Graefes Arch Clin Exp Ophthalmol (2017) 255:789–796
DOI 10.1007/s00417-016-3518-4

GLAUCOMA

Modifiable factors in the management of glaucoma: a systematic review of current evidence

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Received: 19 August 2016 / Revised: 27 September 2016 / Accepted: 3 October 2016 / Published online: 14 October 2016

Abstract
Purpose Primary open angle glaucoma is a chronic optic neuropathy affecting millions of people worldwide and represents a major public health issue. Environmental factors, behaviors, and diet are intimately related to patient health and may play a role in the pathogenesis and progression of glaucoma. This study aims to review the literature, focusing on the last three years, regarding modifiable lifestyle interventions in the management of primary open angle glaucoma.
Methods Electronic databases were searched for studies published between January 2013 and July 2016 on the topic of lifestyle interventions in primary open angle glaucoma.
Results Sleeping with the head elevated and avoiding the worst eye-dependent side during sleep may slightly lower intraocular pressure and reduce visual field loss. Some food supplements and moderate aerobic exercise may also reduce intraocular pressure up to 2.0 and 3.0 mmHg, respectively. Frequency of coffee intake may be associated with disease progression. Potential negative effects are associated with weight-lifting and yoga exercises.
Conclusions Certain lifestyle habits could influence glaucoma progression, yet no specific interventions are currently supported by robust evidence. Awareness of the possible influences of certain habits should help guide clinical advice and is important to help patients avoid adverse outcomes and take an active role in the management of their disease.

Keywords Glaucoma · Diet · Exercise · Caffeine · Sleeping position

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Introduction

Primary open angle glaucoma (POAG) is a chronic optic neuropathy affecting approximately 2 % of adults above the age of 70 years [1]. It is one of the leading causes of blindness worldwide and represents a major public health issue.

There is growing awareness that environmental factors, behaviors, and diet are intimately related to patient health and may play a role in the pathogenesis and progression of glaucoma. Evidence from recent years has shown that some behaviors and environmental factors can affect the intraocular pressure (IOP), the primary risk factor for POAG [2–5].

Patients are interested more than ever in conducting a healthy lifestyle and taking an active role in the management of their ailments. Many seek lifestyle, diet, and other advice from their doctor and other sources. Medical information is readily available on the internet with variable quality, and many POAG patients implement it in their daily lives [6]. It is important, therefore, to be aware of the evidence and potential risks involved in various lifestyle and diet recommendations concerning POAG patients.

The amount of medical literature on the subject of modifiable lifestyle interventions (MLS) in the management of POAG is growing steadily with new aspects explored in the last few years. The conclusions are not always clear and sometimes even contradictory. Several reviews have been published on this subject, the latest by Welte et al. in 2016 published in German, which focuses mainly on alternative

medicine for POAG [7]. The most recent English review has been published by Bhartiya in 2014, which also focuses on alternative medicine and only to a lesser extent on lifestyle modifications [8]. Other reviews evaluate the effects of MLS on the risk of developing glaucoma in healthy subjects [9, 10].

As of yet, there are no guidelines available about what lifestyle advice should be offered to POAG patients, if any. This article aims to review the literature regarding MLS in the management of POAG patients focusing on the last 3 years.

Materials and methods

Literature searches

A systematic search was conducted using Cochrane Library and MEDLINE, PubMed, ClinicalTrials.gov, metaRegister of Controlled Trials (www.controlled-trials.com), WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/search/en) and Google Scholar with the following keywords: glaucoma, POAG, diet, supplement, extract, coffee, caffeine, alcohol, exercise, weight-lifting, yoga, valsalva, sleep, position, supine, complementary, CAM, marijuana, smoking, tobacco, and lifestyle. Additional records were identified by hand-searching bibliographies of relevant studies.

