EDITORIAL

GLP-1 Receptor Agonists, Allostatic Load, and Reframing the Glaucoma Paradigm

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Elevated intraocular pressure (IOP), the defining characteristic of most forms of glaucoma, is only one piece of the puzzle. The underlying pathophysiology of glaucoma is more complex and multifactorial, involving oxidative stress, inflammation, vascular dysfunction, and autonomic dysregulation—all of which lead to cellular senescence.[1–3]

The growing interest in the potential of glucagon-like peptide-1 receptor agonists (GLP-1RAs) for glaucoma prevention[4] offers an evolving framework for deeper insights into the pathophysiology of glaucoma itself. This conceptual shift reframes glaucoma not merely as an isolated ocular disease but as part of a broader systemic process. This emerging idea posits that glaucoma could share common mechanisms with metabolic syndromes driven by insulin resistance, neurodegeneration, and allostatic load—a continuum of multiorgan stressors that takes a physiological toll on the body over time.

So is glaucoma, then, not an ocular disease but one deeply intertwined with the body's broader metabolic stressors? And how does this knowledge, then, impact current glaucoma practice?

Allostatic Load and Glaucoma

Allostatic load refers to the wear and tear on the body resulting from the chronic activation of stress-response systems. In essence, allostasis is the body's ability to maintain stability through change, but when this system is overtaxed—whether through metabolic, psychological, or environmental stressors—it leads to dysregulation and, ultimately, disease.[2]

Much like how chronic stress contributes to the onset of diabetes and cardiovascular disease, these stressors may impair blood flow to the optic nerve, increase inflammatory responses, with resultant oxidative damage and cellular senescence—all of which are implicated in the degeneration of retinal ganglion cells, a hallmark of glaucomatous damage. This also helps explain how the cumulative effects of chronic stress—metabolic, vascular, and inflammatory—can accelerate disease progression in the eye and the systemic associations of glaucoma.[3]

Aging, Alzheimer's Disease, and Glaucoma

Aging and several age-related diseases are a result of the interplay between individual genetic susceptibility and lifestyle triggers.[5] Inflammaging is an inflammation-mediated aging, and along with glycation and oxidative damage, is central to immunosenescence.[6]

Both Alzheimer's disease (AD) and glaucoma are understood to be heterogeneous manifestations of the same pathophysiological process and are both associated with old age.[7–9] It is no surprise then that the meta-analysis of pooled results from 90,61,675 individuals has indicated that primary open-angle glaucoma (POAG) significantly increases the risk of all-cause dementia, AD, and cognitive impairment. On the contrary, the risk of vascular dementia is increased by angle-closure glaucoma.[10]

Another meta-analysis with 1,31,987 subjects has suggested that glaucoma is a risk factor for AD. Impaired insulin signaling is known to be critical to the pathogenesis of AD, earning it the nomenclature of type 3 diabetes, or brain diabetes.[11] Insulin resistance results in increased oxidative stress and inflammation—mechanisms that are common to AD and the optic nerve damage seen in glaucoma.[11]

As a corollary, then, is glaucoma not just Alzheimer's, but also diabetes of the eye?

The GLP-1 Receptor Agonists' Evidence Base

A meta-analysis of 1,56,042 participants revealed no significant difference in the incidence of glaucoma among diabetics who were GLP-1 RA users when compared to those who were not. However, when the study by Shao et al.[12] was excluded from the meta-analysis, the authors reported a statistically significant decrease in the incidence of glaucoma among GLP-1 RA users compared with controls.[4] Given that this study had only 7,000 patients (<5% of the total dataset), it could be a potential confounder with possibly nonrepresentative characteristics. In this study, the control group used sodium–glucose cotransporter-2 (SGLT2) inhibitors, which were found to be associated with a lower risk of the incidence of glaucoma, compared to those on GLP-1 RAs.[12] SGLT-2 inhibitors may improve retinal hypoxia, thereby decreasing oxidative stress and inflammation.

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A recently published review of the TriNetX research network evaluated the risk of glaucoma and ocular hypertension (OHT) in nondiabetic subjects who were diagnosed as overweight or having obesity, and treated with either GLP-1RAs or alternative weight loss drugs. The retrospective cohort study with 1,56,042 participants reported that the risk of both POAG and OHT showed a significant decrease in the GLP-1RA group at 3 and 5 years of follow-up.[13]

Implications for Treatment: Metabolic Approaches in Glaucoma Care

If glaucoma is indeed a manifestation of broader metabolic dysfunction, then managing systemic factors—such as insulin resistance, inflammation, and oxidative stress—may be just as critical as reducing IOP. This shift in perspective encourages clinicians to consider treatments that target these metabolic pathways and cellular senescence, rather than focusing exclusively on lowering IOP.

This is where GLP-1 receptor agonists that work through activation of the glucagon like peptide-1 receptor and subsequent G-protein coupled receptor (GPCR) signaling in a multitude of organ systems could play a transformative role. These drugs are known to offer protective effects beyond glycemic control, including anti-inflammatory and neuroprotective properties that may help mitigate the processes driving neurodegeneration in the optic nerve.

Conclusion

As research into GLP-1RAs and their effects on ocular health grows, we find ourselves on the cusp of a more integrated approach to managing glaucoma. Addressing insulin resistance, oxidative stress, and vascular dysfunction could be a more holistic therapeutic strategy for glaucoma management, reducing both IOP and the broader metabolic stresses that contribute to disease progression.

The concept of allostatic load is pivotal in this reframing, emphasizing that the chronic stressors contributing to glaucoma—oxidative damage, inflammation, and impaired blood flow—are similar to the metabolic dysfunctions seen in diseases such as diabetes. As our understanding of the disease evolves, integrating metabolic health into the management of glaucoma may hold the key to reducing its global burden, offering a holistic approach that targets both systemic and ocular health.

However, as with any new framework, more research is needed to fully understand how best to harness this knowledge in clinical practice. The future of glaucoma treatment may very well be at the intersection of metabolic health and eye care.

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