



Clinical trial

Effects of dietary and lifestyle recommendations on patients with glaucoma: A randomized controlled pilot trial

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ABSTRACT

Introduction: Several studies have shown intra-ocular pressure (IOP) reductions following lifestyle and behavior changes in primary open-angled glaucoma (POAG) in the short term. Our aim in this study was to examine the potential of such interventions as an adjunct treatment and assess their cumulative short-term effect on IOP and illness perception in patients with POAG.

Methods: In this randomized, parallel-arm, single blind controlled trial, POAG patients were randomized in a 1:1 ratio to either a treatment group which received instructions on dietary and lifestyle changes in addition to their standard therapy or to a control group which continued their standard therapy. Recommendations were selected to include those previously reported to reduce IOP; including: Saffron spice supplementation, high fiber diet, avoidance of caffeine, aerobic exercise, head elevation during sleep and others. Illness perception was assessed using the Brief IPQ questionnaire.

Results: 22 participants were enrolled, 3 were lost to follow-up and 19 entered analysis. Mean age was 69 ± 12 and 12 (63%) were female. Concerns about the illness, symptoms, and feelings of control were significantly improved in the treatment group compared with controls (all $P < 0.05$). Mean IOP reduced in the treatment group by 1.0 ± 3.1 mmHg (17.5 ± 4.3 – 16.5 ± 4.7) and by 0.7 ± 4.1 mmHg in the controls (16.8 ± 4.7 – 16.1 ± 6.2) with no significant difference between them ($P = 0.866$).

Conclusions: Dietary and lifestyle changes may improve illness perception and patient well-being, however they do not appear to affect IOP in the short term among patients with POAG.

What was known before

- Several studies have shown intraocular pressure reductions following lifestyle changes in patients with glaucoma.
- These interventions included Saffron spice intake, a high-fiber diet, decreased coffee intake, sleeping with the head elevated and moderate aerobic exercise.
- We aimed to study the cumulative short-term effects of these interventions in a randomized, parallel-arm, single blind controlled trial.

What this study adds

- Lifestyle changes involving diet, sleep and exercise may improve illness perception and patient well-being.
- They do not appear to affect intraocular pressure in the short term among patients with glaucoma.

1. Introduction

Glaucoma is an optic neuropathy characterized by progressive degeneration of optic nerve cells. It affects more than 70 million people worldwide with approximately 10% being effectively blind [1,2]. Reduction of intraocular pressure (IOP) is the only proven method to treat glaucoma and available treatments include topical or oral medications, laser treatment or surgery [2]. Primary open-angled glaucoma (POAG) is perhaps the most common form of glaucoma and with inadequate control of the IOP may lead to irreversible vision loss [3].

In the last few decades the effects of many lifestyle and behavior changes have been studied in respect to glaucoma management [4–7]. These studies examined interventions in a variety of behaviors and activities such as exercise, diet, sleep and others [8–14].

Several interventions produced IOP reductions or equivalent effects in the short term, including: a high fiber diet, intake of Saffron spice, a decreased coffee intake, sleeping with the head elevated, avoiding the

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side of the worse affected eye during sleep and moderate aerobic exercise. Weight lifting and yoga exercises on the other hand, were associated with negative effects. The majority of these studies however were observational or retrospective, non-randomized and most focused only on one specific intervention [15].

Given the lack of randomized controlled trials on the subject, the aim in this study was to examine the short term, cumulative effect of these lifestyle interventions as an adjunct to standard therapy among patients affected by POAG. A lifestyle modification program was designed and tested based on interventions which were shown to produce a consistent IOP reduction or equivalent effect by well-designed individual studies [15].

2. Materials and methods

The research followed the tenets of the Declaration of Helsinki. Approval was obtained from the local Ethics Committee (approval number: 0127-16-WOMC) and all participants gave their written informed consent. The study was approved and registered at ClinicalTrials.gov prior to patient enrollment (Identifier: NCT02972749). The study design, implementation and report are in accordance with the CONSORT (Consolidated Standards of Reporting Trials) statement to improve reporting of randomized controlled trials [16].

