFAs further accentuated the risk of glaucoma. In general, promoting dietary intake of omega-3 and restricting total daily PUFA intake may be beneficial for glaucoma patients. The proposed hypothesis for this benefit is attributed to reduced oxidative stress and inflammation, along with increased antioxidant capacity and ocular blood flow, as observed by Romeo Villadóniga et al. and Harris et al., respectively (Table 1).[17,18]

The role of dietary supplements, such as a blend of vitamins, minerals, botanicals, herbs, extracts, concentrates, or other dietary constituents, has also been evaluated in glaucoma patients in a few population-based descriptive studies and small interventional studies. However, the results remain incoherent.

A randomized controlled trial by Mutolo et al. evaluating a concoction of forskolin, homotaurine, carnosine, B vitamins, and magnesium as a dietary supplement showed a significant reduction in IOP and an improvement in the amplitude of the pattern electroretinogram (PERG) and foveal sensitivity in POAG patients.[19] Similar observations were made by Sisto et al., where a mixture of forskolin extract, rutin, and vitamins B1 and B2 decreased IOP remarkably in the treatment group after 6 months.[20] On the other hand, Garcia-Medina reported no objective effect of treatment with antioxidant supplementation containing vitamins and minerals, with or without omega-3 fatty acids, on visual field indices such as mean deviation (MD), pattern standard deviation (PSD), retinal nerve fiber layer thickness (RNFL), and ganglion cell complex thickness.[21] A large clinico epidemiological study, the Rotterdam Study, recruiting 3,502 participants without glaucoma at baseline visual fields (VF), followed up for up to 9.7 years, concluded that decreased intake of retinol equivalents and vitamin B1, along with increased consumption of magnesium, was associated with an enhanced chance of developing OAG.[22] Another clinical trial conducted in 2012 found that the addition of a dietary supplement containing rutin and forskolin, as an adjunct to maximum topical antiglaucoma medication, resulted in an additional 10% reduction in IOP.[23]

There is abundant evidence suggesting that oxidative stress plays a crucial role in the development of various types of glaucoma. The association of serum vitamin A, C, and E levels, which have antioxidative properties, has also been investigated in population-based studies and small clinical trials, but the results are inconsistent. Yuki and coauthors found that normal-tension glaucoma patients had decreased serum levels of vitamin C, but the levels of uric acid were increased. Wang et al. noted that additional intake of vitamin C in the diet was associated with decreased relative odds for glaucoma; however, serum levels of vitamin C, A, and E did not correlate with the prevalence of glaucoma.[24,25] Similar observations were documented by Kang et al., evaluating the role of vitamins C, E, and A in any dose or duration, through a large prospective cohort study of 1,16,505 females.[26]

The vasoregulatory role of the antioxidant α-tocopherol was explored by Engin et al. in 30 glaucoma patients. Enhanced ocular blood flow was time- and dose-dependent, confirming the neuroprotective properties of α-tocopherol in addition to its antioxidant properties for protecting the retina from glaucomatous neuropathy. This supplementary effect of α-tocopherol on the retina was attributed to the protein kinase C pathway.[27] In contrast, no statistically significant effect on the success rate of trabeculectomy in POAG and pseudoexfoliation glaucoma was found when oral α-tocopherol was given postoperatively by Goldblum and co-workers.[28] Supplementation with nicotinamide in animal studies shows protection against glaucoma, but in humans, the relationship is yet to be explored. Some studies suggest that reduced utilization of retinol equivalents, vitamin B1, and increased consumption of magnesium may be precarious for OAG. Besides magnesium,

