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Beneficial effect of mindfulness based stress reduction on optic disc perfusion in primary open angle glaucoma: A randomized controlled trial

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A B S T R A C T

Background and aim: Glaucoma is one of the leading causes of visual impairment worldwide. Next to intraocular pressure (IOP), vascular factors play a major role in glaucoma. Mindfulness-based stress reduction (MBSR) has been shown to reduce the IOP, normalize the stress biomarkers, modulate gene expression, and also improve the quality of life. This study was aimed to assess the effect of MBSR in optic disc perfusion of patients with primary open angle glaucoma (POAG).
Experimental procedure: POAG patients with controlled IOP (<21 mmHg) were randomised in to intervention group (n = 30) and control group (n = 30). Both the groups continued their routine glaucoma medications while the intervention group practiced 45 min of MBSR every day in addition. IOP and optic disc perfusion using OCT-Angiography were recorded at baseline and at 6 weeks for both the groups.
Results: The mean age of the participants were 53.23 ± 8.4yr in intervention and 50.23 ± 7.3yr in the control group (p = 0.06). All the baseline parameters were comparable in both groups. After MBSR, in the intervention group there was a significant reduction of IOP (p=0.001), increase in circum-papillary vessel density in superior quadrant (15.8%–17.4%, p=0.02) and nasal quadrant (14.2%–16.5%, p=0.01), increase in circum papillary vascular perfusion, in superior quadrant (38.9%–41.1%, p<0.001), in temporal quadrant (42.2%–44.5%, p<0.001), in inferior quadrant (40.1%–43.8%, p<0.001), and in nasal quadrant (40.6%–42.8%, p<0.001). There was also a significant increase in Flux Index after 6weeks (0.38–0.40, p<0.001).
Conclusion: MBSR can reduce barotrauma and improve optic disc perfusion in POAG patients and serve as a useful adjunct to the standard medical therapy.

1. Introduction

Glaucoma is a vision-threatening progressive optic neuropathy with primary open-angle (POAG) predominating other subtypes.[1] It is a complex neurodegenerative disorder characterized by progressive degeneration of retinal ganglion cells (RGCs).[2] The pathophysiology of glaucoma is multifactorial. Although the RGC death is related to the level of intraocular pressure (IOP), the factors which contribute to its progression are not fully characterized. Among the other contributing factors for glaucoma, vascular factor plays a major role in glaucoma.[3] Optic nerve head microcirculation was found to be correlated with visual field defects and nerve fiber loss in glaucoma.[4] Oxidative stress can cause trabecular meshwork dysfunction and may play an important role in the pathogenesis of primary open angle glaucoma.[5] The current treatment protocol is mainly focused on the reduction of IOP to a level where the glaucoma progression is halted or delayed either by medical or surgical management. Various neuroprotective agents, antioxidants have been tried as add-on therapy in glaucoma with limited success.[6,7]

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List of abbrevations

RGC	Retinal Ganglion Cell
IOP	Intraocualr pressure
MBSR	Mindfulness based stress reduction
OCTA	Optical coherence tomography- Angiography
POAG	Primary open angle glaucoma
cpVD	Cumpapillary vessel density
cpVP	Circumpapillary vessel perfusion
NO	Nitric oxide

Psychological stress can lead to an elevation in oxidative stress, vascular dysregulations,[8] elevations in IOP[9] decline in parasympathetic activity, and worsen the glaucoma progression. Stress can be the cause as well as the consequence of vision loss in patients with glaucoma.[10,11] Mindfulness meditation is an effective and most widely used technique to evoke relaxation responses and normalize the stress biomarkers.[12] In primary open angle glaucoma, Mindfulness based stress reduction (MBSR) has been shown to reduce the IOP, normalize the stress biomarkers, modulate gene expression, and also improve the quality of life in glaucoma patients.[13–15]

The invention of Optical coherence tomography-angiography (OCT-A) to assess the retinal vascular density in glaucomatous eyes have allowed the objective study of optic nerve head perfusion. Studies have shown a reduced retinal vascular density and blood flow in eyes with primary open-angle glaucoma (POAG) compared to healthy eyes.[16] The peripapillary and macular vascular density had a negative correlation with the severity of glaucoma.[17] Along with the existing parameters, changes in peripapillary and macular vessel density can also be used to monitor glaucoma progression.