2.1. Trial design

This is a prospective single blind randomized controlled trial, performed in the ophthalmic department of the Edith Wolfson Medical Center in Israel from December 2016 through December 2017. Patients were randomized in a 1:1 ratio to either an intervention or control group. Patients in the intervention group were instructed on lifestyle and behavior changes in addition to standard therapy while those in the control group continued their standard therapy unchanged. Both groups completed the Brief Illness Perception Questionnaire (Brief IPQ) [17] at the initial and follow-up examinations and answered a short questionnaire about their current lifestyle and behavioral preferences. Both groups received a phone call after two weeks of follow-up by a research staff in order to ensure adherence to the lifestyle changes (in the intervention group) and maintenance of pharmacological treatment (in both groups). After one month participants arrived to a follow-up examination. The study design and flow are detailed in Fig. 1.

2.2. Participants

Included were patients with POAG above the age of 18 who were not scheduled for any surgery, nor a change in any pharmacological treatment, diet or lifestyle changes or any major life events (i.e. moving residence) in the following month. POAG was defined by the combination of a characteristic cupping of the optic disk, the presence of a consistent glaucomatous visual field defect and an open anterior chamber angle, without any other abnormality that could have caused the visual field defect.

Excluded were patients with chronic or acute angle-closure glaucoma, those who could not arrive at the follow-up appointment and patients who changed their pharmacologic glaucoma treatment recently or had undergone glaucoma filtration surgery. We also excluded patients who could not adhere to the instructions offered to the intervention group (e.g. could not perform moderate exercise, could not change their diet). Patients who had any ocular surgery two months prior or during the follow-up period were also excluded.

2.2.1. Intervention group

Participants allocated to the intervention group received a sealed envelope containing written instructions on lifestyle recommendations detailed in Table 1, along with instructions on maintaining their current

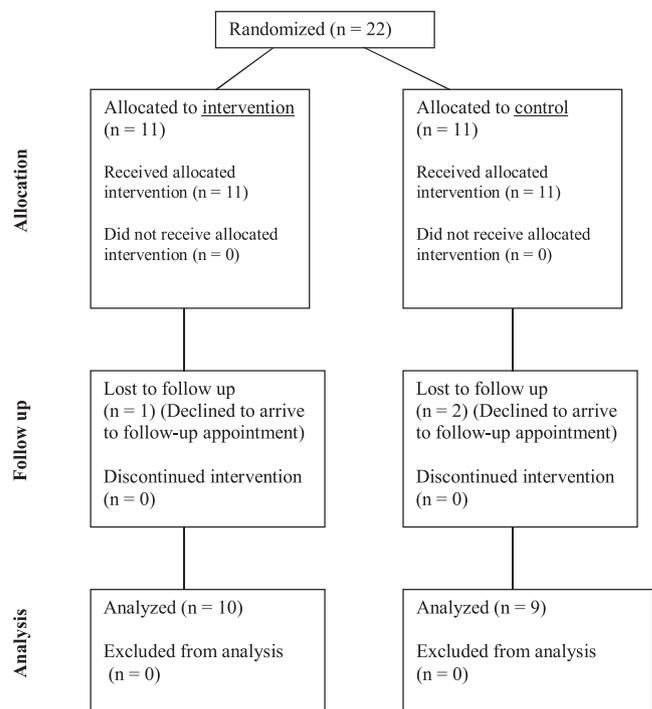


Fig. 1. Diagram showing the flow of participants through each stage of the trial. A flow diagram that illustrates the progress of patients through the trial according to the CONSORT guidelines. [10]

pharmacologic treatment without change. The envelope also contained a small sealed packet of Saffron. After one month participants had a follow-up examination.