Table 1: Summary of association of nutrients and glaucoma

Authors	*Study population*	*Study design*	*Study object*	*Observation*
Kang et al.[11]	*n* = 1,04,987 subjects	Prospective cohort	Dietary nitrate (from green leafy vegetables)	Higher consumption of green leafy vegetables lowers the risk of glaucoma due to increased intake dietary nitrates
Giaconi et al.[12]	*n* = 584 (female subjects)	Cross-sectional	Fruits and vegetables (as source of dietary vitamins)	Increased incorporation of vegetables and fruits rich in vitamin A, vitamin C in diet decreases the chance of inflicting glaucoma
Coleman et al.[13]	*n* = 1,155 (female subjects)	Cross-sectional	Different fruits and vegetables	Higher intake citrus fruits and veggies (kale, carrots, and peaches) lowers the possibility while that of spinach or orange juice raises the risk of glaucoma
Yoserizal et al.[14]	*n* = 581 (61 patients with glaucoma)	Cross-sectional	Relationship between nutrients intake on glaucoma	Increased accrual of iron or lower input of vitamin A, and vegetable fat increases risk of glaucoma
Mylona et al.[15]	*n* = 200 (100 POAG case and 100 suspects, control)	Case–control	Dietary preferences	Consumption of pure fruit juice, cooked meat with less visible fat and modest salt consumption has protective effect on patients at danger or already suffering from POAG
Wang et al.[16]	*n* = 3,865 (participants in NHAN Survey conducted during 2005–2008)	Cross-sectional	Effect of daily intake of polyunsaturated fatty acid (PUFA)	Daily dietary consumption of Omega 3 FA like EPA and DHA lowers the likelihood of getting glaucoma while increased consumption of total PUFAs has higher probability of having glaucoma, which might be have resulted from different proportion of ω-6 and ω-3 fatty acids
Romeo Villadóniga et al.[17]	*n* = 47 (case 23, controls 24)	Open label randomized case-controlled trial	DHA (1 gm)	Antioxidant capacity in plasma increased remarkably, while plasma stress markers, malondialdehyde and plasma IL-6 levels were decreased to a significant level in DHA treated group. Also, there was significant reduction in IOP both eyes
Harris et al.[18]	*n* = 45 (OAG patients in 2 groups)	Randomized controlled trial, cross over study	A commercial preparation of antioxidants nutraceuticals (blend of essential minerals and vitamins, omega-3 PUFA, dietary polyphenolic nutrients, a modified essential amino acid, botanical extracts, and flax seed oil) vs placebo administration	Oral intake of antioxidant supplement increases biomarkers of ocular blood flow within retinal and retrobulbar vascular beds in patients with OAG
Mutolo et al.[19]	*n* = 22 (POAG patients with treatment and without treatment)	Randomized controlled trial	A commercial supplement (mixture of forskolin, homotaurine, carnosine, B1, B2 and B6 vitamins, magnesium) or without treatment	A significant reduction of IOP and refinement of PERG amplitude at 6, 9, and 12 months, and foveal sensitivity at 12 months in the treatment group was observed
Sisto et al.[20]	*n* = 45 patients	Open randomized case-control trial	A commercial product (mixture of forskolin extract, rutin and vitamins B1 and B2) one tablet, twice daily or control group	Significant reduction IOP in the treatment group after 6-month treatment to14.6 mm Hg ($p < 0.05$)

Contd…

Table 1: *Contd…*

Authors	*Study population*	*Study design*	*Study object*	*Observation*
Garcia-Medina et al.[21]	*n* = 117 (POAG patient in 3 groups, 2 group with different supplements and one group with no supplement)	Randomized controlled trial	Antioxidants supplementation with or without omega-3 fatty acids	Visual field indices (MD, PSD, RNFL, GCC) did not had significant difference between the three groups
Ramdas et al.[22]	3,502 adults (≥55 years)	Population-based prospective cohort	Dietary antioxidants and nutrients (carotenoids, vitamins, and flavonoids omega fatty acids and magnesium) for their effect on OAG	Risk of OAG increases with decreased intake of vitamin A and B1 and an increased uptake of magnesium
Vetrugno et al.[23]	*n* = 97 (52 case 45 control)	Open case–control trial	Treatment group were given 2 tablets per day of food supplement containing rutin and forskolin in addition to their usual topical drug treatment, control group continued only topical antiglaucoma drop	Additional 10% reduction in IOP and better control ($p < 0.01$) was obtained with oral administration of supplement in patient nonresponsive to conventional treatment
Yuki et al.[24]	*n* = 91 (47 case of normal-tension glaucoma patients, 44 controls)	Case–control study	Serum levels of vitamins A, B(9), C, E, and uric acid were measured	Serum levels of vitamin C was lower but level of serum uric acid was higher in cases as compared to controls
Wang et al.[25]	*n* = 2,912 participants (≥40 years)	Cross-sectional	Vitamins A, C, E intake and serum concentration	Vitamin C supplementation reduces danger of glaucoma
Kang et al.[26]	*n* = 1,16,505 (females, >40 years)	Prospective cohort with follow-up of average 9.3 years	Dietary antioxidant intake	Consumption of dietary carotenoids, vitamins C and E might reduce the probability of having of POAG glaucoma
Goldblum et al.[28]	*n* = 39 (posttrabeculectomy patients of POAG and PXF)	Randomized controlled trial	Oral consumption of 300 mg alpha tocopheryl acetate daily	No significant difference in the risk of failure or success rate of trabeculectomy and IOP control between the groups
Krefting et al.[31]	*n* = 78 individuals with low serum 25(OH)D	Randomized controlled trial	Capsules of vitamin D3 (20000 IU) biweekly	IOP wasn't affected by additional intake of vitamin D3 in subjects with low levels of 25(OH)D