The present study was designed to answer the research question that whether MBSR can help to increase optic disc perfusion in patients with primary open angle glaucoma (assessed using OCT-A).

2. Methods

This is a prospective, randomized, interventional study conducted at a tertiary care centre in North India after obtaining approval from the institute's ethical committee (IEC, All India Institute of Medical Sciences, New Delhi, Ref. No. IECPG-384) and following the recommendations of the Declaration of Helsinki. Written informed consent was obtained from all the participants. Due to the lack of previous studies to evaluate the effect of MBSR on optic disc perfusion in patients with glaucoma, a convenient sample of 60 patients was decided. Out of 100 patients assessed, 60 patients who fulfilled the criteria were enrolled in the study. Patients were randomized into 2 groups: 30 in the interventional group and 30 in the control group. Randomization was done by computer-based randomization using permuted blocks.

2.1. Study participants

The inclusion criteria were: age >40 years, moderate/severe POAG (according to Hodapp- Parrish-Anderson [HPA] classification) with IOP <21 mmHg with/without topical medical therapy, and best-corrected visual acuity > 6/60 in the better eye. Exclusion criteria were: any co-morbid condition (other than glaucoma) leading to visual loss, previous practice/experience of meditation or yoga in any form, history of ocular surgery in previous 6 months, having chronic systemic diseases like diabetics which could affect OCT-A parameters, medical therapy for any other illnesses, and significant physical/mental disability.

2.2. Baseline parameters assessed

Complete glaucoma workup including IOP, optic disc perfusion using OCT-A was done for participants (both intervention and control group). Baseline vitals (pulse, blood pressure) were also recorded.

OCT-A was performed using Zeiss AngioPlex (Cirrus HD-OCT 5000, Zeiss Meditec. Inc.). The enface images of the optic nerve head for vessel density and vessel perfusion were calculated in a 6×6 mm scan. Three circle scans were drawn on the enface image with a diameter of 1 mm, 3 mm, and 6 mm. 3 mm circle scan was divided into four sectors; superior, temporal, inferior, and nasal. The circumpapillary vessel density (cpVD) and circumpapillary vessel perfusion (cpVP) were calculated in the 3 mm circle scans in all four quadrants. The vessel density was defined as the total length of perfused vasculature per unit area in the region of measurement. The vessel perfusion was defined as the total area of perfused vasculature per unit area of measurement. Using a 4.5*4.5 mm scan we also measured the flux index of all patients. Flux Index indicates the number of blood cells passing through a retinal vessel cross-sectional area per unit of time. The blood flux index can be defined as the mean flow intensity in the vessel area, where the blood flow signal was normalized from 0 to 1 by dividing by the full dynamic range of blood flow signal intensity. Flux Index is a unit-less ratio.

2.3. Intervention

In the intervention group, the patients underwent a 6 weeks course of MBSR for 45 min under a certified YOGA instructor. No change was done to the standard glaucoma treatment of any patient. The session was for 45 min every day in the morning between 9 a.m. and 10 a.m. The Control group was continued on regular glaucoma medications.

After 6 weeks of IOP, optic disc perfusion and other parameters were recorded for the participants. The control group was also waitlisted for MBSR after the completion of the study.

2.4. Statistical analysis

Both eyes of the participants were taken for the analysis. SPSS Software version 26 was used for data analysis. Chi-square test and Fisher's exact test were employed to compare categorical characteristics at baseline. Independent *t*-test was used to compare parameters between two groups and paired *t*-test was used to compare within-group parameters for parametric data. Wilcoxon sign rank test (within-group) and Mann-Whitney test (intergroup) were used for non-parametric data. Spearman correlation test was used to assess correlation. P-value < 0.05 was considered significant.

3. Results

The mean age of the participants (intervention: 53.23 ± 8.4 yr, controls: 50.23 ± 7.3 yr; p = 0.06) were comparable between the two groups. There was male predominance in both the groups with comparable sex distribution (intervention: 4:1, controls: 3.3:1; p = 0.08). The baseline parameters of the eyes (60) like IOP, cup-disk ratio, number of topical glaucoma medications used, mean deviation in the visual field (Humphrey field analyzer, Zeiss, San Leandro, USA) were comparable in both groups (Supplementary

Table 1).