2.2.1.1. Lifestyle interventions. Before initiation of the current study, we performed a literature review of studies examining the effect of various lifestyle interventions on intra-ocular pressure among patients with POAG, results of which are available here [15]. Using the results of this review we isolated interventions which were shown to produce an IOP reducing or equivalent effect. Included were only interventions shown to have an effect in studies which were graded III + or higher using the Scottish Intercollegiate Guideline Network (SIGN) assessment system for individual studies as implemented for Preferred Practice Patterns by the American Academy of Ophthalmology [18], these included meta-analysis, randomized controlled trials, case-control or cohort studies and well-designed case series, while excluding case reports and poorly designed case series. We also excluded interventions with conflicting results in different studies. As several of the studies used one month of follow-up to assess outcomes we similarly defined our follow-up period at one month.

Following this synthesis, a list of instructions was formulated which were provided to the treatment group along with a specific instruction to continue their regular pharmacologic treatment. A detailed description of the supporting evidence for each instruction is presented in Table 1. The instructions were:

1 Diet

- Eat a small portion of the enclosed Saffron spice twice a week so that the package (1 g) will last the entire month.
- Drink no more than one caffeinated coffee per day.
- Eat at least three fruit portions (of about one cup per portion) a day, fresh peaches and oranges are preferred.
- Each week eat at least one portion of collard greens, kale or fresh carrots.
- Each week eat at least two portions of Iceberg lettuce, Romaine lettuce or chards.

Table 1
Lifestyle Instructions Given to the Treatment Group and Their Respective Supporting Studies.

Category	Instruction Given to the Intervention Group	Supporting study (year) [ref]	Summary of Supporting Study Concerning the Intervention
Exercise	Perform at least 30 minutes of moderate aerobic exercise each day.	Agrawal et al. (2015) [23]	90 patients with POAG were randomized to either 30 daily minutes of aerobic exercise or control groups for one month. IOP reductions were 3.0 mmHg higher in the exercise group.
	Avoid strength exercises (weights, push-ups, etc.).	Vieira et al. (2006) [8]	IOP was increased by 2-4 mmHg during bench press exercises.
	Avoid head-stands (e.g. during yoga).	Jasien et al. (2015) [6]	A Head-stand position resulted in a 2-fold increase in IOP among 75 yoga practitioners.
	Avoid swimming goggles.	Morgan et al. (2008) [11]	Wearing swimming goggles elevated IOP by 4.5 mmHg among 35 subjects.
Diet	Drink no more than one caffeinated coffee per day.	Jiwani et al. (2012) [13]	Consuming one cup of caffeinated coffee resulted in about 1 mmHg IOP increase up to 90 minutes following ingestion in 106 POAG, OHT and healthy subjects.
	Eat at least three fruit portions per day, fresh peaches and oranges are preferred.	Giaconi et al. (2012) [4]	Older African-American women consuming 3 or more servings/day of fruits such as fresh oranges and peaches were less likely to have glaucoma than women who ate less than 1 serving/day.
	Each week eat at least one portion of green collard, kale or fresh carrots.	Giaconi et al. (2012) [4]	Older African-American women Consuming more than 1 serving/week of collard greens, kale or carrots had decreased odds of glaucoma.
	Each week eat at least two portions of Iceberg lettuce, Romaine lettuce or Chard greens.	Kang et al. (2016) [9]	Greater intake of green leafy vegetables such as Iceberg lettuce, Romaine lettuce, Kale or Chard greens was associated with lower POAG risk.
	Eat a small portion of the enclosed Saffron spice twice a week so that the package (1 gram) will last the entire month.	Bonyadi et al. (2014) [22]	34 patients with POAG were randomized to either receive 30 mg/day Saffron extract orally or placebo for one month (0.9 grams/month). A 2 mmHg IOP reduction was noted in the Saffron group only.
Sleep	Avoid food supplements containing iron or calcium if taken without medical cause.	Wang et al. (2012) [12]	In a cross-sectional study of 3833 participants, those who consumed supplementary calcium or iron had significantly higher odds of having been diagnosed with glaucoma.
	Sleep with the head elevated to a 30-degree angle (3 pillows or elevation of the bed head-rest).	Buyts et al. (2010) [10]	IOP was 3.2 mmHg lower in the 30-degree head-up sleeping position compared with the flat position among 17 patients with glaucoma.
	If one eye is affected more than the other, avoid sleeping on that eye's side.	Lee et al. (2015) [5]	A 1.3 mmHg increase in IOP was measured in the dependent eye relative to the non-dependent eye of 20 POAG patients after five minutes in a lateral sleeping position.
	Avoid sleeping prone ("on the stomach").	Flatau et al. (2016) [7]	The IOP of 22 glaucoma patients was increased by an equivalent of 2.5 mmHg in the 'face down' sleeping position.
	Try keeping the head elevated or remain in a sitting position during waking hours.	Prata et al. (2010) [14]	In 14 studies on the effect of posture on IOP a horizontal position increased IOP by 1.6-8.6 mmHg compared to a sitting or upright position.