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; PERG, pattern electroretinography; POAG, primary open angle glaucoma; PUFA, poly unsaturated fatty acid

some studies indicate an increased risk of glaucoma with raised levels of calcium, iron, and selenium due to increased oxidative stress.[29]

There is an increased incidence of glaucoma with an accelerated rate of progression in patients with neurodegenerative diseases such as Alzheimer's dementia, Parkinson's disease, depression, and schizophrenia.[30] Since vitamin D has been associated with such diseases, its role in IOP control has also been investigated. A small randomized controlled trial by Krefting et al. in healthy individuals found no correlation between serum 25-hydroxyvitamin D [25(OH)D] levels and IOP. Even supplementation of vitamin D3 to study patients with low levels of 25(OH)D did not influence IOP.[31] Hence, these findings discredit the contribution of vitamin D in IOP regulation.

There has been a meta-analysis of the available literature to quantify the role of different vitamins in glaucoma and to unravel the association between their serum levels and different types of glaucoma. It was concluded that while the consumption of vitamins A and C has a protective effect on OAG, irrespective of their serum concentration, there is no correlation between serum levels of vitamin B6, vitamin B12, or vitamin D with glaucoma.[32] In general, it has been found that dietary modifications recommended for good cardiovascular health, such as restricting saturated fats, salt, and sugar, are beneficial for ocular health as well. Oral DHA or omega-3 supplementation has been recommended as adjunctive therapy for IOP reduction in normal tension and pseudoexfoliation glaucoma patients.

Herbal Extracts and Glaucoma

Herbal medicines containing flavonoids and polyphenols, such as ginkgo biloba extracts (GBE), saffron, and anthocyanins, are increasingly being used in glaucoma patients. They have antioxidant and anti-inflammatory properties and act through multiple mechanisms—decreasing oxidative stress, enhancing blood flow, decreasing blood viscosity, and providing neuroprotection.[33] GBE is advocated as a natural remedial agent for glaucoma, particularly the non-IOP-dependent variety. While animal models have shown favorable outcomes in preventing RGC loss, human studies document conflicting results (Table 2).[34]

Table 2: Summary of association of herbal extracts and glaucoma

Authors	*Study population*	*Study design*	*Study object*	*Observation*
Quaranta et al.[35]	NTG (n = 27, with or without treatment)	Randomized controlled trial	Ginkgo biloba extract (GBE) 40 mg, 3 times/day vs placebo	VF indices improve significantly, however, IOP was not affected
Lee et al.[36]	NTG (n = 42, mean follow-up period 12.3 years	Cohort	GBE, 80 mg twice daily	Progression of VF damage was slowed down with GBE administration especially in the superior central field
Sari et al.[37]	POAG (n = 40)	Randomized controlled trial	40 mg GBE BD vs placebo	Significant improvement ($p < 0.05$) in oxidative stress markers like malondialdehyde, glutathione peroxidase), visual field MD, PSD as well as RNFL thickness at superior and inferior poles ($p = 0.001$ and $p = 0.035$ respectively) was achieved with GBE supplement as compared to no supplement group. IOP was not affected significantly in either group
Shim et al.[38]	NTG (n = 332) (in 3 groups—GBE, anthocyanins, or no medication	Case–control	Ginkgo biloba extract (80 mg BD) vs Vaccinium myrtillus antocyanosid extract (60 mg BD) vs no treatment	Improved visual function was observed in both anthocyanins and GBE
Chung et al.[39]	Healthy volunteers (n = 11)	Randomized controlled trial	Ginkgo biloba extract	GBE enhances velocity of ocular but did not affect the IOP
Park et al.[40]	NTG (n = 30)	Randomized controlled trial	Ginkgo biloba extract vs placebo	Mean blood flow, volume, and velocity increased at almost all points with GBE when compared to the placebo, but there was not any remarkable change in VF indices
Wimpissinger et al.[41]	Healthy volunteers (n = 15) in ginkgo group or placebo	Randomized controlled trial	Ginkgo biloba extract (240 mg)	Optic nerve head perfusion significantly enhanced (+ 17.29 ± 17.3%, with Ginkgo biloba vs baseline $p < 0.002$) but blood flow to retina did not differ in both groups
Guo et al.[42]	NTG (n = 35 in 2 groups: treated vs placebo)	Randomized controlled trial	Ginkgo biloba extract 40 mg or placebo	VF mean defect or contrast sensitivity remained unaffected
Bonyadi et al.[43]	POAG (n = 34 in 2 groups	Randomized controlled trial	Saffron extract 30 mg/day or placebo	A statistically significant IOP reduction was noted after 3 weeks with saffron extract supplement
Ohguro et al.[44]	NTG (n = 30) 6 months	Pilot uncontrolled study	Anthocyanins extract from black currant in tablet form once daily	Blood flow of the optic nerve head and adjacent retina increased significantly. IOP or visual field didn't change remarkably
Ohguro et al.[45]	21 glaucoma patients on single antiglaucoma medication	A placebo-controlled, double-masked, crossover study	Black currant anthocyanins (BCACs—50 mg/day) vs placebos administered orally for 4 weeks	Significant decrease in the mean IOP was observed at 2 weeks and 4 weeks in treatment group in contrast to placebo
Ohguro et al.[46]	OAG (n = 38, in 2 groups)	Randomized controlled trial	BCACs extract 50 mg/day vs placebo	Increased ocular blood flow was seen in treated group with less deterioration in VF mean deviation
Zhong et al.[48]	POAG (n = 40)	Randomized controlled trial	*Erigeron breviscapus* (Vant.) Hand-Mazz. (EBHM), a Chinese herbal drug	Mean deviation and mean sensitivity improved significantly in general in the entire group with supplement at 6 months, while in patients of moderate and late glaucoma the decrease in mean deviation was evident at 2 months, in contrast to the placebo. visual acuity, IOP, cup-to-disk ratio remained unaffected.