3.1. Changes in optic nerve head perfusion

After 6 weeks, a 3 mm circle scan showed a significant increase in cpVD in the superior and nasal quadrant for the intervention group, while there was no significant change in the controls (Table 1). The 3 mm circle scan also showed a significant increase in cpVP in all four quadrants for the intervention group (Fig. 1a and b), while there was no significant change in the controls (Table 1).

Flux Index: There was a statistically significant increase in the flux index in the intervention group (Fig. 1a and b), while there was no significant change in the controls (Table 1).

After 6 weeks of MBSR, there was a statistically significant reduction of IOP in the intervention group ($p = 0.001$) compared to the control group ($p = 0.16$) (Table 2). In the intervention group, 23 (38%) eyes had less than 10% reduction in IOP, 33 (55%) eyes had a 10–15% reduction in IOP, and 4 (7%) eyes had more than 15% reduction in IOP; while the control group had only 4% reduction in IOP. In the intervention group, there was no significant correlation between IOP reduction and the changes in OCTA parameters (cpVD: $r = 0.1, p = 0.4$; cpVP: $r = 0.25, p = 0.06$; flux index: $r = 0.06, p = 0.69$). There was a statistically significant decrease in heart rate ($p < 0.001$), systolic blood pressure ($p = 0.001$), and diastolic blood pressure ($p = 0.001$) at 6 weeks from baseline after Mindfulness-Based Stress Reduction (MBSR) in the intervention group (Table 2).

4. Discussion

In glaucoma along with the RGCs; the optic nerve (retrobulbar and intracranial part), the nucleus of the lateral geniculate body, and the visual cortex of the brain are also affected.[18–20] There is a reduced ocular blood flow in patients with POAG.[21] This could be either due to increased resistance due to anatomical variations, functional vascular dysregulation, or reduced perfusion pressure due to increased IOP. Various studies showed that Meditation increases cerebral blood flow including the occipital cortex.[22] A short course of MBSR enhanced brain oxygenation in patients with POAG.[15] However no study has been performed to evaluate the effect of MBSR on optic nerve head perfusion using OCT -A.

Various methods used to assess the ocular blood flow like fluorescein angiography, laser doppler, colour doppler, blue field entoptic technique, etc have previously demonstrated a reduced ocular blood flow.[23–25] OCTA, a relatively new, non-invasive technology can be used to assess the microvasculature in the optic nerve, peripapillary retina, and macula.[16] Previous studies suggest that vessel density (cpVD) was associated with glaucomatous changes measured by parameters like RNFL thickness, GCC, vertical cup disc ratio, visual field mean deviation, and lower cpVD was associated with faster visual field progression.[26,27] Thus optic disc perfusion can be used for diagnosing and monitoring glaucoma. Weindel et al. showed that tafluprost therapy can increase the peripapillary flow density measured with OCTA.[28]

In our study, we used OCTA to assess cpVD, cpVP, and flux index; 6 weeks of MBSR significantly improved the cpVD (superior and nasal quadrant), cpVP, and flux index. Thus MBSR leads to an enhancement of optic disc perfusion in patients with glaucoma.

4.1. Probable cause for the increase in optic disc perfusion

The optic nerve and its vasculature have both sympathetic and parasympathetic innervations from the cervical sympathetic system and oculomotor nerve respectively. The autonomic perivascular network around the choroidal vessels is formed by choroidal neuroplexus. The autonomic dysfunction leading to failure of optic nerve blood flow could play a significant role in the pathogenesis of POAG.[29] Kurysheva et al. have shown that patients with normal-tension glaucoma have autonomic dysfunction, with a predominance of sympathetic activity.[30] Azam MA et al. showed that meditation improves parasympathetic function.[31] MBSR improves autonomic dysfunction and increases parasympathetic activity.[32] In our study, after MBSR there was a significant decrease in heart rate, systolic and diastolic blood pressure showing a decrease in sympathetic activity and an increase in parasympathetic activity. Thus MBSR can decrease the sympathetic drive (vasoconstriction) leading to vasodilation and there may be subsequent enhancement of ocular blood flow. So the increase in optic disc perfusion could be attributed to improvement in autonomic dysfunction after MBSR. Nitric oxide (NO) is also an important agent which regulates ocular blood flow.[33,34] Decreased levels of NO and cGMP were found in plasma and aqueous humor of patients with glaucoma. A rise in NO could be beneficial for lowering IOP in glaucoma and potentially increasing the blood flow to the optic nerve head. NO levels have shown to rise following MBSR.[13,35] This could also explain the increase in optic disc perfusion in our patients after MBSR.

