Mindfulness Meditation Reduces Intraocular Pressure, Lowers Stress Biomarkers and Modulates Gene Expression in Glaucoma: A Randomized Controlled Trial

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Background: Reducing intraocular pressure (IOP) in primary open-angle glaucoma (POAG) is currently the only approach to prevent further optic nerve head damage. However, other mechanisms such as ischemia, oxidative stress, glutamate excitotoxicity, neurotrophin loss, inflammation/glial activation, and vascular dysregulation are not addressed. Because stress is a key risk factor affecting these mechanisms, we evaluated whether mindfulness-based stress reduction can lower IOP and normalize typical stress biomarkers.

Materials and Methods: In a prospective, randomized trial 90 POAG patients (180 eyes; age above 45 y) were assigned to a waitlist control or mindfulness meditation group which practiced daily for 21 days. We measured IOP (primary endpoint), quality of life (QOL), stress-related serum biomarkers [cortisol, β-endorphins, IL6, TNF-α, brain-derived neurotrophic factor (BDNF), reactive oxygen species (ROS), total antioxidant capacity (TAC)], and whole genome expression.

Results: Between-group comparisons revealed significantly lowered IOP in meditators (OD: 18.8 to 12.7, OS 19.0 to 13.1 mm Hg) which correlated with significantly lowered stress-biomarker levels including cortisol (497.3 to 392.3 ng/mL), IL6 (2.8 to 1.5 ng/mL), TNF-α (57.1 to 45.4 pg/mL), ROS (1625 to 987 RLU/min/104 neutrophils), and elevated β-endorphins (38.4 to 52.7 pg/mL), BDNF (56.1 to 83.9 ng/mL), and TAC (5.9 to 9.3) (all $P < 0.001$). These changes correlated well with gene expression profiling. Meditators improved in QOL ($P < 0.05$).

Conclusions: A short course of mindfulness-based stress reduction by meditation in POAG, reduces IOP, improves QOL, normalizes stress biomarkers, and positively modifies gene expression. Mindfulness meditation can be recommended as adjunctive therapy for POAG.

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Glaucoma is a neurodegenerative disease[1] with progressive damage of the optic nerve head (ONH) as well as visual and nonvisual centers of the brain.[2] It is the second leading cause of blindness affecting ~65 million people worldwide, 10% of whom are blind.[3] Loss of vision in glaucoma is considered irreversible which is a huge psychological and economic burden on patients and caregivers. In primary open-angle glaucoma (POAG) intraocular pressure (IOP) is a major risk factor, but there are other pathogenic mechanisms involved such as (i) ischemia/hypoxia with endothelial dysfunction and vascular dysregulation,[4] (ii) mitochondrial dysfunction with oxidative stress,[5] (iii) glutamate excitotoxicity,[6] (v) decrease in neurotrophins,[7] (vi) inflammation and glial activation,[8] and (vii) nitric oxide dysregulation[9] and (viii) central insulin resistance[2] which might explain the vision loss progression despite lowering of IOP. Glaucoma patients have high levels of anxiety and depression with poor psychosocial functioning and stress due to anticipated vision loss which may be a contributing factor to the worsening of the disease condition.[10] Stress-associated somatic/biochemical changes are known "risk factors" for glaucoma progression. Although it is still unclear whether stress is only the consequence or also a cause of glaucoma, the similarity between glaucoma biomarkers and the bodily reaction to mental stress is evident. Stress leads to vascular dysregulation/endothelial dysfunction,[4] a decline in parasympathetic activity, elevation in oxidative stress, glutamate excitotoxicity,[11] downregulation of neurotrophins,[12] and glial activation.[13] Taken together, this raises the possibility that glaucoma parameters could be improved when stress biomarkers are normalized by eliciting a relaxation response (RR).

The practice of mindfulness meditation (MM) is known since ancient times and is among the most widely used and effective techniques to evoke an RR.[14,15] Scientific studies of different mindfulness techniques have showed positive effects of preventing and/or ameliorating mental stress as confirmed not only by subjective reports of relaxation, improved well-being and quality of life (QOL), but by confirmatory evidence of positive influence on various biomarkers: it lowers cortisol levels (thereby lowering IOP and improving vascular function),[16] improves perfusion and oxygenation of brain,[17] increases neurotrophin levels,[18] ameliorates parasympathetic activity, and it

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reduces oxidative stress, glutamate excitotoxicity,[19] and proinflammatory processes.