Eligibility criteria

The aim of this review was to identify studies which relate to effects of different MLS interventions on patients affected by POAG. We included studies meeting the following criteria: 1. The study population included a POAG patient group. 2. Studies examining any objective outcome measure relating to POAG (e.g., IOP, visual field (VF) changes, pattern electroretinogram amplitude, or foveal sensitivity). 3. Examining any MLS such as diet change, food supplements, sleeping position, caffeine intake, physical activities. 4. Written in English. 5. Full publications (not an abstract or letter to the editor). 6. Published between 2013 and 2016. Our exclusion criteria were 1. Studies focused on incidence or prevalence in healthy populations 2. Studies performed on animals, cadavers, healthy subjects, or those affected by conditions other than POAG. 3. Case reports and non-empirical opinion articles were also excluded.

Screening and synthesis

The review process was conducted under the guidance of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria to support reporting [11]. Two reviewers (IH, AA) independently conducted the search for relevant publications. Selected publications were then approved by a senior investigator (ZB). Individual studies were graded using the Scottish Intercollegiate Guideline Network (SIGN) assessment system for individual studies as implemented for Preferred Practice Patterns by the American Academy of Ophthalmology [12]. Figure 1 shows a flow diagram of the inclusion process.

Results

Data was extracted from 12 publications that met our criteria. Most were cross-sectional or retrospective in nature, and four were randomized controlled trials. Table 1 shows a summary of the studies. Table 2 presents a comparison of the recent evidence to previous evidence with clinical correlations.

Diet

Previous studies have shown that higher intake of fruit, especially fresh oranges and peaches, may be associated with decreased odds of glaucoma in healthy subjects [13]. Vegetables such as fresh carrots, green collards, kale, and iceberg or romaine lettuce may also be associated with a decreased risk of glaucoma in some populations [14, 15]. One study showed that dietary supplementation with oxidants such as iron and calcium may increase the risk of glaucoma [16].

Three randomized controlled studies published in recent years explored different food supplementation options in the management of POAG.

A study focusing on dietary supplementation was recently published by Mutolo et al. [2]. Twenty-two POAG patients were randomized into a control group and a food supplement group which was given two tablets a day containing homotaurine, coleus forskohlii root extract, l-carnosine, folic acid, vitamins B1, B2, B6, and magnesium. The groups were then followed for one year. The treatment group showed a progressive decrease of IOP peaking at about 2 mmHg after 12 months, while the control group showed no significant reductions ($P < 0.01$). Furthermore, a significant improvement of pattern electroretinogram amplitude (2.9 μV, $P < 0.01$) and foveal sensitivity (4.8 dB, $P < 0.05$) was observed in treated patients, but not in controls.

Another study conducted by Garcia-Medina et al. showed less promising results [17]. One hundred and seventeen POAG patients were randomized into a control group and two treatment groups who were given slightly dissimilar tablets once a day, containing a combination of vitamins, lutein, zinc, copper, magnesium selenium, and ω-3 fatty acids. Patients were then examined every 6 months for a period of 2 years. No significant difference was found between the groups in any of the outcome measures which included visual field examinations and optical coherence tomography scans.