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Table 2: *Contd…*

Authors	*Study population*	*Study design*	*Study object*	*Observation*
Ning-Li et al.[49]	Posttrabeculectomy POAG or chronic angle-closure glaucoma (*n* = 99)	Randomized controlled trial	EBHM vs placebo	Visual fields indices in improved significantly with treatment as compared to the placebo group at 2, 4, and 6 months. IOP and visual acuity did not change significantly in either group
Falsini et al.[50]	OAG and ocular hypertension (OHT) *n* = 18 each group	Randomized controlled trial	Epigallocatechin gallate	PERG significantly improved in OAG patients after treatment or placebo as compared to baseline ($p < 0.05$). No change in visual fields was noticed
Steigerwalt et al.[51]	OHT (*n* = 38, 20 treatment group, 18 no treatment group)	Randomized controlled trial	A supplement Mirtogenol® (40 mg French maritime pine bark extract, and 80 mg of standardized bilberry extract) twice daily or no treatment	Treatment group had increased arterial flow velocity and reduction in IOP at 3 months which was statistically significant as compared to the baseline as well as the control group values ($p < 0.05$)
Kim et al.[52]	OAG (*n* = 36 12 weeks treatment + 8 weeks washout + 12 weeks placebo and vice versa in two groups	Randomized controlled trial	1.5 gm Korean Red Ginseng, (Ginsenoside)	Blood flow around the optic nerve head in the temporal region significantly improved ($p = 0.005$) during treatment phases when compared to baseline but no change during placebo phases. IOP and VF indices remained unaffected
Pescosolido et al.[53]	Hypertensive POAG (*n* = 10) despite multiple antiglaucoma medication	Pilot prospective study	Agomelatine (25 mg/day)	The systemic agomelatine consumption fetched 30% reduction IOP in both eyes of all POAG patients ($p < 0.001$)
Ozates et al.[55]	Pseudoexfoliation glaucoma (*n* = 64 eyes of 64 patients)	Prospective, randomized clinical study	The pseudo-exfoliative glaucoma + Coqun group received topical Coqun (100 mg CQ10, 500 mg vitamin E twice daily for 1 month while the pseudo-exfoliative glaucoma group consisted of pseudo-exfoliative glaucoma cases who had not taken Coqun Aqueous humor tapping was done intraoperatively while cataract extraction	Level of superoxide dismutase in aqueous was notably higher in the isolated pseudo-exfoliative glaucoma group than that with Coqun or pseudoexfoliation syndrome groups