Given the similarity of biomarker alterations in both glaucoma and the stress response, there is a possibility that mental stress could be a major (though not the only) causal contributor to the development and/or progression of glaucoma. The aim of present study was to investigate the effect of RR on biomarkers of glaucoma and to test the hypothesis that lowering stress by mindfulness-based stress reduction (MBSR) through meditation can lower IOP and be therefore used as an adjunctive therapy. To achieve this aim, we lowered stress by MBSR and studied whether this intervention normalizes glaucoma biomarkers.

Here we describe a randomized controlled trial to evaluate the efficacy of MBSR on various parameters of glaucoma: sociopsychological (QOL), clinical (IOP, visual field, etc.), biological [cortisol, TNF, β-endorphins, IL6, reactive oxygen species (ROS), etc.], and genetic (whole genome expression profiling). We show for the first time, MM significantly reduces IOP, improves QOL, and normalizes stress biomarkers with associated gene expression pattern changes indicating that stress may be a major mediator of glaucomatous disease process.

MATERIALS AND METHODS

Study Design

This prospective, single-blinded, randomized controlled trial with POAG patients aimed at investigating the effect of MM on IOP, QOL, serum cortisol, β-endorphins, brain-derived neurotrophic factor (BDNF), total antioxidant capacity (TAC), ROS, inflammatory markers, and whole genome expression pattern. The study protocol (Fig. 1) complies with the Consolidated Standards of Reporting Trials (CONSORT).

Participants

POAG patients were recruited from our outpatient clinic and randomized either to a control which was waitlisted for later intervention or to a treatment group which participated in an MBSR course (see CONSORT statement, Fig. 1).

Inclusion/Exclusion Criteria

The inclusion criteria were: age above 45 years, moderate/severe POAG [according to Hodapp-Parrish-Anderson (HPA) classification] with IOP range (12 to 21) mm Hg and best-corrected visual acuity of 20/40 or better in both eyes. Exclusion criteria were: any comorbid condition of visual loss, previous practice/experience of meditation or yoga in any form, chronic systemic diseases affecting QOL, history of ocular surgery in previous 6 months, medical therapy for any other illnesses, significant physical disability, and newly diagnosed/uncontrolled glaucoma. Current glaucoma medication or dose was not a criterion for inclusion or exclusion. Both groups were comparable regarding the number of patients on IOP-lowering eye drops.

Randomization

Each participant was deidentified by assigning a code before randomization using the sealed envelope method. All investigators interviewing patients, evaluating the QOL, and measuring the biochemical and molecular markers were blind to the patients' group identities.