IOP, Intraocular pressure. OHT, Ocular hypertension, POAG, Primary open-angled glaucoma.

- Avoid food supplements containing iron or calcium if taken without medical cause (if instructed to use them by a medical care provider – continue taking them). Foods containing iron or calcium such as meats and dairy are allowed.

2 Exercise

- Perform at least 30 min of moderate aerobic exercise each day (for example walking, running or cycling).
- Avoid strength exercises (weights, push-ups, etc.).
- Avoid head-stands (e.g. during yoga exercises).
- Avoid swimming goggles (swimming without goggles is allowed).

3 Sleep

- Sleep with the head elevated to a 30-degree angle (3 pillows or elevation of the bed head-rest).
- If one eye is affected more than the other, avoid sleeping on that eye's side.
- Avoid sleeping prone ("on the stomach").
- Try keeping the head elevated or remain in a sitting position during waking hours (for example while watching television or reading).

Participants were advised to split the Saffron spice quantity into four, and consume each portion throughout every week in a measured manner. Adherence to the intervention program was assessed using checklists regarding the different instructions which were filled out by the participants and collected by a research staff member (I.H) at the end of the follow-up period. The checklists were filled at the end of each week and concerned each aspect of the intervention in each day of the preceding week.

2.2.2. Control group

Participants allocated to control group received a sealed envelope

containing written instructions to maintain their current pharmacologic treatment without change. For blinding purposes the envelope also contained a small sealed packet identical to that of the intervention group but empty. After one month participants arrived to the follow-up examination.

2.3. Outcomes

The primary outcome measure was change in IOP after one month. Measurements were performed by an experienced glaucoma specialist (Z.B) who was blinded to the patient allocation. IOP was measured using Goldmann applanation tonometry (GAT) (Haag Streit International, Koeniz, Switzerland) according to the manufacturer's guidelines [19,20]. The mean of two consecutive IOP readings was considered for analysis. To minimize the potential confounding effect of diurnal variation in IOP, all measurements were taken between 09:30 AM to 11:30 AM. We randomly chose to include only the right eye of each patient in the analysis of the main outcome.

The secondary outcome measure was the cognitive and emotional representations of illness assessed using the Brief IPQ questionnaire after one month [21,17]. This questionnaire was designed to provide simple and rapid assessment of illness perceptions [17,21]. The shortened version was used, which includes seven items compared to the original which includes nine. Six of the seven items are answered on a scale from one to ten to assess each dimension, where higher scores indicate stronger perceptions along that dimension. The items include perceived consequences, timeline (acute-chronic), amount of perceived personal control, treatment control, identity (symptoms), concern about the illness and coherence of the illness and emotional representation. The last (seventh) item assesses causal perceptions by asking patients to list the three most likely causes for their illness [21].

Table 2
Clinical Characteristics of the Intervention and Control Groups at Baseline.

