

Reply to the reviewers' comments

Reviewer Number	Original comments of the reviewer	Reply by the author(s)	Changes done on page number and line number
1	The authors should differentiate the influence of factors such as diabetes or arterial hypertension on IOP from a direct influence on glaucoma damage. See e.g. PMID: 33074964	Dear Reviewer, Diabetes and elevated blood sugar levels could affect lipid metabolism, raising oxidative stress and cell apoptosis, resembling mechanisms in glaucoma-related retinal cell loss. Alterations in diabetes-related connective tissue might impact both the lamina cribrosa and potentially the trabecular meshwork, possibly influencing optic nerve biomechanics and fluid drainage, potentially raising the risk of glaucoma. The above paragraph has been added in the manuscript.	Page no. 7 Line no. 17
1	Many important terms should either be more clearly defined or correctly referenced, such as vascular dysregulation (see: PMID: 23742177) or Flammer syndrome (PMID: 25075228)	Dear Reviewer, Using color Doppler imaging, the study confirmed that retrobulbar vascular dysregulation significantly contributes to glaucoma progression, particularly in normal tension glaucoma patients with progressive visual field damage. Vascular dysregulation, the inadequate regulation of blood flow for tissue needs, includes primary vascular dysregulation (PVD, formerly called	Page no.3 Line no. 6 & Page no.6 Line no.1

		vasospastic syndrome) and secondary vascular dysregulation. In subjects with PVD, retinal vessels are stiffer and more irregular, and both neurovascular coupling and autoregulation capacity are reduced while retinal venous pressure is often increased. Systemic disorders like migraine, systemic hypotension, Alzheimer's disease, primary vascular dysregulation, and Flammer syndrome contribute to NTG progression. Flammer syndrome, describes a phenotype characterized by primary vascular dysregulation, involves various symptoms triggered by stimuli like cold or stress. Nearly all organs, particularly the eye, can be involved. While it has protective aspects against conditions like atherosclerosis, it's also associated with diseases such as normal tension glaucoma (NTG). The above paragraphs has been added in the manuscript.	
1	HRV is interesting. However, it should be mentioned that it cannot simply be the cause of vascular dysregulation, as this vascular dysregulation can also be observed and measured in	Dear Reviewer, Elevated sympathetic neural activity raises vascular resistance, particularly in cases of endothelial dysfunction,	Page no.8 Line no.21

	the non-innervated retinal blood vessels using the dynamic vessel analyzer. However, vascular endothelial cells play an important role for vascular dysregulation (see e.g.: PMID: 28824736) corneal and the incision made is scleral	impacting glaucoma development. Blood supply to different organs or vascular beds is regulated by the vascular endothelium. Endothelial dysfunction can lead to inadequate organ perfusion due to vascular dysregulation, especially in individuals with a predisposition. This may result in characteristic vascular - mediated diseases such as normal-tension glaucoma. The above paragraph has been added in the manuscript.	
1	Our current research and knowledge are based on what our ancestors have already built up. It would therefore be appropriate to point this out, e. g: PMID: 12150988	Dear Reviewer, Two principal theories for the pathogenesis of GON have been described--a mechanical and a vascular theory. Both have been defended by various research groups over the past 150 years. The mechanical theory of glaucoma links optic nerve damage to increased IOP. However, the vascular theory suggests that GON arises from insufficient blood supply, either due to elevated IOP or other factors reducing ocular blood flow (OBF). While conditions like congenital or angle-closure glaucoma demonstrate IOP's role in GON, NTG challenges this pressure-centric view. Numerous studies in NTG patients highlight reduced	Page no.6 Line no.6

		ocular perfusion compared to normal subjects, implying factors beyond pressure may contribute significantly to NTG's development. The above paragraph has been added in the manuscript.	
1	Ideally, retinal venous pressure should also be discussed in connection with perfusion pressure (e.g. PMID: 26504500)	Dear Reviewer, A number of studies have shown that a reduced OPP and increased fluctuation of OPP are risk factors for glaucoma progression. Retinal venous pressure (RVP), which refers to the blood pressure within the veins of the retina, has been commonly presumed to be equivalent to Intraocular Pressure (IOP) in most of these studies. Meanwhile, it has been shown that in the majority of glaucoma patients, RVP is far above IOP therefore, the OPP in such cases is much lower than was previously assumed. High RVP reduces the OPP and therefore reduces circulation of both the retina and the (ONH) Optic Nerve Head. The reduction of ONH perfusion contributes to glaucomatous damage. Changes has been done as suggested.	Page no. 5 Line no. 4
1	With CCBs, a distinction should be made between the normal dose used to treat arterial hypertension and the much smaller dose used to treat vascular	Dear Reviewer, A differentiation is necessary between normal doses for arterial	Page no. 9 Line no. 21

	dysregulation. (See e.g.: PMID: 34575340)	hypertension and the significantly smaller doses used for treating vascular dysregulation. This distinction is vital considering that very low doses are employed, which minimally impact blood pressure (BP). CCB may have negligible BP-lowering effects in individuals with already low BP. Despite individuals with Flammer syndrome often having lower BP, some may develop high BP with age. In such instances, a cautious approach with a low-dose CCB in antihypertensive treatment is recommended. The above paragraph has been added in the manuscript.	
1	In the case of beta-blockers, it could be pointed out that there are important differences between the various beta-blockers (PMID: 19733652).	Dear Reviewer, All β-blockers lower IOP via inhibition of β2-adrenoceptors present on the ciliary epithelium, thus reducing aqueous humor flow. Beta-blockers can be classified into non-selective and selective types based on their affinity for β1 and β2 receptors. Non-selective β-blockers like propranolol block both β1 and β2 receptors, affecting not only the eye but also other organs like the heart and lungs. Selective β-blockers, such as betaxolol, predominantly target β1 receptors and have a lesser impact on	Page no. 9 Line no. 12

		β2 receptors in comparison to non-selective blockers. The above paragraph has been added in the manuscript.	
Editor	Before final acceptance, the author(s) must add a table/figure to the manuscript.	Dear Editor, Table has been added.	
Editor	To this end, authors are advised to apply PubMed, or a new tool, the RCA, of which data source is PubMed.	Dear Editor, Changes has been done as suggested.	