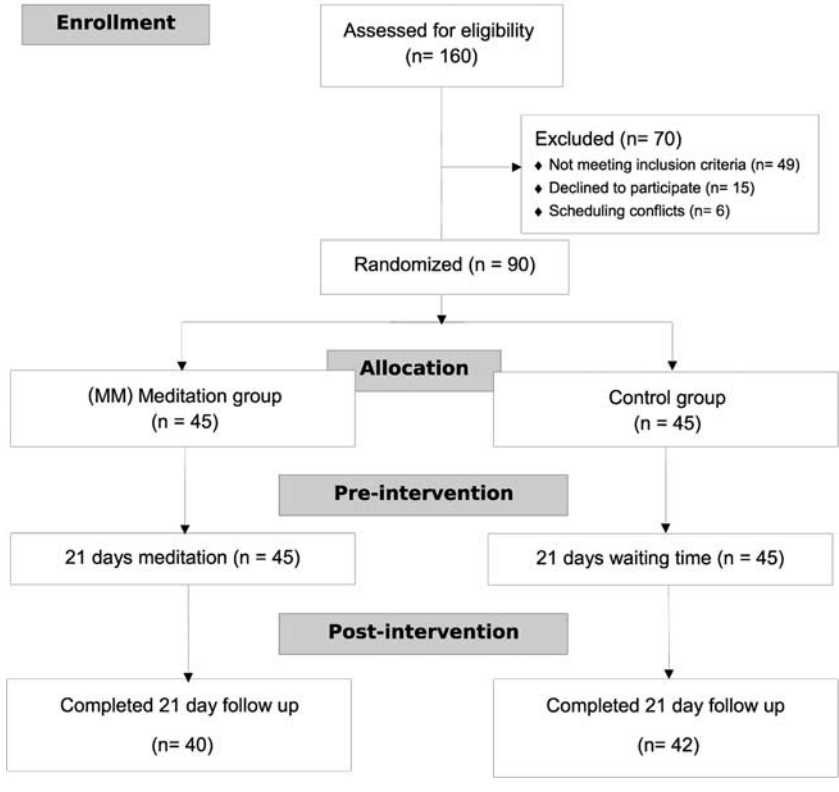

FIGURE 1. CONSORT flow chart of the clinical trials.

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Intervention

MBSR/MM (being attentive to the present moment in a nonjudgmental way with an awareness of breathing) was practiced in daily group meetings for 21 days starting at 8.00 AM for 60 minutes under the supervision of a certified meditation teacher. On day 1 (D-1) patients of the treatment group were introduced to the meditation technique, followed by practical instructions of slow and deep breathing exercises. From day 2 till 21 they practiced breathing exercises for relaxation (15 min) followed by 45 minutes of meditation.

QOL, IOP, and Visual Assessment

QOL was assessed with the abbreviated World Health Organization QOL Questionnaire (WHOQOL-BREF) in Hindi or English (www.who.int/mental_health/media/en/76.pdf). Goldmann applanation tonometry was used to measure IOP for all patients at 2:00 PM, postprandial, and 5 hours after the last meditation session. This timing of IOP measurement was deliberate to control for a possible transient change in IOP caused by the meditative state itself. Regarding visual fields, although we did not expect any change in visual field after the 21-day intervention, perimetry was performed as part of the complete glaucoma assessment.

Blood Sampling, Chemicals, and Reagents

In total, 8 mL blood sample was collected on D-1 and D-21 at 8.00 AM and split to 1 mL in heparinized vacutainer (ROS studies), 3 mL in a plain vacutainer (serum), and the 4 mL in EDTA vacutainer (microarray analysis).

Biochemical Marker Analysis

Commercial kits were used as per the manufacturer's instructions to determine levels of β-endorphin (Cat-No. EK-022-14, Phoenix Pharmaceuticals Inc.), cortisol (Cat-No. EIA-1887, DRG Diagnostic, Germany), IL6 (Cat-No. 950.035.048, Gen-Probe, Diaclone Diagnostic, France), TNF-α (Cat-No. ab100654, Abcam), BDNF (Cat-No. ab99978, Abcam), and TAC (Cat-No. ab65329, Abcam). Luminol (Cat-No. 123072) and Cy3 Dye were from Sigma Aldrich. ROS was estimated as previously described by us.[20]

Gene Expression Profiling

Total RNA was extracted from whole blood using RNeasy Qiagen Kit (RNeasy; Qiagen, Valencia, CA; Cat-No. 74106), converted to cRNA and labeled with Cy3 dye using the Agilent's Quick-Amp labeling Kit (Cat-No. 5190-0442). Labeled cRNA samples were hybridized on Agilent human whole genome oligo microarrays (8×60 K) for 18 hours at 65°C in 1 color experiment. Analysis of the expression data using Agilent Genespring 13.1.1 software and Metacore analysis (https://portal.genego.com/) allowed identification of differentially expressed genes which was evaluated with unpaired *t* test and Benjamin Hochberg using false discovery rate estimation for multiple testing correction with a $P < 0.01$ and fold change (FC) cutoff of > 1.5 as a basis for gene shortlisting for networking, pathway, and correlation analysis.

Statistical Analysis

Power calculations were based on the results of Kaluza and Strempel.[21] We estimated that enrollment of 90 participants (180 eyes) would yield a power of 80% to determine an absolute between-group difference of 30 percentage points in lowering of IOP (and a superiority margin of 20% in the intervention group) with a 2-sided alpha-level of 5% while assuming that 10% of the enrolled patients would be lost to follow-up.