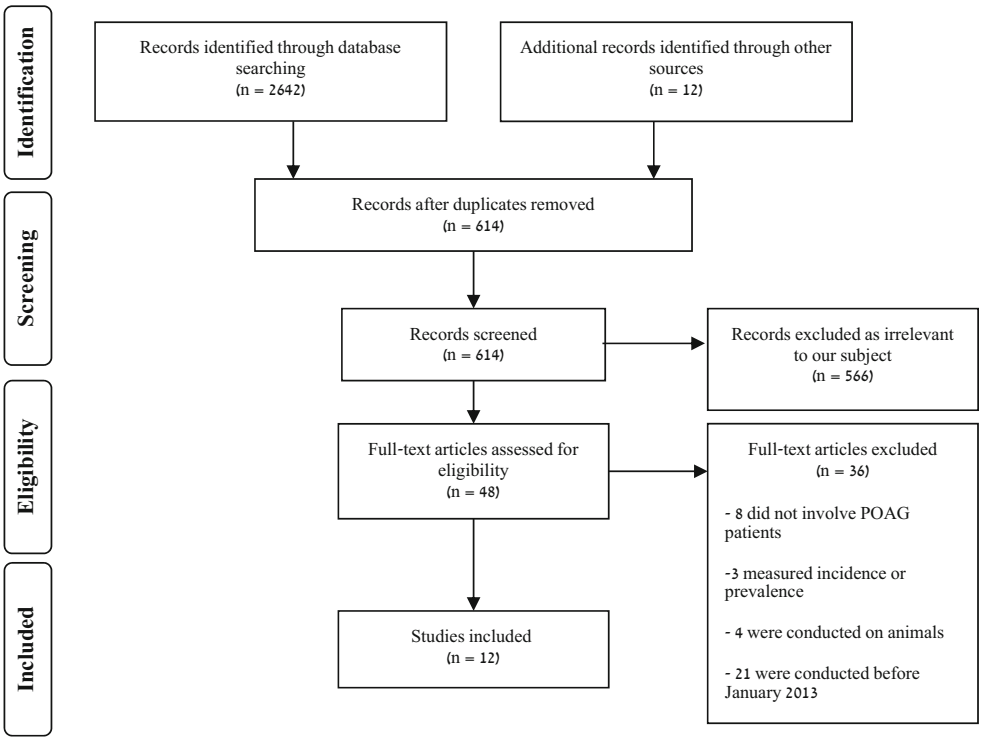

Fig. 1 Flow diagram of inclusion process based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]

Finally, in 2014 Bonyadi et al. published a study focusing on the effect of saffron [18]. Thirty-four POAG patients were randomized into a control group, who were given a placebo, and a treatment group, given oral aqueous saffron extract for 1 month, both groups were then followed for an additional month. The treatment group showed a significant decrease of IOP relative to the control group (saffron: from 12.9 ± 3.7 to 10.6 ± 3.0 mmHg vs. control: from 14.0 ± 2.5 to 13.8 ± 2.2 mmHg; $P = 0.001$) with IOP values returning to normal once the treatment was discontinued.

Sleeping position

The way glaucoma patients sleep may also influence IOP. It has been demonstrated that IOP is higher at night when patients are asleep and in the supine position [19]. The extent of IOP increase may be mitigated by sleeping with a slight head elevation [20]. In recent years several groups investigated the significance of specific sleeping positions relative to others.

A retrospective study on 692 POAG patients was conducted by Kim et al. in 2014, investigating the relationship between preferred sleeping position and VF loss [21]. In a questionnaire survey approximately a third of patients preferred a lateral sleeping position; 66–72 % of those habitually sleep on the worse eye-dependent side.

Lee et al. demonstrated a significant increase in IOP (1.3 ± 0.99, $P < 0.001$) of the dependent eye relative to the non-dependent eye of 20 POAG patients after five minutes in a lateral position, regardless of the eye in which the glaucoma was worse or the head elevation [22].

These results seem somewhat at odds with the work of Kaplowitz et al. who examined sleep behavior of POAG patients using sleep laboratory videos, surveys, and home recordings of 261 POAG patients in total [23]. The authors have found that a lateral sleeping position was preferred by most POAG patients and that surprisingly the non-dependent eye was the one correlated with a worse VF loss ($P = 0.002$). The authors speculate that this may be a result of reduced perfusion in the non-dependent eyes.

Flatau et al. explored the possibility that IOP elevation is influenced by mechanical force created by the pillow on the eye [24]. They examined the eyes of 22 glaucoma patients and 11 controls in the "face down" sleeping position. The IOP of the glaucoma patients was increased by an equivalent of 2.5 ± 1.1 mmHg in the "face down" position ($P = 0.03$), however, was unchanged in the controls ($P = 0.33$).

