Is Diabetes Mellitus a Blessing in Disguise for Primary Open-angle Glaucoma?

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**Abstract:** Although numbers of studies have addressed this question, the relationship between diabetes mellitus and primary open-angle glaucoma is still unclear. This article discusses progress in understanding the complex relationship between these 2 entities and recent shifts in perspective that challenge the traditional dogma regarding diabetes mellitus and primary open-angle glaucoma. There are still many unanswered questions.

**Key Words:** primary open-angle glaucoma, diabetes mellitus, ocular hypertension, metformin, neuroprotection

(J Glaucoma 2021;30:1–4)

The Ocular Hypertension Treatment Study (OHTS) reported in 2002 that a history of diabetes mellitus (DM) at baseline protected ocular hypertensive subjects from developing primary open-angle glaucoma (POAG). Participants were classified as having a history of DM if they responded affirmatively to the question “Has a doctor ever told you that you have…diabetes, or sugar in the blood?” at baseline. To address this “unexpected” finding, in 2003, the OHTS changed the classification criterion to “respond yes to the above question at baseline or follow-up.” Moreover, the consistency of the response was not required during the study. As a result, 409 OHTS participants who responded affirmatively to the above question during follow-up were classified as having DM. This was more than a 2-fold increase from the initial 191 who were identified as having DM using the original criterion restricted to baseline responses. On the basis of these data, is it possible ocular hypertensive is a risk factor for DM?

Although not seemingly biologically plausible, such a conclusion is supported by results from the Blue Mountains Eye Study in which glaucoma was often diagnosed before DM. The prevalence of DM in OHTS subjects was not reported, and it is difficult to estimate because participants who reported affirmatively at baseline also likely did so during follow-up. If we only consider the 409 subjects, 25% (409/1636) of this OHTS cohort had DM, which is much higher than the reported prevalence of DM (10.5%) in the American population. In contrast, the African Descent and Glaucoma Evaluation/Diagnostic Innovations and Glaucoma Study reported a self-reported DM prevalence <10.1% in glaucoma patients. It seems that the OHTS may have been highly enriched with DM if the self-report was accurate. It is notable, however, that the OHTS showed that a history of DM was not predictive for the development of POAG. Moreover, the relationship between DM and glaucoma is unclear, particularly as both have numerous associated risk factors.

If there is a relationship between DM and POAG, it may be related to common underlying pathophysiologic processes such as retinal neurodegeneration or impairment of vascular supply to the optic nerve head (ONH). Although epidemiologic data have been inconsistent, experimental models based on animal-induced chronic hyperglycemia have shown a consistent association of the 2 diseases. To consider the discrepancies between animal studies and epidemiologic studies in humans, factors such as DM type, stage (complications), glycemic control, and medication should be evaluated for a comprehensive understanding in an individual patient. Therefore, it is meaningful to reconsider DM dogma. In this article, we not only discuss the pathophysiologic similarities between DM and POAG, but we also consider mechanisms by which “DM condition” may confer a protective effect against POAG progression.

**ARE THERE PATHOPHYSIOLOGIC SIMILARITIES OF THESE 2 CONDITIONS?**

**Do DM Patients Have Higher IOP?**

Several studies have found a positive correlation between hyperglycemia, insulin resistance, diabetes presence, and intraocular pressure (IOP). However, correlations with IOP may be driven in part by differences in corneal characteristics. A meta-analysis of 12 population-based and clinical-based studies showed that central corneal thickness (CCT) was 12.8 µm (95% confidence intervals, 8.2-17.5 µm) thicker in eyes of patients with DM than in healthy controls. Only in DM patients, thicker CCT was associated with higher random glucose and higher hemoglobin A1c (HbA1c) levels. CCT was significantly increased (by 31 to 61 µm) in DM patients with diabetic peripheral neuropathy (DPN), and this increase was mostly because of corneal stromal thickening. In addition, DM may influence the biomechanical properties of the cornea. The corneal resistance factor was higher in glaucoma eyes of DM patients compared with glaucoma eyes of patients without DM, and was also positively associated with HbA1c level. Although these studies suggested that the relationship between DM and IOP may be attributable to mechanical properties of the cornea (ie, thickness, resistance), a recent study reported that CCT contributes only 11% of the total effect of DM on IOP, suggesting that the high IOP observed in DM is mainly because of the direct association of DM and IOP.
Is DM Protective Against POAG?