A few randomized controlled trials evaluating GBE in POAG and NTG reported refinements in visual field indices in patients receiving GBE that were statistically significant compared to the placebo group, although IOP lowering remained unaffected.[35–38] Some clinical trials reported that GBE enhances peripapillary blood flow significantly in normal tension glaucoma patients compared to the placebo.[39–41] Contrarily, Guo and colleagues reported no such beneficial effect either in visual field indices or in contrast sensitivity in GBE-treated groups compared to the placebo.[42] Besides GBE, other herbal extracts containing different kinds of flavones and flavonoids, such as saffron extract, *Erigeron breviscapus* (Vant.) Hand-Mazz. (EBHM), anthocyanins, epigallocatechin gallate (EGCG), and red ginseng, have also been investigated. Bonyadi et al. investigated the additional pressure-lowering effects of saffron extracts in open angle glaucoma patients under treatment with timolol and dorzolamide eye drops. Further reduction in IOP was documented after 3 weeks of therapy with oral saffron extract.[43] Anthocyanins, a type of polyphenols present profusely in druplets such as black currant, have antioxidant and anti-inflammatory effects. They increase ocular blood flow to the nervus opticus without affecting the IOP.[44,45] A randomized, placebo-controlled trial by Ohguro and coworkers demonstrated a decreased mean deviation in visual field tests and enhanced ocular blood flow in OAG patients with black currant anthocyanin (BCAC) supplement compared to placebo-treated ones, but there was no change in IOP.[46] A meta-analysis investigating various flavonoid supplements in glaucoma or ocular hypertension patients has established the role of these agents in retarding visual field loss progression and improving ocular blood flow.[47] A Chinese herb, *Erigeron breviscapus* (Vant.) Hand-Mazz. (EBHM), improved scoring of visual field indices in the treatment group considerably compared to the placebo but had no effect on IOP, visual acuity, or cup–disk ratio.[48] Mutolo and coworkers investigated forskolin, a natural compound that decreases IOP by reducing the production of aqueous in animals. Gangliolife, a food supplement comprising mainly of forskolin, homotaurine, and l-carnosine, offered advantageous repercussions on different ocular indices and affirmed neuroactivity in RGC of POAG patients. It was noticed that this supplement refined the amplitude of pattern electroretinography (PERG) and enhanced the sensitivity of the fovea in patients receiving treatment.[19] Similar changes in PERG were recorded with epigallocatechin gallate (EGCG), a green tea component and catechin-based flavonoid, but visual fields were not affected.[50] Kronek, a product of forskolin and rutin, produced an improvement in the amplitude of the electroretinogram in POAG patients after supplementation for about 6 months, indicating the possibility of a neuroprotective effect of the combination of these molecules.[20] Mirtogenol, a combination of bilberry extract and pine bark, consumed for 6 months, reduced IOP and facilitated ocular blood flow compared to the control.[51] Ginsenoside, Korean red ginseng, significantly improved ocular blood flow in POAG in a clinical trial.[52] Agomelatine, an atypical antidepressant and melatonin agonist, has antiapoptotic and antioxidant properties and can cause an additional 30% reduction in IOP when consumed in a dose of 25 mg/day in POAG patients under medical treatment.[53] A mitochondrially targeted antioxidant, topical coenzyme Q10 (CoQ10), has been proven to prevent programmed cell death of RGC in animal models.[54] The outcome of topical CoQ10 therapy along with vitamin (CoQun) was investigated in cases of POAG and pseudoexfoliation glaucoma, and its beneficial effect on RGC's visual function has been reported. There were also significantly lower oxidative stress markers like malondialdehyde and superoxide dismutase levels in the treatment group.[55,56] Table 2 provides a summary of different herbal extracts investigated for their association with glaucoma.

Exercise and Glaucoma

Exercises, in general, contribute substantially to the physical and mental well-being of an individual. Their role has previously been studied in different systemic and ocular conditions. The influence of physical activities on ocular blood flow, IOP, neuroprotection, and mental well-being in different subsets of glaucoma patients has been extensively investigated in recent years.[57] A decrease in IOP (0.56–5.6 mm Hg) has been reported after some dynamic exercises like walking, jogging, cycling, and stepping. However, the impact of isometric exercises, such as weight-bearing and hand-gripping, on ocular pressure is contentious.[58] Castejon et al. documented a rise in IOP after isometric exercises in both animal and human studies, while Vieira et al. attributed this IOP elevation to the raised episcleral venous pressure secondary to the associated Valsalva maneuver.[59,60] Avoidance of the Valsalva maneuver could partly relieve the raised IOP. In fact, IOP was not affected at all in isometric activities when the Valsalva maneuver was avoided.[61]

IOP reduction after dynamic exercise is more profound in eyes with myopia compared to emmetropic ones, and the magnitude of reduction increases with the severity of exercise but is not affected by the duration.[62] A meta-analysis by Roddy et al. reported almost double the IOP reduction after physical exercise in sedentary persons compared to their active counterparts.[63] Interestingly, in 1995, Qureshi concluded that the IOP reduction secondary to the severity and time span of exercise could be more notable in virgin eyes of glaucoma patients—those not on any treatment—compared to normal subjects.[64] Recently, a study by Yokota et al. in 2016 reported that the average IOP reduction in open-angle glaucoma cases who habitually worked out for an average of half an hour per week was 1.5 mm Hg lower than their counterparts.[65] The exact mechanism resulting in transient IOP reduction postexercise remains uncertain; however, it has been postulated to be secondary to the release of nitric oxide, transferring the blood flow to the muscles, and an increase in blood lactate, decreasing the blood pH.[66]