Exploring the effect of head elevation, Lazzaro et al. examined 30 patients in a sleep laboratory, half of which had glaucoma [3]. On two separate nights they slept either lying flat or lying on a wedge pillow at a 20-degree head elevation. They measured IOP before and during the night at 2-h intervals. Patients sleeping with a head elevation demonstrated a lesser elevation of IOP throughout the night (1.51 mmHg) compared with those sleeping supine (supine: 16.02 ± 1.65 vs. head-elevation: 14.5 ± 1.36; $P < 0.001$). These results are in line with previous studies on the subject.

Table 1 Summary of studies

Category	Study [Ref]	Year	Design	Topic	Number of Patients (Allocation)	Follow-up	Results	Strength of Evidence[a]
Diet	Mutolo et al. [2]	2016	Open-label, prospective, randomized controlled trial	Food supplements containing folic acid, magnesium, vitamins B1, B2, B6, and natural extracts	22 (11 in each group)	12 months	Progressive decrease of IOP up to 1.9 mmHg and significant improvement of PERG amplitude and foveal sensitivity in the treatment group	I-
	Garcia-Medina et al. [17]	2015	Open-label, prospective, randomized controlled trial	Food supplements containing magnesium, vitamins, lutein, zinc, copper and selenium	117 (54 in treatment group, 63 in control group)	24 months	No significant difference	I-
	Bonyadi et al. [18]	2014	Prospective, double-blind, randomized controlled trial	Oral saffron extract	34 (17 in each group)	1 month	Significant decrease of IOP up to 2.3 mmHg in the treatment group	I+
Sleeping Position	Kim et al. [21]	2014	Retrospective, cross-sectional study	Preferred sleeping position	692	None	Preferred lateral decubitus sleeping side was associated with worse affected eye	II-
	Lee et al. [22]	2015	Comparative case series	Different head positions	20	None	IOP was higher (1.3 ± 0.99) in the dependent eyes in the lateral decubitus position	III
	Kaplowitz et al. [23]	2015	Retrospective study	Sleep behavior	261	None	Right-sided sleeping position was correlated with a worse left sided VF loss	II-
	Flatau et al. [24]	2016	Comparative case series	Eye contact with pillow	33	None	IOP was higher (2.5 ± 1.1) in a "face down" position	III
	Lazzaro et al. [3]	2014	Comparative case series	20° head elevation	30	None	IOP was 1.51 mmHg lower with a head elevation compared with a supine position	III
	Park et al. [25]	2016	Comparative case series	Different methods of head elevation	71	None	Bed head angle elevation reduces IOP by 2.0 mmHg but not multiple pillows	III
Caffeine	Aziz et al. [32]	2015	Retrospective, cross-sectional study	Coffee consumption	91	None	Daily coffee consumption was associated with disease progression	II-
Exercise	Agrawal et al. [37]	2015	Open-label, prospective, randomized controlled trial	Aerobic exercise	90 (30 in treatment group, 60 in control group)	1 month	IOP reductions were 3.0 mmHg higher in the exercise group	I-
Yoga	Jasien et al. [39]	2015	Comparative case series	Yoga positions	20	None	IOP was increased approximately 10 mmHg in various yoga positions	III

Summary of studies reporting on the effects of MLS on patients affected by POAG

[a] Strength of evidence was graded using the Scottish Intercollegiate Guideline Network (SIGN) assessment system for individual studies as implemented for Preferred Practice Patterns by the American Academy of Ophthalmology [12]. (For example: I = meta-analysis, systemic reviews of RCT or RCT; II = systemic reviews, case–control or cohort studies; III = case reports or case series. + and – signs designate risk of confounding or bias)