Statistical analysis (STATA 11.2 software) for pretreatment and posttreatment differences were calculated for all our data. The χ^2 test and the Fisher exact test were used to compare categorical characteristics at baseline, the student *t* test compared normality distribution of continuous variables and Wilcoxon rank-sum test for nonparametric continuous data. Intention-to-treat analyses were carried out for both primary and secondary outcomes.

Correlation analyses were performed only for patients that completed the trial. The paired *t* test for within group comparisons and independent *t* test between-group comparisons were used with significant *P*-values set at $P < 0.001$ (except QOL, $P < 0.05$) to adjust alpha for multiple comparisons. Microarray data analysis used unpaired *t* test for between-group comparison (Agilent Genespring 13.1.1 software) with $P < 0.01$ considered to be significant. The Pearson correlations were calculated using percent change over baseline of all parameters with false discovery rate correction to reduce spurious findings.

RESULTS

Demographics

There were no significant differences in the baseline characteristics between the 2 groups (Table 1).

IOP (Primary Endpoint)

Before treatment both groups had comparable IOP. Between-group comparison pretreatment versus posttreatment showed that only in the meditation group the mean IOP decreased significantly by D-21. Noteworthy, 30 of 40 participants who completed the meditation course (75%) showed > 25% IOP reduction (Fig. 2).

Visual Field

No pretreatment to posttreatment change was observed in visual fields in any of the 2 groups.

QOL

At baseline, the mean WHOQOL-BREF scores at D-0 were comparable in both groups but after meditation it

TABLE 1. Clinical Characteristics and Demographic Features of the Participant Included in this Trial

	Mean ± SD		
Particular	**Age (y)**	**IOP (OD/OS) (mm Hg)**	**VF (OD/OS) (MD)**
MM group (N = 45) (25 males/20 females)	57.88 ± 8.17	18.8 ± 2.34/19 ± 1.63	−13.93 ± 3.85/−12.86 ± 4.29
Control group (N = 45) (25 males/20 females)	56.63 ± 7.12	19 ± 1.87/19.45 ± 1.36	−14.14 ± 3.94/−13.41 ± 3.76

IOP indicates intraocular pressure; MD, mean deviation; MM, mindfulness meditation; OD, right eye; OS, left eye; VF, visual field.