Certain forms of glaucoma, like pigment dispersion glaucoma (PDG), behave differently and report remarkable IOP elevation due to enhanced pigment release after vigorous exercise.[67] Likewise, certain types of dynamic exercise, like swimming with goggles, scuba diving, and bungee jumping, can cause visual impairment and visual field defects, either due to raised IOP or ocular barotrauma, especially in glaucoma patients.[68–70]

Besides variably affecting IOP, physical exercise, both isometric and dynamic, remarkably increases the OPP due to the phenomenon of autoregulation, a complex interplay between OPP and OBF at the central retina of the eye.[71]

Neuroprotection from exercise has been found in various degenerative diseases of the retina in animal models, although the category and way of exercise were incompatible and unrivaled. Possible underlying mechanisms incorporate boosting neurotrophin expression, such as brain-derived neurotrophic factor (BDNF), potentiating mitochondrial function, and decreasing inflammation.[72]

Yoga, Meditation, and Glaucoma

Yoga and meditation, an emerging treatment modality worldwide, are often practiced together with great enthusiasm and anticipation as viable supplements to conventional medical management for various ailments.[73] Certain yogasanas that require body inversion were found to have severe consequences on IOP. Common head-down yoga positions, namely Adho Mukha Svanasana, Uttanasana, Halasana, and Viparita Karani, may cause a rise in IOP in 16% to 70% of subjects.[74,75] In an observational study by Morya et al., Bhastrika Pranayama and control of breathing exercises (Pranayama) for 5 minutes/day, 5 days per week for 12 weeks, can lead to a significant increase in IOP in healthy volunteers, while Surya Namaskar, Kapalabhati Pranayama, Anulom Vilom, Adho Mukha Svanasana, Viparita Karani, and deep meditation showed a significant reduction in IOP at each follow-up.[76] However, the effect is temporary, but this transient IOP elevation can contribute to the disease worsening in confirmed patients with glaucoma, especially in the advanced stage. Since some yoga-based practices could reduce intraocular pressure and further damage, while some can have significant adverse effects, also, some yogasanas have contradictory effects in different studies, hence lack reliable justification to incorporate them into the armamentarium of patients with glaucoma. A meta-analysis of published clinical trials (including case reports) with yogasanas as interventions in glaucoma patients was done to statistically review the effects of various yoga practices on intraocular pressure by Chetry et al. It was evident that Jyoti-tratak (gazing steadily at a point or candle flame) and slow yoga breathing exercises like Nadishodhana or Anuloma Vilom or Pranayama/alternate nostril yoga breathing, diaphragmatic breathing, and meditation reduce intraocular pressure, while head-down yoga postures cause a rapid increase in intraocular pressure.[77]

Head-down positions increase intracranial pressure, which in turn affects the choroidal vessels draining into the superior ophthalmic vein and cavernous sinus intracranially.[78] Hence, these head-down postures act as a threat for the progression of glaucoma and should definitely be averted in patients suffering from or at high risk of glaucoma.

Meditation, a practice of "quieting" the mind by focusing on breathing, mantra, or sound, has also been investigated for its effect on glaucoma in recent years. It has been called a polypill in the comprehensive management of glaucoma that decreases IOP by multiple mechanisms, like increasing melatonin and its analogues, nitric oxide, augmenting blood flow and brain oxygenation, lowering oxidative stress, decreasing serum cortisol and cerebral glutamate, and decreasing inflammation, thereby preventing glaucoma progression and enhancing quality of life.[79] In a randomized controlled trial in 90 POAG patients by Dada et al., meditation for an hour over 21 days had a significant lowering of IOP as compared with controls, and the reduction was directly correlated with a decrease in stress-related serum biomarkers like cortisol, β, IL-6, TNF-α, reactive oxygen species (ROS), and positively modifying gene expression in serum as well.[80] Hence, mindfulness meditation can be recommended as adjunctive therapy for POAG. However, its acceptance and adherence worldwide can have barriers driven by attitudes and cultural background.[81]

Mental Health in Glaucoma and Exercise

The role of different workouts in the mental well-being of a person has been extensively researched. Increased physical activity is directly associated with a decrease in mood disorders, as reported by De Moor et al.[82] The pervasiveness of mental illness, like depression or anxiety, in patients with glaucoma is as high as 30–60%, which not only affects subjective well-being but promotes disease pathogenesis.[83] Mental strain was found to induce insomnia and a rise in IOP significantly, as reported by Marc and Stan.[84] Surprisingly, the use of drugs belonging to the sedative-hypnotic group, such as zolpidem, contributed to further peril in the risk of glaucoma development. Contrary to this, mindful meditation reduces stress, decreases IOP, and promotes ocular health.[85]

In conclusion, besides averting RGC loss by virtue of IOP management and enhancing ocular blood flow, physical workout may be advantageous in improving the general well-being of patients suffering from glaucoma, and hence their plenitude.