IOP Intraocular pressure

MLS Modifiable lifestyle interventions

POAG Primary open angle glaucoma

Table 2 Comparison of recent evidence to previous evidence

Factor	Prior to 2013	Since 2013	Overall possible effect
Diet	Certain fruit and vegetables such as carrots, green collards, kale, oranges, and peaches may reduce the risk of glaucoma [13, 14]	Food supplementation with vitamins, fatty acids and certain spices may produce some favorable outcomes in the short term, but the evidence is inconclusive [2, 17, 18]	There is insufficient evidence supporting diet change in POAG patients at this time
Sleeping Position	IOP is higher in the supine position [19] Head elevation of approximately 30° during sleep may produce a decrease of average IOP [20]	Avoidance of the worse eye-dependent side during sleep may reduce average IOP in that eye [22]	There may be a benefit in a slight head elevation and avoidance of the worst eye-dependent side during sleep
Caffeine	Consumption of about one cup of coffee elevates IOP 1–2 mmHg for about 2 h [28, 29] Heavy caffeine consumption may increase the risk of glaucoma in susceptible individuals, yet the role in disease progression warrants further study [30, 31]	Frequency of coffee intake may be associated with disease progression [32]	It might be reasonable to advise patients to moderate caffeine intake and avoid it entirely ahead of visits requiring IOP measurement
Exercise	Aerobic exercise reduces IOP whereas weight lifting exercises may elevate it [35]	Advising aerobic exercise to POAG patients may produce a reduction in average IOP [37]	It might be reasonable to recommend moderate aerobic exercise and avoiding exercises, which include valsalva-like manoeuvers
Yoga	The head-stand position has been shown to elevate IOP [5]	Other popular yoga positions also increase IOP for a short period [39]	Patients should be advised to avoid yoga positions that incorporate a low head-position
Swimming Goggles	Swimming goggles may elevate IOP and decrease blood flow to the optic nerve head [40–42]	No association was found between frequent swimming goggles use and glaucoma [44]	Whether swimming goggles use should be limited is not yet clear
Neck-tie	Extended neck-tie wear probably has no clinical effect [45]		No neck-tie restrictions are necessary

Effects of various MLS on POAG patients tabulated by evidence before and after 2013

IOP Intraocular pressure

MLS Modifiable lifestyle interventions

POAG Primary open angle glaucoma

In 2016 Park et al. investigated whether different methods of head elevation achieve the same outcome [25]. Their results show that a bed head angle elevation of 30 degrees significantly lowered the IOP of POAG patients by an average of 2.0 mmHg ($P < 0.001$), while using multiple pillows for the same elevation caused no significant change in IOP ($P = 0.081$).

Caffeine

Caffeine is a popular pharmaceutically active substance found in many beverages, food products, and medications. Most studies indicate that caffeine consumption equivalent to one cup of coffee elevates IOP about 1–2 mmHg for a 2-h period in both healthy patients and those affected by POAG [26–29]. Several studies have demonstrated a relationship between heavy caffeine consumption (≥3 cups a day) and the risk of glaucoma in susceptible individuals [30, 31], yet the implications in POAG patients themselves has hardly been studied.

A recent study by Aziz et al. addresses this question [32]. Ninety-one POAG patients had their coffee consumption habits recorded and analyzed with respect to their disease severity and progression. The results show that despite no significant association between coffee drinking and the disease severity ($P = 0.863$), frequency of coffee intake was significantly associated with disease progression ($P = 0.001$). In this small cross-sectional study daily coffee consumption was associated with an eightfold increase in the risk of progression (95 % confidence interval; OR 2.5 to 9.6).

Exercise

In healthy individuals aerobic exercise such as jogging, cycling, and walking reduces IOP, whereas exercises such as heavy-weight lifting may elevate IOP [4, 33, 34]. In POAG patient these responses to exercise seem to be similar or even more pronounced [35]. There is some debate over the benefits of exercise in POAG patients [36], yet few prospective studies exist.

In 2015 Agrawal et al. randomized 90 newly diagnosed POAG patients into three groups, two groups received medical treatment only while the third was also advised to exercise 30 min daily [37]. The exercise group achieved significantly lower IOP values compared with the patients treated identically, but without exercise (9 mmHg and 6 mmHg reductions respectively; P value not reported) and noted better visual quality of life after 30 days.