A recent study found thicker prelaminar tissue in glaucoma eyes with DM compared with glaucoma eyes without DM after adjustment for disc area and visual field mean deviation. The prelaminar tissue is composed of neuronal and glial tissue. With the progression of glaucoma, prelaminar tissue thickness decreases. A protective effect of DM to optic nerve damage in POAG patients was reported by Akkaya et al. They found a statistically higher ONH rim area and rim volume of POAG patients with DM compared with those without DM. They also reported that HbA1c levels were negatively associated with ONH parameters. Moreover, a longitudinal study that excluded any patient with a sign of complications reported the protective effect of type 2 DM status against glaucomatous ONH RNFL thinning. These data are consistent with glycemic control and DM complications affecting the influence of DM in POAG.

Several mechanisms may contribute to DM protection from glaucomatous damage. Upregulation of vascular endothelial growth factor (VEGF) is an early response to retinal hyperglycemia. VEGF-A plays an important role in neuronal development and neuroprotection, including in the neural retina. In pre-DR or early DR, VEGF may not be a proangiogenic factor, but a prosurvival factor. It has been reported that the optic nerve and RGC in a rat model of experimental glaucoma were protected from degeneration by short-term hyperglycemia. VEGF-A acts directly on RGCs to promote survival in experimental hypertensive glaucoma, and VEGF-A blockade significantly exacerbates neuronal cell death in the hypertensive glaucoma model.

Insulin/insulin signaling also is important for neuronal survival, particularly of RGCs. Mitochondrial dysfunction leading to oxidative stress contributes to glaucomatous damage and insulin is required for healthy functioning of the mitochondria, insulin is important in the production of nitric oxide by trabecular meshwork cells, which regulate aqueous outflow. Insulin is also an anti-inflammatory moiety with an important role in preventing glial activation, another putative factor in glaucoma pathophysiology. In a study of type 1 DM, there was a positive correlation between the daily insulin dose and ONH RNFL thickness. The “Brain Diabetes Hypothesis of Glaucoma” seeks to explain insulin’s protective effect for glaucoma, and proposes that glaucoma is brain-specific DM, namely “Type 4 DM.” In other words, it suggests that there is a neurodegenerative type of DM that exists independent of the peripheral DM. This condition demonstrates “central insulin resistance.” If confirmed, the treatment of DM would benefit glaucoma and also improve insulin resistance.

Metformin has been proven to be one of the most safe and effective antihyperglycemic agents. Guidelines of pharmacological management of type 2 DM agree that metformin should initiate treatment of most type 2 DM patients. Metformin also has been shown to be an effective neuroprotective agent. A retrospective cohort study of 150,016 patients with DM showed a dose-dependent reduction in OAG risk among DM patients using metformin, and risk is reduced even when accounting for glycemic control in the form of HbA1c. After adjusting for confounding factors, every 1g increase in metformin hydrochloride use was associated with a 0.16% reduction in OAG risk. This suggests that taking a standard dose of 2g of metformin hydrochloride daily for 2 years would result in a 20.8% reduction in the risk of OAG. Another retrospective study found treatment with metformin decreased the odds of glaucoma (odds ratio = 0.14; 95% confidence intervals, 0.03-0.57) compared with other oral antihyperglycemic agents in type 2 DM patients. It is notable that in a longitudinal study showing slower RNFL thinning in POAG eyes of DM patients, 84% of the DM patients were using metformin. Thus, the treatment of DM with metformin may mediate some of the observed protective effects of DM on POAG.

CONCLUSIONS

The relationship of DM and anti-DM medications to glaucoma remains unclear. More objective and accurate data regarding subjects’ diagnoses, disease duration, complications, and medication regimens are needed to better understand this relationship. Ocular effects of such factors as blood glucose fluctuation, chronic mild hyperglycemia, and selective central nervous system insulin resistance, and the neuroprotective effects of anti-DM medications (particularly metformin), are poorly understood and should be studied. Investigating these factors may ultimately uncover
novel therapeutic approaches for the clinical management of POAG to help mitigate vision loss.

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