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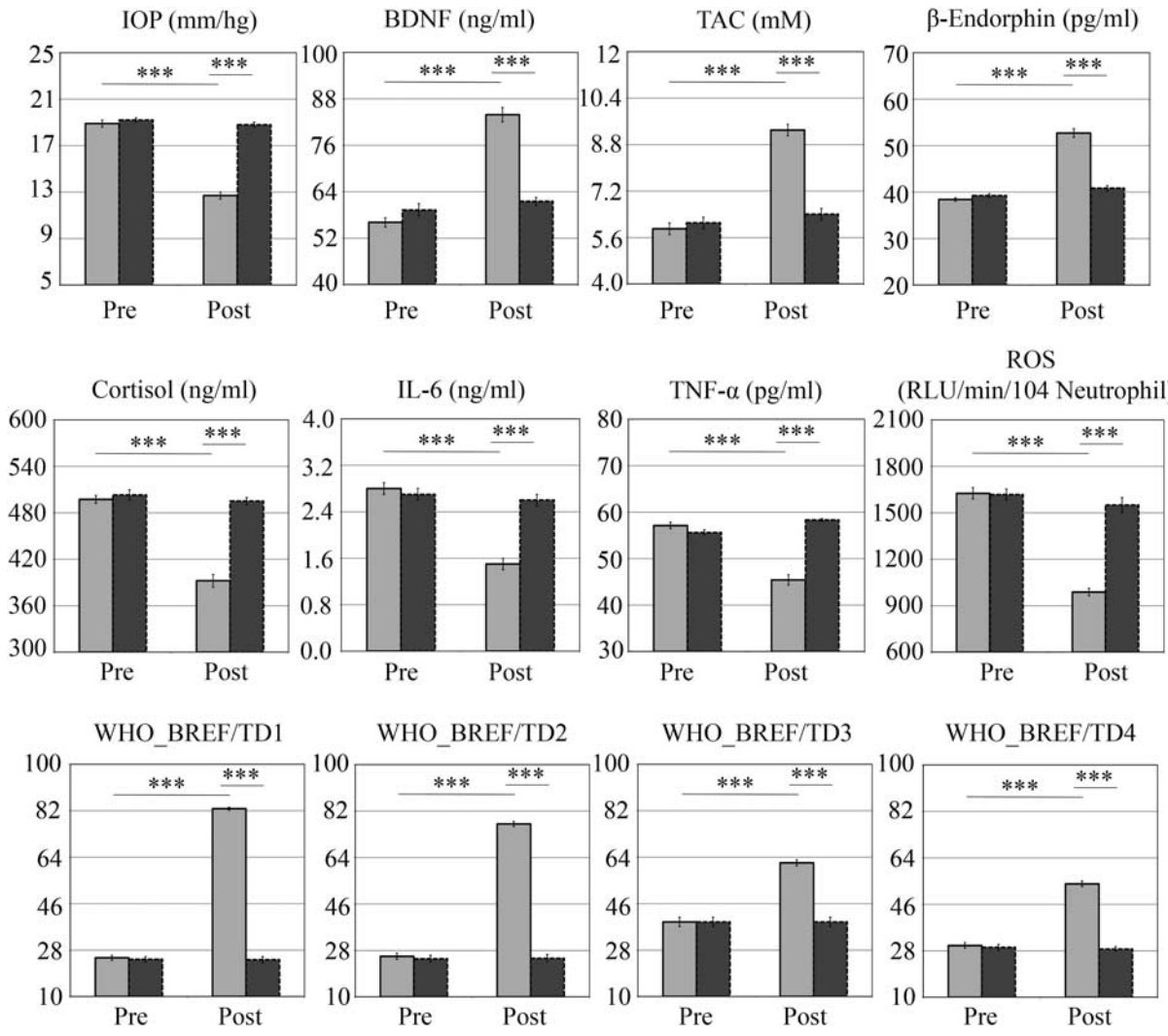

FIGURE 2. Outcome of IOP, psychological, and biomarkers for the meditation (light gray) vs. control group (dark gray). BDNF indicates brain-derived neurotrophic factor; IOP, intraocular pressure; ROS, reactive oxygen species; TAC, total antioxidant capacity. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$ (2-tailed; mean ± SE).

improved significantly by D-21 in all the domains while there was no significant change in controls (Fig. 2).

Biomarker Assays

Both groups were comparable in all biological markers at baseline but differed after intervention. The mental stress biomarker cortisol significantly decreased in meditators and β-endorphin levels increased. The inflamatory markers (TNF-α, IL-6 and ROS) significantly decreased whereas, BDNF and TAC levels increased in meditation group (Fig. 2).

Differential Gene Expression

In the meditation group, 109 genes were identified to be significantly and differentially expressed postmeditation as compared with controls. Among these genes, 54 were upregulated and 55 downregulated. Here, we just limit our report to the most relevant genes selected: *NGFR, TAZ, BNP, IL2, IL4, FGFR1*, and metallothionein-I were significantly upregulated, whereas *RAR, CYP26A1, I-kB, EGFR, ERK7, PTGER3, EGFR*, and *IL21A* genes were significantly downregulated.

Networking analysis identified significant modulation of biological processes having critical roles in neuronal death and survival, apoptosis, inflammation, glutamate toxicity, neurite growth, synaptic maturation, and ocular hypertension mediated retinal ganglion cell (RGC) death (see Supplementary Appendix, Supplemental Digital Content 1, http://links.lww.com/IJG/A215 for details).

Adverse Events

No serious or nonserious adverse event was observed.

Correlation Analyses

Significant correlations between IOP changes, QOL scores, biomarkers, and gene expression pattern were observed (Fig. 3). IOP improvement correlated positively with the changes of parameters representing QOL and relaxation/well-being (BDNF, TAC, and endorphin) but negatively with the changes of parameters representing the stress response (cortisol, ROS, IL6).