Obesity and Glaucoma

In general, obesity has been enmeshed with raised IOP, but Lin et al. have reported an association of lower BMI, particularly in middle-aged women, with an increased incidence of normal pressure glaucoma.[86] It has been observed that females with lower BMI incurred more paracentral visual disorders in comparison to females with greater BMI.[87] The consequences of rapid weight reduction, especially *via* surgical procedures like bariatric surgery, on IOP have been investigated in some studies. Lam and coworkers described that a decrease of 10 units in BMI is equivalent to a reduction in IOP by a 2.4 mm Hg fall.[88]

Caffeine, Alcohol, Smoking, and Glaucoma

Caffeine, a widely consumed product in different beverages as a ubiquitous ingredient, is basically a methylxanthine alkaloid. It has been acclaimed to cause a temporary spike in IOP and OPP in healthy subjects as well as in patients with OHT, NTG, POAG, and exfoliation, as summarized in Table 3.[89–95]

Table 3: Summary of association of caffeine and glaucoma

Authors	*Study population*	*Study design*	*Study object*	*Observation*
Avisar et al.[89]	OHT (22) and NTG (6) patients	Randomized controlled trial	Effect of caffeinated and decaffeinated coffee at intervals of 30, 60, and 90 minutes after ingestion	Significant rise in intraocular pressure after 60 and 90 minutes was noted in both groups with ingestion of regular caffeinated coffee
Ajayi et al.[90]	40 healthy subjects	Randomized controlled trial	400 mg of coffee in 100 mL	A 4 mm Hg elevation in IOP ($p < 0.05$) was recorded after ingestion of caffeinated coffee
Jiwani et al.[91]	POAG ($n = 22$), NTG ($n = 18$), OHT ($n = 20$), glaucoma suspect ($n = 21$), and healthy individuals ($n = 25$)	Randomized control trial	Caffeinated (182 mg) vs decaffeinated (4 mg) coffee	Consumption of one cup of caffeinated coffee (182 mg caffeine) statistically increases IOP and OPP, but insufficient to produce an overall clinical impact after pooling all category
Vera et al.[92]	40 healthy individuals ($n = 21$ low caffeine consumer) and $n = 19$ high caffeine consumers as per their daily caffeine consumption	Placebo-controlled, double-blind, and balanced crossover study	Caffeine (4 mg/kg) or placebo. IOP and OPP were measured at an interval of 30 minutes after ingesting caffeine or placebo	Caffeine intake causes transient the IOP rise ($p < 0.001$) in caffeine group but the amount of IOP rise was less in high-caffeine consumers suggesting tolerance to caffeine as the factor guiding IOP spike
Wu et al.[93]	1,678 survey subjects	Cross-sectional study	Caffeinated and decaffeinated beverages (hot tea, coffee, soft drinks, ice tea)	While the consumption of coffee, cold or decaffeinated tea and soft drinks had no significant associations with glaucoma, hot tea consumers had lower risk of glaucoma compared to the nonconsumers
Pasquale et al.[94]	1,20,179 subjects, >40 years (78,977 women 41,202 men)	Prospective cohort	Risk of developing exfoliation glaucoma or exfoliation glaucoma suspect (EG/EGS) with consumption of caffeine or any caffeinated beverage	A positive correlation between coffee intake and increased risk of developing exfoliation glaucoma/exfoliation glaucoma suspect noted
Chandrasekaran et al.[95]	3,654 subjects	Cross-sectional	Daily intake of tea and coffee (average)	Open-angle glaucoma case had direct correlation between coffee consumption and IOP (more is the caffeine intake, higher is the intraocular pressure

A meta-analysis of available literature suggests a variable effect of caffeine on IOP and OPP in different sets of individuals. It was found that in nonglaucomatous subjects, IOP does not change with caffeine ingestion, while known cases of glaucoma or raised IOP responded with a significant rise in IOP.[96] However, more illustrious clinical trials are needed to certify this. This effect is basically attributed to raised levels of cAMP intracellularly and increased hydrostatic pressure, which leads to overproduction of aqueous humor. Further, raised cyclic AMP results in decreased outflow due to relaxation of smooth muscle tone.[97]