In our study, the mean percentage reduction in IOP after 6 weeks of MBSR was 10–25% in about two-thirds of the participants. It was comparable to other studies where a 3 weeks or 6 weeks course of MBSR produced an IOP reduction varied from 10 to 25% or more in all or about two-thirds of the participants.[13–15] Major randomized trials demonstrated that reduction in IOP either prevents or delays the progression of glaucoma.[36] Till now, reduction of IOP achieved

Table-1
Baseline and Post MBSR comparison of optic disc perfusion in both groups.

Parameters	Group-1 (MBSR-intervention)			Group-2 (Controls)			G1 vs G2 Baseline P value[#]	G1 vs G2 6 Weeks P value[#]
	Baseline Mean ± SD	At 6 Weeks Mean ± SD	P Value[a]	Baseline Mean ± SD	At 6 Weeks Mean ± SD	P Value[a]		
Circumpapillary Vessel Density (in %)								
Superior	15.83 ± 2.3	17.42 ± 2.91	**0.02**	15.22 ± 2.61	16.52 ± 2.83	0.10	0.45	**0.02**
Temporal	12.47 ± 1.2	13.92 ± 2.82	0.43	13.73 ± 1.80	13.90 ± 1.03	0.62	0.38	0.79
Inferior	13.02 ± 2.49	13.40 ± 2.088	0.59	14.09 ± 2.77	14.53 ± 2.75	0.61	0.54	0.36
Nasal	14.28 ± 2.47	16.52 ± 2.62	**0.01**	15.00 ± 2.56	16.97 ± 2.53	0.53	0.48	**0.04**
Average Vessel Density	13.07 ± 2.41	14.57 ± 2.35	0.14	14.65 ± 1.99	14.55 ± 2.03	0.07	0.22	0.81
Circumpapillary Vessel Perfusion (in %)								
Superior	38.96 ± 3.22	41.15 ± 3.14	**<0.001**	40.29 ± 3.24	40.17 ± 3.21	0.59	0.98	**0.02**
Temporal	42.21 ± 4.45	44.53 ± 1.89	**<0.001**	44.95 ± 2.58	44.81 ± 2.56	0.56	0.49	**0.02**
Inferior	40.15 ± 2.86	43.85 ± 2.61	**<0.001**	41.55 ± 3.71	41.33 ± 3.68	0.69	0.41	**0.05**
Nasal	40.60 ± 3.31	42.88 ± 2.31	**<0.001**	41.61 ± 2.36	41.52 ± 2.41	0.34	0.40	**0.01**
Flux Index	0.384 ± 0.04	0.40 ± 0.04	**<0.001**	0.38 ± 0.43	0.37 ± 0.43	0.74	0.53	**<0.001**

[a] Paired *t*-test, # Independent *t*-test.

