Commentary - Association of metformin use among diabetics and the incidence of primary open-angle glaucoma – The Chennai Eye Disease Incidence Study

Glaucoma is one of the leading causes of blindness worldwide, with primary open-angle glaucoma (POAG) being the most common subtype. Progression of POAG is influenced by risk factors such as increased intraocular pressure (IOP), ancestry, family history, and age. Diabetes mellitus (DM) has emerged as a major global health problem in the recent past. DM is considered a risk factor for the development and progression of glaucoma.[1] Recent studies have shown that the diabetic population has a greater risk of developing POAG. Patients with DM have an increased corneal thickness, increased corneal stiffness, altered corneal hysteresis, and compromised vascular autoregulation at the level of optic nerve head. All these factors contribute to the progression of glaucoma.[1] Certain mechanisms are postulated to be common to the pathogenesis of glaucoma and diabetic retinopathy (DR) in patients with DM. Hyperglycemia in DM causes increased glycation of lipids, abnormalities in lipid metabolism, vascular dysregulation, upregulation of nitric oxide levels, and increased oxidative stress. These factors lead to promotion of cellular apoptosis and loss of retinal ganglion cells (RGCs), contributing to development and progression of glaucoma. The proposed mechanisms common to the development of glaucoma and DR also include an increase in inflammatory cytokines, increased protein kinase C levels, increased glial cell dysfunction, and retrograde axonal transport. Moreover, overexpression of matrix metalloprotease-9 has also been postulated to be associated with structural optic nerve head changes in patients with DM.[1] An increase in RGC apoptosis and retinal nerve fiber loss are the key structural findings seen in glaucoma as well as DR. Studies have shown that the loss of RGCs in glaucoma is specific to the magnocellular and parvocellular pathways, which is also seen in DR.[1,2] As such, the strong association between DM and glaucoma is now well documented in the literature.

Metformin is one of the most commonly used oral anti-hyperglycemic agents in the treatment of DM. It is a calorie-restriction mimetic drug. It has anti-inflammatory, anti-angiogenic, and anti-aging effects. The beneficial effects of the drug in the reversal of age-related neurodegenerative complications are well documented in the literature.[2] Metformin has been found to have a significant protective role in preventing systemic (cardiovascular complications, systemic macrovascular involvement, and cancers) and ocular complications (cataract, glaucoma, and DR) in patients with DM. Aging is a major risk factor in glaucoma progression. Metformin has been proposed to have a gero-protective role and reduces the risk of diseases that progress with age. Intraocular pressure (IOP) elevation is another major risk factor influencing the progression of glaucoma.[2] Studies have hypothesized that metformin upregulates adenosine monophosphate-activated protein kinase (AMPK).[3-5] AMPK upregulation alters the tone of cells in the trabecular meshwork, thus lowering the IOP and preventing the progression of glaucoma.[6,7] Preliminary results from animal studies have also shown that metformin exerts neuroprotective effect by upregulation of AMPK. Metformin regulates the methylation at cellular levels and promotes ganglion cell survival. It improves glycemic control and prevents macro and microvascular complications by improving vascular perfusion. Moreover, metformin affects neurogenesis and longevity pathways and protects cells from ischemia and reperfusion injury.[3-5]

Maleškić *et al*.[6] postulated that the gero-protective effect of metformin could delay tissue damage, which can be a major factor in delaying the progression of glaucoma. Lin *et al*.[2] have also highlighted that metformin has the potential to reduce the risk of POAG secondary to its anti-aging effect. Lin *et al*.[2], in their study using a large population-based database, proposed that metformin reduces the risk of POAG in diabetic patients. The study concluded that metformin produces a dose-dependent decrease in the risk of POAG. This study also highlighted that in addition to its known hypoglycemic effect (reduction in HBA1C levels), metformin may be acting via alternate (anti-angiogenic, neurogenesis, and longevity) pathways. Vergroesen *et al*.[3] proposed that metformin decreased the risk of POAG in a duration-dependent manner. However, both studies did not highlight any direct effect of metformin on IOP reduction.[2,3] Mechanisms other than IOP reduction have been proposed to be involved in the reduction of POAG risk in these studies.[2,3,6]

The current population-based study did not find any beneficial effects of metformin usage in the reduction of POAG risk.[8] Previously, Wang *et al*.[4] have also reported similar findings. In their study, the administration of metformin did not halt the progression of POAG. However, shortcomings of the current study, such as the self-reported diagnosis of DM and nonavailability of exact metformin dosage, may have altered the results.[8] With an increase in the diabetic population, a large proportion of the DM patients being prescribed metformin, and DM being a risk factor for POAG, randomized controlled trials and prospective studies may be planned to ascertain whether metformin indeed lowers the risk of POAG. Further studies should provide newer insights into the disease pathology and provide new opportunities to introduce novel treatment options for treatment and prevention of glaucoma.

Nitin Kumar

Department of Ophthalmology, All India Institute of Medical Sciences, Bilaspur, Himachal Pradesh, India

Correspondence to: Dr. Nitin Kumar, Department of Ophthalmology, All India Institute of Medical Sciences, Bilaspur - 174 001, Himachal Pradesh, India.
E-mail: nitinkumarmenia@gmail.com

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