Yoga

Yoga on the other hand, might be detrimental. The headstand position performed by yoga practitioners has been shown to elevate IOP approximately twofold during and following the exercise, particularly in glaucoma patients [5, 38]. A recent study by Jasien et al. on POAG patients showed similar IOP increases in yoga positions such as the "downward facing dog" position (17 ± 3.2 mmHg to 28 ± 3.8 mmHg; $P < 0.01$) and the "forward bend" position (17 ± 3.9 mmHg to 27 ± 3.4 mmHg; $P < 0.01$), amongst others [39].

Swimming goggles

Swimming goggles may elevate IOP up to 4.5 mmHg and may decrease blood flow to the optic nerve head [40–42]. They have also been reported to extend drainage blebs in patients who have undergone trabeculectomy [43]. However, a study from 2015 by Franchina et al. found no association between frequent swimming goggles use and glaucoma [44]. The long term effect of swimming goggles on POAG patients is yet unresolved.

Additional modifiable factors

Wearing a tight neck-tie may elevate IOP in POAG patients for a short period, yet extended wear has practically no effect [45].

We identified no studies on the effect of alcohol on POAG patients; however, some studies show alcohol consumption does not affect the risk of glaucoma [46].

Similarly, we identified no studies concerning the influence of tobacco smoking on patients affected by POAG. Some studies have suggested smoking might be a risk factor for the development of glaucoma, yet a recent meta-analysis of six observational studies found no causal association [47, 48].

Additionally, no studies regarding the effects of marijuana met our inclusion criteria. Several small studies from the 1980s, however, showed that cannabinoids may reduce IOP transiently [49].

Discussion

There is currently insufficient evidence that changing lifestyle habits has a proven effect on the progression of glaucoma. It is possible that lifestyle plays an important role, yet the lack of robust randomized controlled trials precludes any definite conclusions. Awareness of the possible influences of certain habits, however, should help guide clinical advice on an individual patient basis.

Moderate aerobic exercise and a high fiber diet containing fruits and vegetables may favorably influence glaucomatous disease progression and is also consistent with a healthy lifestyle. Moderating caffeine intake and changing sleeping positions may also have a positive impact. Regarding weightlifting and yoga exercises, patients should be informed of the potential negative effects these activities might have.

Each intervention discussed in this review may provide a modest reduction in IOP or a reduction for a modest period of time. Exercise and diet might reduce IOP merely 2–3 mmHg each, caffeine restrictions might reduce IOP only 1–2 mmHg for a short period, and sleeping with a head elevation may achieve just 1–2 mmHg IOP reductions during sleep. The cumulative effect, however, might be significant.

The risk of progression in glaucoma is dependent on IOP. In the Early Manifest Glaucoma Trial the magnitude of this dependence was estimated at 10 % decrease in risk of progression with each IOP reduction of 1 mmHg [50]. Using simple and inexpensive methods to achieve even a modest reduction in IOP may be a worthwhile cause and have a dramatic impact on POAG patients.

Most measurements of IOP are performed in an office setting during the patient's visit. They provide only a brief glimpse of the actual average pressure the patient is exposed to. Over a 24-h period IOP fluctuates markedly and may vary up to 10 mmHg [51, 52]. Many behaviors and environmental factors may cause this fluctuation. Understanding these factors and advising patients regarding their potential effects might influence average IOP and disease progression even with seemingly no change in IOP measured by conventional means.

Certain MLS have been shown to have a large impact on other eye conditions. In 2001 the Age-Related Eye Disease Study Research group showed that supplementation with their formula led to a significant decrease in progression of age-related macular degeneration [53]. Some of the components of their formulae (vitamins C, E, and zinc) are discussed in this review in the context of glaucoma. The fact that well known simple dietary compounds can produce such outcomes in other conditions provides ample justification for investigating their effects in respect to glaucoma.

Given the retrospective nature of the evidence and the limited amount of randomized controlled trials on this subject, drawing clinical correlations is difficult. This work may

provide the basis for future studies to test the clinical correlations gathered in this review and to initiate randomized controlled trials examining the effects of MLS on patients affected by POAG.

Compliance with ethical standards

Funding No funding was received for this research.

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Human and animal rights and informed consent This article does not contain any studies with human participants or animals performed by any of the authors.

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