Variable	Intervention		Control		P-value
	N (%)	SD	N (%)	SD	
Number of Patients	10 (53)		9 (47)		
Age	71.8	9.5	65.2	13	.235
Male Gender	4 (40)		3 (33)		.764
Baseline IOP	17.5	4.3	16.8	4.7	.733
Years Since Diagnosis	8.6	6.7	7.1	3.5	.590
Interest in Lifestyle Modifications was Rated High or Very High*	8 (80)		6 (67)		.335
Body Weight	75.3	12	70.2	12	.389
BMI	28.9	4.3	25.3	4.1	.092
Illness Perception					
IPQ Question 1 Baseline	4.5	3.3	4.4	3.0	.935
IPQ Question 2 Baseline	4.4	2.4	6.2	1.2	.193
IPQ Question 3 Baseline	4.8	2.5	5.7	2.2	.453
IPQ Question 4 Baseline	6.2	2.6	6.1	2.5	.951
IPQ Question 5 Baseline	5.1	2.7	5.0	1.8	.934
IPQ Question 6 Baseline	3.2	2.9	3.7	1.8	.669
Sleeping Habits^a					
Prefer Sleeping On The Side	9 (90)		6 (67)		.559
If Sleeping On The Side, Prefer Right Side	3 (33)		3 (50)		.732
If Sleeping On The Side, Prefer Both Sides Equally	3 (33)		1 (17)		.475
If Sleeping On The Side, Prefer The Side of The Worse Affected Eye ^b	4 (57)		2 (40)		.551
Prefer Sleeping On The Back	1 (10)		1 (11)		.466
Prefer Sleeping On The Stomach	0		1 (11)		.572
Exercise Habits					
Aerobic Exercises Per Week [†]	1.2	2.6	2.4	1.7	.289
Strength Exercises Per Week [†]	0		1.7	1.2	.001
Head-Stand Exercises Per Week [†]	0		0.13	0.3	.276
Swimming Goggles Use Per Week [†]	0		1.14	2.0	.111
Neck-Tie Use Per Week [†]	0		0		
Diet					
Food Supplements Use Per Week [†]	1.4	2.4	1.43	1.8	.989
Saffron Spice Use Per Week [†]	0		0		
Coffee Cups Per Day [†]	2.6	2.3	2.1	2.2	.667
Vegetable Portions Consumed Per Day [†]	1.6	0.8	3.0	1.5	.028
Fruit Portions Consumed Per Day [†]	1.4	0.8	2.2	1.8	.208

Clinical and demographic characteristics of 19 patients with glaucoma randomized to receive lifestyle instructions in addition to standard therapy or standard therapy alone. * Interest in lifestyle modifications were determined by a questionnaire question graded between no interest (1) to very high interest (4) by the participants. † On average during the month prior to the study period. ^aOne patient from the control group did not disclose his sleeping habits. ^bThe worse affected eye was defined as the eye with higher IOP or worse visual field. SD – Standard Deviation.

The questionnaire has shown good test–retest reliability, concurrent validity with relevant measures and good predictive validity to mental and physical functioning [17]. Participants filled out the questionnaire twice, at recruitment and at the follow-up examination.

2.4. Sample size

For the sample calculation, the IOP changes from a study of 34 patients given Saffron spice for one month [22], another study of 71 patients examining different head elevation positions and a third study of 90 patients examining the effect of aerobic exercise was used [23,24]. Although multiple concomitant interventions could possibly produce a cumulative effect, we nevertheless took a conservative approach and assumed that no such cumulative effect will be observed. Based on these studies, the mean IOP change was set as 2.1 ± 3.0 . We found that a sample size of 18 patients (9 for each group) was required to detect a significant difference between groups with a significance level of 0.05 and a power of 80%. We expected a 20% loss to follow-up

and so decided to enroll 20% more (total of 22). Calculations were performed using GLIMPSE online software [25].

2.5. Randomization sequence generation

A computer-generated randomized sequence, using blocks of 20 subjects (randomization.com), was generated by a research staff member (I.H.).