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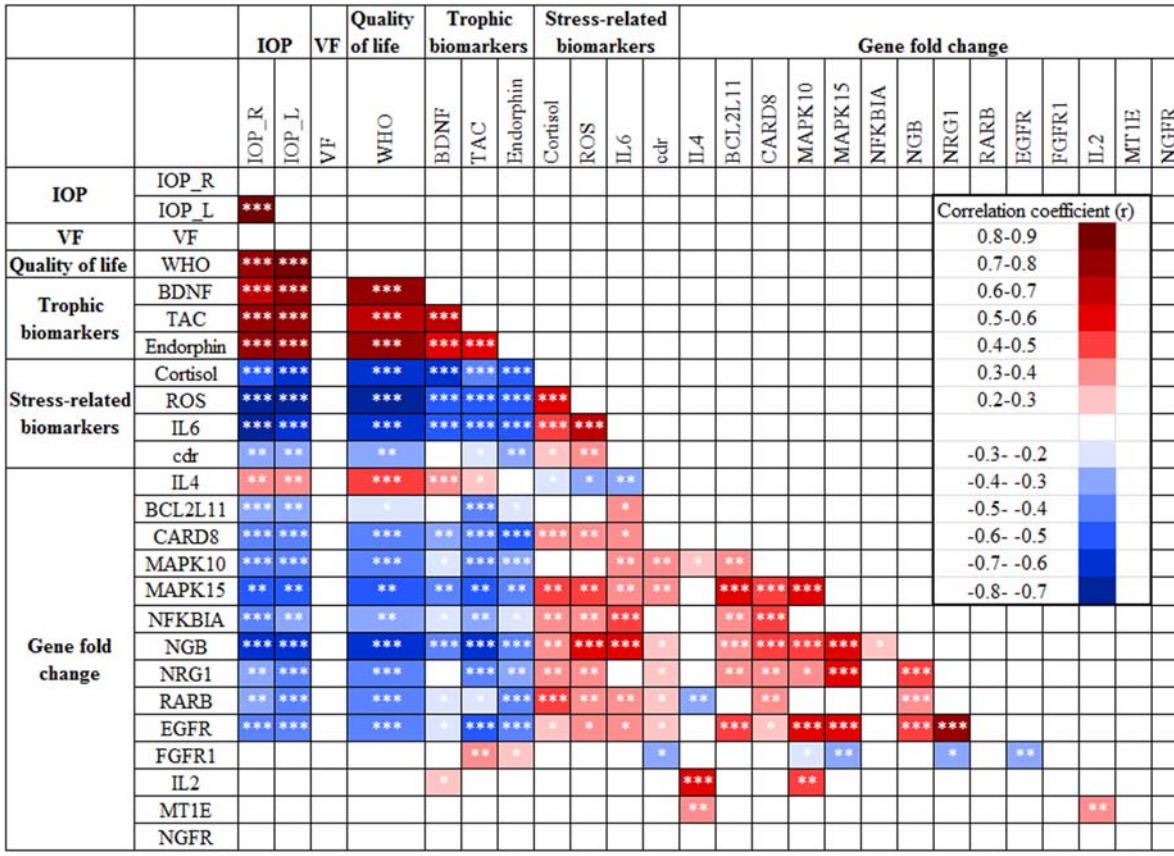

FIGURE 3. Correlations analysis of pre-post differences (changes) between IOP, quality of life measures, "trophic" and "stress-related" biomarkers and their respective gene expressions with probability levels of ***$P < 0.001$, **0.01, and *0.05 (2-tailed). To facilitate interpretation of the results, the change of IOP and general quality of life scores was reversed so that positive values represent positive outcomes. False discovery rate corrections were applied to reduce spurious findings. As the table shows, IOP reductions were positively correlated with trophic (relaxation associated) and negatively with stress-related changes at all levels of analysis. BDNF indicates brain-derived neurotrophic factor; IOP, intraocular pressure; ROS, reactive oxygen species; TAC, total antioxidant capacity; VF, visual field. Figure 3 can be viewed in color online at www.glaucomajournal.com.