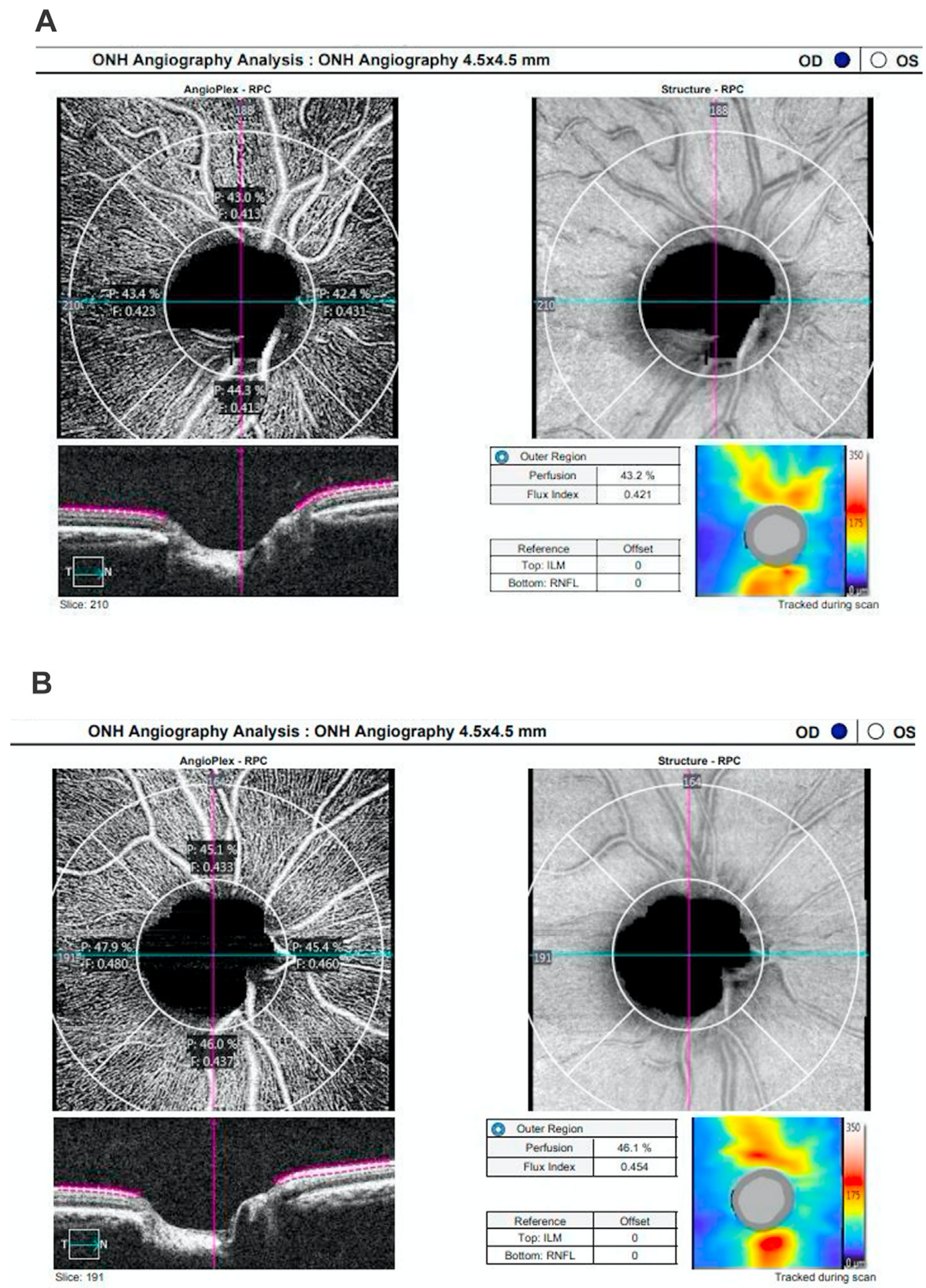

Fig. 1. a OCT-Angiography of the right eye of a patient before MBSR showing circumpapillary vascular perfusion and flux index and (1b) after MBSR showing increase in circumpapillary vascular perfusion and flux index.

Table 2
Baseline and Post MBSR comparison of Heart Rate and Blood Pressure in both groups.

Parameters	Group-1 (MBSR-intervention)			Group-2 (Controls)			G1 vs G2 Baseline P value#	G1 vs G2 6 Weeks P value#
	Baseline Mean ± SD	At 6 Weeks Mean ± SD	P Value[a]	Baseline Mean ± SD	At 6 Weeks Mean ± SD	P Value[a]		
Intraocular pressure (in mmHg)	18.06 ± 1.38	16.34 ± 1.32	**p=0.001**	18.46 ± 1.46	17.65 ± 1.12	0.16	0.13	**<0.001**
Heart Rate (In bpm)	78.23 ± 8.45	74.43 ± 7.44	**p=0.001**	77.93 ± 9.61	77.91 ± 9.29	0.98	0.35	**<0.001**
Systolic Blood Pressure (In mmHg)	136.63 ± 8.42	132.17 ± 9.40	**p=0.001**	134.37 ± 7.37	135.37 ± 8.51	0.06	0.12	**0.04**
Diastolic Blood Pressure (In mmHg)	78.17 ± 4.95	74.40 ± 4.95	**p=0.001**	80.93 ± 5.76	81.77 ± 6.24	0.06	0.09	**<0.001**