2.6. Allocation concealment mechanism

Patients were enrolled sequentially by the care provider (Z.B) and each received the correspondingly numbered envelope belonging randomly to either the treatment or control group, according to the previously generated random sequence. The envelopes were brown, opaque and identical. Patients were instructed not to open the envelope until after they had left the clinic and to not discuss their contents or their intervention experience with their care provider.

2.7. Blinding

Random sequence generation, envelope arrangement and data analysis were performed by a (non-masked) research staff member (I.H.). An experienced glaucoma specialist (Z.B) recruited the participants and assessed the outcomes and was blinded to the allocation. Participants were not blinded to the allocation.

2.8. Statistical analysis

Statistical analysis was performed using SPSS software for windows version 20.0 by IBM. P values less than 0.05 on a two-sided test were considered statistically significant. We conducted χ^2 tests for categorical variables. Clinical parameters distributions were tested for normality by the Shapiro-Wilk test. Independent and paired T tests were conducted for continuous variables with a normal distribution and Wilcoxon signed–rank test and the Mann–Whitney-U test for variables with a non-normal distribution. Unless otherwise specified, data is presented as mean \pm standard deviation (SD).

3. Results

3.1. Participant flow

The participant recruitment flow is presented in Fig. 1. Twenty-two patients were initially recruited and randomized to the control group (N = 11) and the intervention group (N = 11). During the month of follow up 3 patients were lost to follow-up (1 in the intervention group and 2 the control group). 19 eyes of the 19 patients who arrived at the follow-up appointment were included in the analysis.

3.2. Baseline data

The baseline characteristics of the participants are detailed in Table 2. Both groups were similar in baseline characteristics. The mean age was 72 ± 9.5 in the intervention group and 65 ± 13 in the controls (P = 0.235), 40% were male in the treatment group compared to 33% in the control (P = 0.764) and patients in the intervention group had a mean of 8.6 ± 6.7 years since diagnosis compared to 7.1 ± 3.5 in the controls (P = 0.590). Body mass was also not significantly different with a mean BMI of 29 ± 4.3 in the treatment group compared with 25 ± 4.1 in the controls (P = 0.092).

Lifestyle and behavioral preferences in the month prior to the trial were also fairly similar between the groups with no significant differences in sleeping habits, and no significant differences in diet or exercise habits except for a slightly larger number of strength exercises per week in the controls (1.7 ± 1.2 compared with 0, P = 0.001) and a

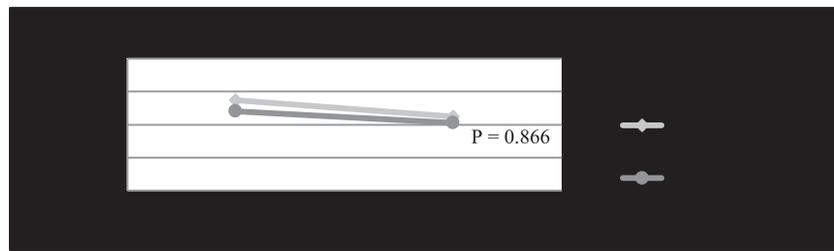


Fig. 2. IOP Values at Baseline and Following the Trial Period.

larger intake of vegetable portions per day in the controls (3.0 ± 1.5 compared with 1.6 ± 0.8 , $P = 0.028$), further detailed in Table 2.

Prior to the trial period the IOP values of both groups were similar with no significant difference (17.5 ± 4.3 mmHg in the treatment group and 16.8 ± 4.7 mmHg in the control group, $P = 0.733$). Illness perception was also similar with no significant differences between the baseline values of any item of the Brief IPQ Questionnaire (Table 2).

3.3. Main outcome: intra-ocular pressures

In the treatment group IOP decreased by 1.0 mmHg (from 17.5 ± 4.3 – 16.5 ± 4.7 mmHg) and in the control group by 0.7 mmHg (from 16.8 ± 4.7 – 16.1 ± 6.2 mmHg). There were no significant differences in the IOP change between the treatment and control groups ($P = 0.866$, Fig. 2). In both groups the reduction in IOP was not significant (pairwise analysis, both $P > 0.05$).