Among the 14 genes, IOP improvement correlated positively with the FC of IL4 (anti-inflammatory cytokine) and negatively with the FCs of BCL2L11 (apoptosis facilitator), CARD8 (apoptosis and Inflammation), MAPK10 (neuronal apoptosis, inflammation), MAPK15, NFKBIA, RARB (binds to retinoic acid matrix homeostasis) and EGFR (maintenance of trabecular meshwork and IOP regulation, transcription factor promoting cell growth, division, and cell survival).

DISCUSSIONS

Although RR evoked by mind-body interventions is known to reduce stress and ameliorate a multitude of chronic conditions such as diabetes and cardiovascular diseases,[22] here we report, for the first time, confirmatory evidence of the therapeutic effect of MM in POAG. We showed that meditation significantly lowered IOP which correlated highly with lowered stress-biomarker levels (cortisol, IL6, TNF-α, ROS) and a rise of β-endorphins, BDNF and TAC which, in turn, correlated with modulation of gene expression profiling. Meditation also improved QOL.

Our findings are compatible with prior exploratory evidence that meditation can counteract glaucoma-related reduction in QOL and IOP elevation (in angle-closure glaucoma), decrease cortisol, increase endorphins, and elevate cerebral blood flow and oxygenation in different brain areas.[23] Meditation also reduces hypoxic injury at the ONH and improves parasympathetic function that benefit trabecular outflow by opening up the passageway and constricting the pupil in addition to improving vagal tone.[24] But these studies were only of exploratory level of evidence making a confirmatory prospective trial necessary. Our study now presents this confirmatory evidence, for the first time, in a large sample and demonstrates close association between mental stress and glaucomatous neurodegeneration indicating that stress is a major causal factor of IOP elevation; stress reduction by a RR-elliciting meditation not only normalizes IOP but also improves stress biomarkers, gene expression changes, and QOL (Fig. 4).

Mental or "psychological" stress are known to be associated with IOP elevation,[25] and in those who already have glaucoma, stress raises IOP even further. Mental stress may thus play a key role in acceleration of glaucoma pathogenesis and aggravation of its severity.

Alterations of neurotrophic factors that regulate CNS cell survival and death were also previously reported. One classic neurotrophic factor, BDNF is reduced in plasma of POAG patients.[26] Interestingly, BDNF expression in hippocampus is dramatically reduced in response to acute stress and hence

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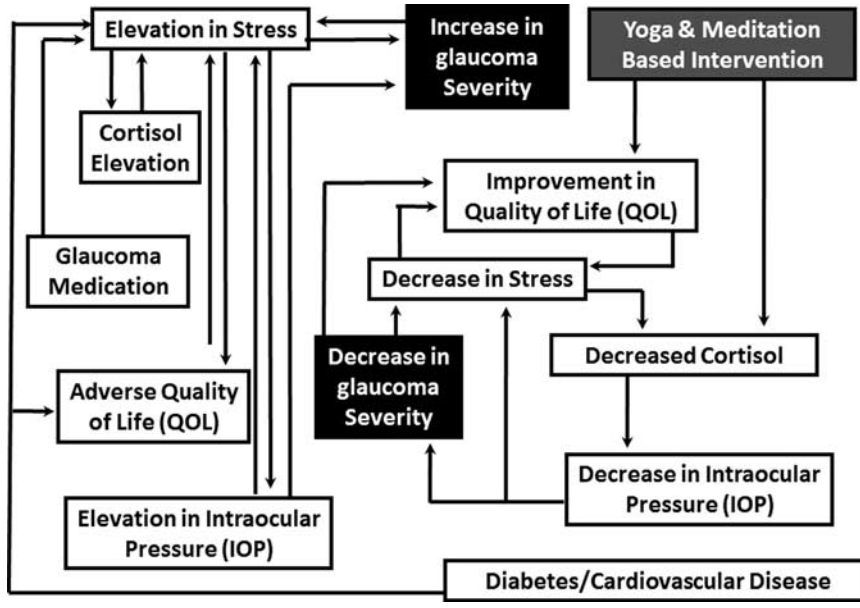

FIGURE 4. Flow chart of the psychobiology of IOP reduction. IOP indicates intraocular pressure; QOL, quality of life.

