The role of big data analysis in identifying a relationship between glaucoma and diabetes mellitus

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Glaucoma is a major degenerative disease of the optic nerve (1). Progressive degeneration of retinal ganglion cells in the optic nerve is irreversible in patients with glaucoma. Primary open-angle glaucoma (POAG) is the most common subtype of glaucoma, characterized by normal anterior chamber angles and increased intraocular pressure (IOP). Although the exact mechanism of POAG is not completely understood, neurodegenerative changes are believed to contribute to its pathophysiology (2). Diabetes mellitus (DM) is the most prevalent systemic endocrine disease and is associated with an increased risk of glaucoma (3). Previous epidemiological studies have reported a greater risk of POAG in patients with DM (4). With an increase in the incidence rate of DM worldwide, the risk of the additional burden of POAG in individuals with diabetes is increasing in an aging society, in addition to neovascular glaucoma in severely diabetic patients. However, recent studies have reported different results related to DM and glaucoma. One meta-analysis concluded that DM was associated with elevated IOP but had no significant association with POAG (5). Another study showed that diabetic retinopathy in patients with severe DM was not associated with POAG (6). These meta-analyses have the limitations of high heterogeneity and few study participants. They suggest that it is not easy to identify whether DM is relevant to the development of glaucoma because there are many confounding factors related to both DM and glaucoma.

A recent study by Jiang *et al.* found that DM was significantly associated with an increased risk of glaucoma in a large Australian population-based cohort study (7). Additionally, they found that DM was not associated with surgical glaucoma, including filtering operations, laser-based iridectomy, and cyclo-destructive procedures. Considering the definition of glaucoma in this study, the authors mainly aimed to analyze POAG. The study showed a significant relationship between DM and glaucoma based on a well-performed big data analysis, which clarified a statistical relationship that has not been revealed in previous small-scale studies. Statistical bias was minimized by long-term follow-up as well as by collecting various variables and controlling confounding variables. After adjustment for smoking, blood pressure, and cardiovascular disease variables, DM remained an independent risk factor for glaucoma. This study is one of the largest big data analyses with the longest follow-up period to estimate the relationship between DM and glaucoma. This result is consistent with that of a large nationwide cohort study conducted in South Korea (8). It should be noted that an uncorrectable bias caused by glaucoma diagnosis may affect the incidence rate of glaucoma in the claims data owing to its asymptomatic development.

DM is one of the most commonly studied systemic

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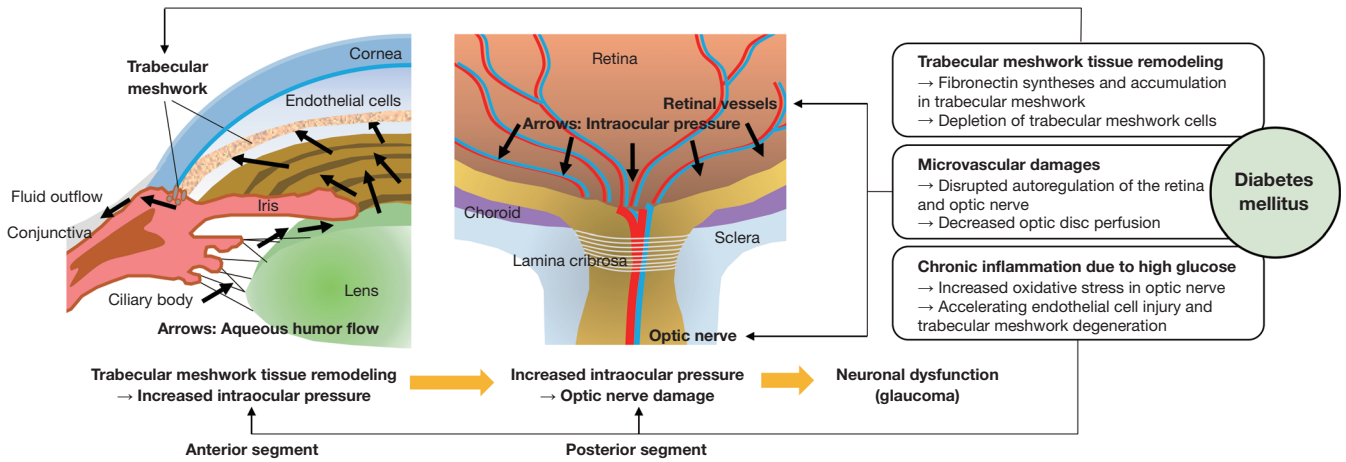

Figure 1 Schematic diagram of the possible pathogenesis of glaucoma (mainly primary open-angle glaucoma) in diabetic eyes. These associations are not causal but indicate the possible ways in which diabetes might lead to glaucoma.