The effect of alcohol intake on glaucomatous optic neuropathy is not yet clear. A few studies show no alliance between the two, while some cohort studies do report a definite correlation between the consumption of alcohol and a rise in IOP. Such heterogeneous responses have been accredited to individual variation in alcohol metabolism, which can modify the IOP measurement.[98]

Tobacco consumption, in general, is potentially detrimental to health. While nicotine potentially enhances blood circulation in general, its consequence on optic nerve head perfusion remains conflicting. Some research has reported a neuroprotective effect of nicotine on the retina, ameliorating excitotoxicity induced by glutamate in RGCs.[99] Alternatively, it has vasospastic properties that may result in reduced blood flow and glaucomatous nerve damage. The difference in results can be attributed to the multitudinous mechanisms of action of nicotine. Variation in IOP recording has been explained as a corollary of the type and route of administration of cannabis.[100]

Sleep Posture and Glaucoma

Sleep position has been suspected to influence the value of intraocular pressure (IOP) in addition to ocular perfusion pressure (OPP). Lee et al. investigated the changing value of IOP with different positions of the head and body in normal individuals while sleeping and reported a relative elevation of the marks in the supine position in comparison to that in the sitting position.[101] Changing posture to the lateral decubitus position increases the IOP on the dependent side while OPP remains unaltered. On the other hand, slight elevation of the head in the supine position decreases the IOP.[102] Both sideways and prone sleeping positions result in a considerable rise in IOP in both eyes, irrespective of the dependency status, in some special conditions like pigment dispersion glaucoma. A bed-head elevation of 30° or use of customized pillows has been suggested to avert IOP spikes while sleeping.[103]

Smart Phones and Glaucoma

Smartphone devices nowadays have become an integral part of our lives. Reading and writing on smartphones can cause a significant increase in IOP, especially under low-light conditions.[104] The exact pathophysiology for these changes is not known; however, the phenomena of convergence and accommodation owing to the contraction of extraocular muscles (EOM) have been acclaimed for this change. In addition to this mechanism, psychophysiological stress, associated dry eye, and neck-flexion posture with the use of smartphones also contribute to the rise in IOP.[105]

Conclusion

Certain modifications in our daily lifestyle do seem to have therapeutic potential on the health of our optic nerve (Table 4).

Table 4: Summary of lifestyle factors and their effect on glaucoma

	Increased risk	*Beneficial*
Diet	Increased intake of iron, calcium, magnesium, and selenium	Low carbohydrate Low salt Low saturated fat (EPA and DHA), vit A, C, B1, and E Green leafy vegetables
Herbal extracts		Ginkgo biloba, saffron extract, anthocyanins
Exercise	Excessive exercise Swimming with goggles Scuba diving Bunjee jumping Head stand/head down yogasanas (Sirsasanas, Uttanasana, Adho Mukha Svanasana, Halasana, and Viparita Karani)	Aerobic exercise Brisk walking Treadmill Mindful meditation
BMI	High BMI, low BMI	BMI within a normal range
Caffeine	Increased intake of caffeine	
Smoking	Cigarette smoking	
Sleep posture	Lateral decubitus and prone	Bed head end elevation of 30°
Electronic gadgets	Using mobile, laptop in low illumination	

The underlying mechanism can work either independently as a preventive measure in glaucoma suspects or as a complementary therapy to IOP-based treatments in confirmed cases of glaucoma. Lifestyle measures include physical activity, exercises, eating habits, sleep postures, and even addictions to smoking, alcohol, or use of electronic gadgets. Some practices, like preferring a diet high in antioxidants but low in carbohydrates and saturated fat, taking a magnesium supplement, doing aerobic exercise, mindful meditation, avoiding cigarette smoking, alcohol, excess caffeine, and head-down yoga positions, might have a protective effect on the retinal ganglion cells in subjects with glaucoma. However, the current weight of evidence is insufficient to formulate any definite guidelines since most of the studies are qualitative with subjective functional outcomes. There is a dearth of analysis of structural markers, such as measuring the nerve fiber layer in the retina and morphometry of optic nerve head parameters with reproducible imaging modalities like optical coherence tomography (OCT), which can produce more measurable data compared to the functional outcomes in the published studies. Inferences drawn from various epidemiological and clinical studies need to be further explored and validated with well-structured clinical trials and meta-analyses for making strong recommendations. Having knowledge about such beneficial lifestyle factors can definitely make the patient feel empowered and improve their quality of life substantially.

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