

## Association Between Diabetes Mellitus And Glaucoma

Editorial

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It has not been determined definitively whether there is a significant association between diabetes mellitus (DM) and glaucoma. Some population-based studies have shown a positive association between diabetes and glaucoma [1-3], and others have shown negative association between diabetes and glaucoma [4-6]. However in many studies that showed a lack of a significant association between diabetes and glaucoma, the diagnosis of DM was made by self-presentation [4,5]. On the other hand, DM was diagnosed by the serum glucose level or by glucose tolerance tests in the Rotterdam Study. The study concluded that the risk of open angle glaucoma was increased by more than three times in patients with diabetes than without diabetes [1]. The results of a recent meta-analysis suggested that diabetes was a significant risk factor for open angle glaucoma [7]. However, two of 12 studies included in the meta-analysis used only high intraocular pressure (IOP) as a definition of open angle glaucoma [7]. Thus, patients with normal tension glaucoma were not included in the glaucoma group. More exact definitions of DM and glaucoma should be used to determine more accurately the association between DM and glaucoma. The results of these studies indicate that there is insufficient clinical evidence to conclude that there is a significant relationship between diabetes mellitus and glaucoma.

There are animal studies that showed that diabetic stress enhances retinal ganglion cell (RGC) death after mechanical injury or high IOP [8,9]. The higher IOP may also impose a pressure-induced stress on RGCs and their axons leading to a blockage of axonal transport. This blockage can reduce the level of neurotrophic factors delivered to the RGC bodies which would make the RGCs more susceptible to diabetic and oxidative stress.

There are population studies that showed that diabetic patients have significantly higher IOPs than non-diabetic patients [10], and

also that the RGC damage induced by the stress caused by higher IOPs may be enhanced under severe diabetic conditions [8,9].

On the other hand, the results of the Ocular Hypertensions Treatment Study showed that diabetes had a protective effect on the progression of open angle glaucoma. However, patients with diabetic retinopathy (DR) were excluded from this study, and the definition of DM was based only on self-presentation [11,12]. Although these studies did not include a representative group of patients with diabetes, some investigators cite this study as evidence that diabetes had a neuroprotective effect on RGCs. They hypothesized that DM is neuroprotective because higher levels of vascular endothelial growth factor (VEGF) are present in eyes with DM, and the VEGF is involved in neuroprotection of RGCs. Although VEGF is an endogenous neurotrophic factor, high glucose [13] and accumulation of advanced glycation end-products (AGEs) in diabetic patients are toxic for retinal neurons [14]. Our recent study showed that low concentrations (10 µg/ml) of AGEs enhanced retinal neuronal cell death and inhibited neurite regeneration. Because approximately 1-120 µg/ml of AGEs are circulating in diabetic patients, we suggested that the imbalance between the endogenous neurotrophic factors and the toxic factors causes retinal neuronal damage in eyes with DR [14]. Overall, the pathological mechanisms causing neuronal cell death in DR is not as simple as we had expected.

We hypothesized that RGCs are under stress by the higher IOPs in glaucomatous eyes, RGC death would be enhanced by diabetic oxidative stress. If so, the visual field defects may progress faster in glaucoma patients with DM than in glaucoma patients without DM. In support of this, Kim et al. reported that systemic vascular factors including the severity of DM and IOP play significant roles in the progression of normal tension glaucoma [15].

Taken together, there appears to be more significant associations between DM and glaucoma especially in studies with more exact diagnosis of DM. Further studies with the precise definition of DM are needed to demonstrate the association of DM and glaucoma.

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