[a] Paired *t*-test, # Independent *t*-test.

by either medical or surgical means is the only proven or practiced method to treat glaucoma. Recent studies proved that a short course of MBSR can reduce the IOP.[13–15] Meditation can reduce IOP by various possible mechanisms like an increase in melatonin which acts on MT2, MT3 receptors and potentiates the effect of beta-blockers and alpha-agonists; increase in nitric oxide which increases conventional outflow; decreases in serum cortisol level; by increasing activity of the parasympathetic nervous system and decreasing the activity of sympathetic nervous system.[32,37,38]

Reduction in stress hormones by MBSR has a positive impact on both IOP and optic disc perfusion.[10,11,39] Decrease in IOP itself has been shown to increase optic disc perfusion.[40] In our study, there was no significant correlation between the reduction in IOP and changes in optic disc perfusion measured by OCTA. So MBSR could be attributed as the possible cause of improvement in optic disc perfusion, independent of the factors that have caused IOP reduction.

5. Limitation

Subjective improvement in vision or visual field defects has not been documented in the present study and long-term documentation of the functional changes would be useful. Compliance of the patient to do MBSR every day in the absence of a trained instructor is also questionable. The control group did not get any placebo condition.

6. Conclusion

Previous studies about meditation in glaucoma patients have shown to reduce IOP, reduce stress biomarkers, modulate gene expression, improve brain oxygenation, and also improve quality of life.[13–15,32] This is the first study that demonstrates that MBSR can also improve optic nerve perfusion measured with help of OCTA.

MBSR can be recommended as an adjuvant therapy along with glaucoma medications to augment optic nerve head perfusion and reduce IOP which may positively impact the progression of glaucomatous optic neuropathy.

Declaration of competing interest

There are no conflicts of interests among authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtcme.2021.06.006.