BDNF may play an important part in modulating stress and depression. In an experimental glaucoma model, topical eye treatment with BDNF was found to be a safe and feasible strategy to preserve visual function and reduce RGC vulnerability to ocular hypertension.[27,28] As we showed, meditation exercises were sufficient to raise BDNF plasma levels which, in a speculative spirit could enhance CNS cell survival and synaptic plasticity in glaucoma; an issue requiring further study.

The proposal that elevated IOP may be caused by prolonged stress which leads to increased cortisol release is compatible with our findings that meditation lowered cortisol levels which are highly correlated with IOP normalization. Stimulating the arcuate nuclei in rabbit brains is known to release endorphins with subsequent reduction in IOP,[29] suggesting β-endorphins to play a role in IOP control and possibly glaucoma pathogenesis. Our POAG patients had significantly elevated β-endorphin levels when they practiced meditation, supporting the notion of stress as an etiological factor and stress reduction as an adjunct treatment to routine POAG care.

Our findings are also compatible with the observations that psychological stress acts as a major provocative factor in chronic inflammatory conditions measured by IL6 and TNF-α. In glaucoma patients, IL6 is elevated in aqueous humor and short-term yoga-based meditation reduces IL6 levels in patients with chronic inflammatory conditions[30] and mind-body therapies reduce biomarkers of inflammation.[30,31]

TNF-α is also elevated both in glaucoma patients and other stressful conditions; we showed, it is downregulated by meditation. TNF-α upregulates matrix metalloproteinases and plays a crucial role in tissue remodeling in the glaucomatous ONH[32,33] and metalloproteinase activity is associated with RGC death mediated by IOP elevation.

Oxidative stress damages the human trabecular meshwork[34,35] (especially its endothelial cells), yet another contributor to POAG pathogenesis. Decreased levels of TAC have been found in patients of major depressive disorder and a balance between oxidative stress and TAC is essential for homeostasis. Erdurmuş et al[36] suggested that decreased antioxidant defence (by TAC) and increased oxidative stress plays an important role in pathogenesis of both POAG and pseudoexfoliation glaucoma.

Expression changes in various genes like TNF-∞, NFκβ, IL6, etc. have already been implicated and our findings have enriched the list while confirming the previous reports. Noteworthy to mention that the processes, these genes are involved in, display complete agreement with the previous reports about these genes, related genes, and relevant pathways/networks.

In a previous study we demonstrated that patients with primary glaucoma have inferior QOL as compared with a control population[37] and our correlation analysis results now show that meditation-induced IOP normalization is associated with significantly improved QOL. MM may thus improve an individual's psychological state of mind toward optimism, improved awareness, and reduced feeling of pressure and tension, all of which contribute to better QOL. IOP normalization, stress and QOL, therefore, are tightly related.

Limitations of the Study

The study could not be designed double-blind to completely avoid expectation biases by the patients. But even if expectation alone would explain the effect, this would, in fact, support our argument that a positive state of mind (with less stress) impact IOP. Another possible limitation of our study is the assumption that the circulating stress biomarkers reach the ocular and brain tissues. However, it is reasonable to make this assumption that nutrients, molecules, and growth factors present in blood are circulated throughout the body and can theoretically impact organs, such as the eye and brain. Another concern might be that we measured IOP at only 1 time of the day and that this limits our conclusions because IOP varies diurnally; yet, any such variance would create, if anything, a bias against our hypothesis. Furthermore, in future studies the issue should be addressed if IOP changes are long-lasting, that is, far beyond 5 hours, for example, days or weeks which one

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might expect given that gene expression changes were observed. Finally, the question is still open whether meditation helps visual field function in the long run.

CONCLUSIONS

MM is a useful adjunctive therapy for POAG patients. It can help in lowering IOP, improving QOL, ameliorating biomarkers of stress, and produce parallel changes in gene expression. Mental stress thus seems to play a fundamental role in POAG and is associated with aggravation of most of the glaucoma-related pathogenic factors including IOP, therefore, studies aimed at exploring stress as a causal factor in glaucoma are warranted.

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