3.4. Secondary outcome: illness perception

The changes in illness perception as estimated by the IPQ questionnaire are detailed in Table 3. In 3 items there was a significant improvement in the treatment group compared with the controls. These items included Question 2: "How much control do you feel you have over your illness?", question 4: "How much do you experience symptoms from your illness?" and question 5: "How concerned are you about your illness?". These items all improved significantly by about 3–4 points compared to no improvement or a negative change in the controls (Table 3). In the remaining 3 items there were no significant differences between the groups (all $P > 0.05$). These items included question 1: "How much does your illness affect your life?", question 3: "How much do you think your treatment can help your illness?" and question 6: "How much does your illness affect you emotionally?" (Table 3).

3.5. Adherence to treatment

Adherence to the intervention program was relatively high. The

highest adherence was reported for the continuation of the regular pharmacological treatment at 91% of days out of the follow-up period reported with full adherence, followed by 78% of days to fruit and vegetable consumption, 70% of days to caffeine intake and 65% to sleep and rest recommendations. Adherence to exercise and Saffron spice use were slightly lower with 57% and 54% of days, respectively.

3.6. Ancillary analyses

In our cohort, 15 of 19 patients preferred sleeping on their side. We tested for correlation between the preferred sleeping side (right or left) and the worse affected eye, defined as the eye with higher IOP or worse visual field. Six patients were habitually sleeping on the side of the worse affected eye and 6 on the side of the less affected eye (in the other 3 cases both eyes were affected equally). The differences were non-significant ($P = 0.558$).

Patients with baseline IOP values above the median value which was 16 mmHg (from both groups) were isolated and examined for associations with baseline lifestyle and behavioral preferences. Baseline IOP values were not correlated with any behavioral preference apart from a strong positive correlation with the number of food supplements consumed per week ($R = 0.650$, $P = 0.006$) as illustrated in the online supplement (Supplemental Figure).

3.7. Harms and side effects

No harms or unwanted side effects were reported. Two patients from the intervention group who were overweight reported that they lost 4–5 pounds of weight during the month of follow-up.

4. Discussion

In this study we examined the potential of lifestyle interventions such as diet, exercise and sleep on intra-ocular pressure and illness perception on patients with POAG in a single blind, parallel-arm, randomized controlled design. We report two main findings: 1. there was no significant effect on IOP following the intervention, and 2. Illness

Table 3
Clinical Outcomes.

Variable	Intervention Change	SD	Control Change	SD	P-value
Main Outcome					
IOP (mmHg)	-1.0	3.1	-0.7	4.1	.866
Secondary Outcomes					
IPQ question 1 (How much does your illness affect your life?)	0.4	4.2	0.7	1.6	.886
IPQ question 2 (How much control do you feel you have over your illness?)	2.8	2.6	-2.3	4.0	.040
IPQ question 3 (How much do you think your treatment can help your illness?)	3.4	3.2	3.4	3.8	.982
IPQ question 4 (How much do you experience symptoms from your illness?)	-3.7	2.4	-0.7	1.4	.007
IPQ question 5 (How concerned are you about your illness?)	-2.7	1.5	0.7	2.3	.003

Clinical outcomes of 19 patients with glaucoma randomized to receive lifestyle instructions in addition to standard therapy or standard therapy alone. IPQ questionnaire answers are graded on a scale of 1 (least) to 10 (most).

SD – Standard Deviation. IPQ – The brief Illness Perception Questionnaire.

perception was significantly improved in the treatment arm in items concerning feeling of control, symptoms, and concern about the illness.