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Presentation at a meeting

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References

1. Bourne RRA, Jonas JB, Bron AM, et al. Prevalence and causes of vision loss in high-income countries and in Eastern and Central Europe in 2015: magnitude, temporal trends and projections. *Br J Ophthalmol*. 2018;102(5):575–585. https://doi.org/10.1136/bjophthalmol-2017-311258.
2. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. *J Am Med Assoc*. 2014;311(18):1901–1911. https://doi.org/10.1001/jama.2014.3192.
3. Flammer J, Orgül S. Optic nerve blood-flow abnormalities in glaucoma. *Prog Retin Eye Res*. 1998;17(2):267–289. https://doi.org/10.1016/s1350-9462(97)00006-2.
4. Yokoyama Y, Aizawa N, Chiba N, et al. Significant correlations between optic nerve head microcirculation and visual field defects and nerve fiber layer loss in glaucoma patients with myopic glaucomatous disk. *Clin Ophthalmol Auckl NZ*. 2011;5:1721–1727. https://doi.org/10.2147/OPTH.S23204.
5. Erdurmuş M, Yağcı R, Atış Ö, Karadağ R, Akbaş A, Hepşen IF. Antioxidant status and oxidative stress in primary open angle glaucoma and pseudoexfoliative glaucoma. *Curr Eye Res*. 2011;36(8):713–718. https://doi.org/10.3109/02713683.2011.584370.
6. Vasudevan SK, Gupta V, Crowston JG. Neuroprotection in glaucoma. *Indian J Ophthalmol*. 2011;59(7):102. https://doi.org/10.4103/0301-4738.73700.
7. Mahalingam K, Chaurasia AK, Gowtham L, et al. Therapeutic potential of valproic acid in advanced glaucoma: a pilot study. *Indian J Ophthalmol*. 2018;66(8):1104–1108. https://doi.org/10.4103/ijo.IJO_108_18.
8. Flammer J, Konieczka K, Flammer AJ. The primary vascular dysregulation syndrome: implications for eye diseases. *EPMA J*. 2013;4(1):14. https://doi.org/10.1186/1878-5085-4-14.
9. Abe RY, Silva TC, Dantas I, et al. Can psychologic stress elevate intraocular pressure in healthy individuals? *Ophthalmol Glaucoma*. 2020;3(6):426–433. https://doi.org/10.1016/j.ogla.2020.06.011.
10. Sabel BA, Wang J, Cárdenas-Morales L, Faiq M, Heim C. Mental stress as consequence and cause of vision loss: the dawn of psychosomatic ophthalmology for preventive and personalized medicine. *EPMA J*. 2018;9(2):133–160. https://doi.org/10.1007/s13167-018-0136-8.
11. Dada T, Mahalingam K, Gupta V. Allostatic load and glaucoma: are we missing the big picture? *J Curr Glaucoma Pract*. 2020;14(2):47–49. https://doi.org/10.5005/jp-journals-10078-1280.
12. Kutz I, Borysenko JZ, Benson H. Meditation and psychotherapy: a rationale for the integration of dynamic psychotherapy, the relaxation response, and mindfulness meditation. *Am J Psychiatr*. 1985;142(1):1–8. https://doi.org/10.1176/ajp.142.1.1.
13. Dada T, Mittal D, Mohanty K, et al. Mindfulness meditation reduces intraocular pressure, lowers stress biomarkers and modulates gene expression in glaucoma: a randomized controlled trial. *J Glaucoma*. 2018;27(12):1061–1067. https://doi.org/10.1097/IJG.0000000000001088.
14. Dada T, Bhai N, Midha N, et al. Effect of mindfulness meditation on intraocular pressure and trabecular meshwork gene expression: a randomised controlled trial. *Am J Ophthalmol*. 2020. https://doi.org/10.1016/j.ajo.2020.10.012, 0(0).
15. Gagrani M, Faiq MA, Sidhu T, et al. Meditation enhances brain oxygenation, upregulates BDNF and improves quality of life in patients with primary open angle glaucoma: a randomized controlled trial. *Restor Neurol Neurosci*. 2018;36(6):741–753. https://doi.org/10.3233/RNN-180857.
16. Chen HS-L, Liu C-H, Wu W-C, Tseng H-J, Lee Y-S. Optical coherence tomography angiography of the superficial microvasculature in the macular and peripapillary areas in glaucomatous and healthy eyes. *Invest Ophthalmol Vis Sci*. 2017;58(9):3637–3645. https://doi.org/10.1167/iovs.17-21846.
17. Li Z, Xu Z, Liu Q, Chen X, Li L. Comparisons of retinal vessel density and glaucomatous parameters in optical coherence tomography angiography. *PloS One*. 2020;15(6), e0234816. https://doi.org/10.1371/journal.pone.0234816.
18. Gupta N, Yücel YH. What changes can we expect in the brain of glaucoma patients? *Surv Ophthalmol*. 2007;52(Suppl 2):S122–S126. https://doi.org/10.1016/j.survophthal.2007.08.006.
19. Yücel YH, Zhang Q, Weinreb RN, Kaufman PL, Gupta N. Effects of retinal ganglion cell loss on magno-, parvo-, koniocellular pathways in the lateral geniculate nucleus and visual cortex in glaucoma. *Prog Retin Eye Res*. 2003;22(4):465–481. https://doi.org/10.1016/S1350-9462(03)00026-0.
20. Weber AJ, Chen H, Hubbard WC, Kaufman PL. Experimental glaucoma and cell size, density, and number in the primate lateral geniculate nucleus. *Invest Ophthalmol Vis Sci*. 2000;41(6):1370–1379.
21. Flammer J, Orgül S, Costa VP, et al. The impact of ocular blood flow in glaucoma. *Prog Retin Eye Res*. 2002;21(4):359–393. https://doi.org/10.1016/s1350-9462(02)00008-3.
22. Lauritzen M. Relationship of spikes, synaptic activity, and local changes of cerebral blood flow. *J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab*. 2001;21(12):1367–1383. https://doi.org/10.1097/00004647-200112000-00001.
23. Logean E, Geiser MH, Petrig BL, Riva CE. Portable ocular laser Doppler red blood cell velocimeter. *Rev Sci Instrum*. 1997;68(7):2878–2882. https://doi.org/10.1063/1.1148211.
24. Cheng CY, Liu CJ, Chiou HJ, Chou JC, Hsu WM, Liu JH. Color Doppler imaging study of retrobulbar hemodynamics in chronic angle-closure glaucoma. *Ophthalmology*. 2001;108(8):1445–1451. https://doi.org/10.1016/s0161-6420(01)00603-0.
25. Gugleta K, Orgül S, Flammer J. Is corneal temperature correlated with blood-flow velocity in the ophthalmic artery? *Curr Eye Res*. 1999;19(6):496–501. https://doi.org/10.1076/ceyr.19.6.496.5286.
26. Zhang S, Wu C, Liu L, et al. Optical coherence tomography angiography of the peripapillary retina in primary angle-closure glaucoma. *Am J Ophthalmol*. 2017;182:194–200. https://doi.org/10.1016/j.ajo.2017.07.024.
27. Rao HL, Srinivasan T, Pradhan ZS, et al. Optical coherence tomography angiography and visual field progression in primary angle closure glaucoma. *J Glaucoma*. 2020. https://doi.org/10.1097/IJG.0000000000001745. Published online December 2.

28. Weindler H, Spitzer MS, Schultheiß M, Kromer R. OCT angiography analysis of retinal vessel density in primary open-angle glaucoma with and without Tafluprost therapy. *BMC Ophthalmol*. 2020;20(1):444. https://doi.org/10.1186/s12886-020-01707-3.
29. Clark CV, Mapstone R. Systemic autonomic neuropathy in open-angle glaucoma. *Doc Ophthalmol Adv Ophthalmol*. 1986;64(2):179–185. https://doi.org/10.1007/BF00159992.
30. Kurysheva NI, Shlapak VN, Ryabova TY. Heart rate variability in normal tension glaucoma: a case-control study. *Medicine (Baltim)*. 2018;97(5), e9744. https://doi.org/10.1097/MD.0000000000009744.
31. Azam MA, Katz J, Fashler SR, Changoor T, Azargive S, Ritvo P. Heart rate variability is enhanced in controls but not maladaptive perfectionists during brief mindfulness meditation following stress-induction: a stratified-randomized trial. *Int J Psychophysiol Off J Int Organ Psychophysiol*. 2015;98(1):27–34. https://doi.org/10.1016/j.ijpsycho.2015.06.005.
32. Dada T, Ramesh P, Shakrawal J. Meditation: a polypill for comprehensive management of glaucoma patients. *J Glaucoma*. 2020;29(2):133–140. https://doi.org/10.1097/IJG.0000000000001406.
33. Toda N, Nakanishi-Toda M. Nitric oxide: ocular blood flow, glaucoma, and diabetic retinopathy. *Prog Retin Eye Res*. 2007;26(3):205–238. https://doi.org/10.1016/j.preteyeres.2007.01.004.
34. Schmidl D, Boltz A, Kaya S, et al. Role of nitric oxide in optic nerve head blood flow regulation during isometric exercise in healthy humans. *Invest Ophthalmol Vis Sci*. 2013;54(3):1964–1970. https://doi.org/10.1167/iovs.12-11406.
35. Kemper KJ, Powell D, Helms CC, Kim-Shapiro DB. Loving-kindness meditation's effects on nitric oxide and perceived well-being: a pilot study in experienced and inexperienced meditators. *Explore N Y N*. 2015;11(1):32–39. https://doi.org/10.1016/j.explore.2014.10.002.
36. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol Chic Ill*. 1960;120(6):701–713. https://doi.org/10.1001/archopht.120.6.701, 2002, discussion 829-830.
37. Cavet ME, Vittitow JL, Impagnatiello F, Ongini E, Bastia E. Nitric oxide (NO): an emerging target for the treatment of glaucoma. *Invest Ophthalmol Vis Sci*. 2014;55(8):5005–5015. https://doi.org/10.1167/iovs.14-14515.
38. Newberg AB, Iversen J. The neural basis of the complex mental task of meditation: neurotransmitter and neurochemical considerations. *Med Hypotheses*. 2003;61(2):282–291. https://doi.org/10.1016/s0306-9877(03)00175-0.
39. Sabel BA, Flammer J, Merabet LB. Residual vision activation and the brain-eye-vascular triad: dysregulation, plasticity and restoration in low vision and blindness - a review. *Restor Neurol Neurosci*. 2018;36(6):767–791. https://doi.org/10.3233/RNN-180880.
40. Holló G. Influence of large intraocular pressure reduction on peripapillary OCT vessel density in ocular hypertensive and glaucoma eyes. *J Glaucoma*. 2017;26(1):e7–e10. https://doi.org/10.1097/IJG.0000000000000527.