The possibility of using lifestyle interventions as an adjunct to standard therapy is greatly appealing. These interventions are relatively simple, cheap, accessible and have few side-effects. Interventions such as exercise and diet have been shown to improve other health outcomes and reduce mortality [26]. In our view, these beneficial consequences provide ample justifications to explore these treatment modalities, even if at first they might seem unconventional

This study found no significant difference in IOP between the groups. It is interesting to note that some of the instructions to the intervention group, such as changing the head position during sleep and avoiding swimming goggles, were likely to influence IOP during the activity, and in a manner not obviously apparent several hours later at the clinic. It is possible that despite the lack of effect on IOP observed in our study some lifestyle changes might influence disease progression by affecting the overall average IOP. Further research into long term outcomes, including visual fields, might be able to confirm or exclude these possible subtle effects with more confidence.

Another possible influence may have been the baseline habits of the local population. For example the recommendation to eat at least three portions of fruit per day is based on a study in which the control group ate less than 1 per day [4]. However in our study population the baseline fruit consumption was 1.8 ± 1.4 per day. The baseline vegetable consumption was also high (2.2 ± 1.3 per day), coffee intake was relatively low (2.4 cups per day) and patients naturally exercised 1.7 times a week (Table 2). Since no restriction was imposed on the control group it is possible that in these categories the recommendations to the intervention group constituted only a small change from their regular routine and was not dissimilar to what the control group naturally performed. This highlights the difficulty in implementing lifestyle changes at an individual level, based on studies performed on a population scale.

Three questions in the Illness Perception Questionnaire (IPQ), out of a total of six questions answered on the scale, improved significantly in the treatment arm. Patients in the treatment arm had improved feeling of control, fewer symptoms and were less concerned about their illness. These are all important and clinically significant results. Improved perception of wellness and reduced concern regarding the disease could have meaningful implications for overall well-being as anxiety and depression are highly prevalent in chronic disease and contribute to perceived symptom burden, morbidity and mortality. [27,28]. There was no difference between groups in how much the illness affected their life, the perceived importance of their treatment or in emotional effects of the illness. It is perhaps possible for lifestyle changes to improve feelings of control and reduce symptoms by affecting patient's overall well-being but also by mechanisms similar to those of the placebo effect [29]. It is interesting to note that patients in the treatment arm almost did not change their response to the question "How much does your illness affect your life?" after the intervention (0.4 points increase) despite the time consuming and sometimes inconvenient changes they made to their lifestyle.

This study has several limitations. First, the study is single blind in that the participants were not blinded to their group assignment. Double-blinding could have been achieved with a "sham" intervention, however this might have had unexpected results. Second, although participants were clearly instructed to not share their intervention experience with their care provider, some influence on the care provider's blinding could still exist. Third, the research staff member conducting the follow-up phone calls was also not blinded to the participant allocation. Fourth, a phone call to insure adherence is unrealistic in daily clinical practice, creating adherence standards which might not be attainable during usual care. Fifth, this study was performed using a short follow-up period and a small sample size and so reflects mainly on distinct and short-term benefits. Finally, given the short follow-up period we did not include functional outcomes such as visual field loss

and our results cannot be generalized to these outcomes.

This trial was designed to have high sensitivity, aimed at exposing any benefit in IOP reduction. Multiple interventions were used at once, patients received an adherence reminder and expensive supplements (Saffron spice) were provided free of charge, conditions which is usually not available during usual care. Despite these measures, and despite adequate power, no difference in IOP was discovered between the groups. It is interesting to note that even the potential biases previously discussed, had a potential influence to the benefit of the intervention (e.g. placebo effect, outcome assessment bias). It is therefore reasonable to assume that these lifestyle changes implemented during usual care, and not as part of a study, would similarly result in no IOP reduction in the short term.

To conclude, lifestyle changes involving diet, sleep and exercise do not appear to affect IOP in the short term among patients with POAG. These lifestyle changes however may positively influence illness perception and patient well-being among patients with POAG.

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Registration

The study was approved by the Wolfson Medical Center Ethics Committee (Approval number: 0127-16-WOMC) and approved and registered at ClinicalTrials.gov (Identifier: NCT02972749) prior to patient enrollment.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.eujim.2018.12.002>.

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