diseases as a risk factor for POAG. The risk of glaucoma in patients with DM is well established. Generally, the relationship between DM and POAG can be explained by various mechanisms (*Figure 1*). Previous studies have mostly focused on the relationship between DM and increased IOP (9). High glucose levels in aqueous humor can induce fibronectin accumulation in the trabecular meshwork and depletion of trabecular meshwork cells (10). Trabecular meshwork remodeling may increase IOP and cause POAG. Vascular factors in DM, including poor ocular blood flow and hypoxic damage, may also play a critical role in the development of POAG (11). Microvascular damage due to high blood glucose levels can disrupt autoregulation of the retina and optic nerve and decrease optic disc perfusion (12). Chronic inflammation due to DM can also cause increased oxidative stress in the optic nerve (13). This factor may also accelerate endothelial cell injury in the ocular vessels and degeneration of the trabecular meshwork. This relationship has been reported in molecular biology experiments and case-control studies. Finally, it was verified in the follow-up observation results of real-world patients based on a big data analysis conducted by Jiang *et al.* (7).

Big-data analysis can be defined as the handling of very large datasets with complex data structures that are difficult to analyze using traditional techniques or tools (14). Recently, studies using big data, such as national claims data, have expanded medical knowledge by processing huge amounts of information that have not been covered in previous studies (15). Big data studies targeting DM and glaucoma can be expanded to various diagnostic and treatment areas in the future (*Figure 2*). For example, it is expected that a comprehensive big data analysis can help build a mathematical model that can predict blood sugar levels based on optic nerve conditions and IOP. This may help patients manage glaucoma and monitor blood sugar. In addition, it is necessary to further clarify the relationship between DM therapies and glaucoma occurrence through big data researches. For example, the relationship between administration of metformin, which has been used as a first-line treatment for diabetes, and glaucoma has been studied (16). The neuroprotective effects of metformin have not yet been confirmed in epidemiological studies. It should also be clarified through a big data approach to provide practical help in preventing and treating glaucoma in the clinic. In summary, we believe that big data-driven analyses will identify better monitoring and treatment strategies for glaucoma in patients with diabetes by exploring the relationship between DM and glaucoma. In addition, there are several technical issues in big data analysis, including missing values, curse of dimensionality, and bias control (17). Generally, these issues are not easy to handle and critically affect the analysis results. Researchers should consider these issues before building or interpreting datasets and mathematical models based on medical big data such as national claims datasets.

According to the findings of Jiang *et al.* (7), lowering blood sugar levels is recommended to prevent glaucoma (mainly POAG) in patients with DM. Glaucoma is the leading cause of irreversible blindness worldwide. Therefore, the early management of risk factors is important

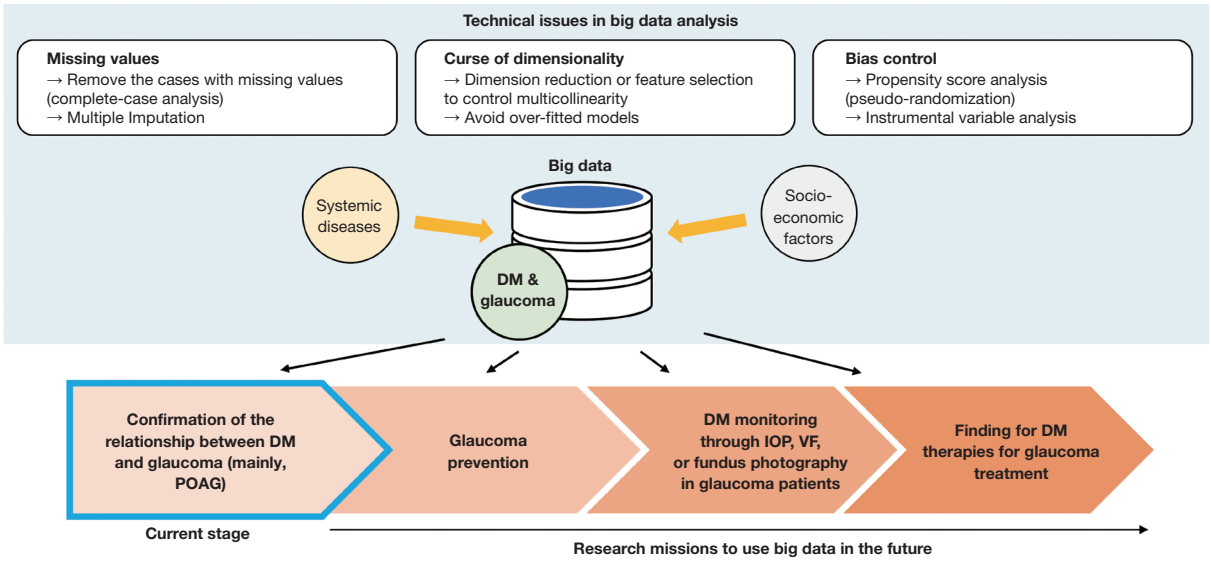

Figure 2 Big data analysis applications based on the relationship between glaucoma and DM. POAG is the most common subtype of glaucoma. Future research should target the prevention and treatment of glaucoma with anti-diabetic therapies. IOP, increased intraocular pressure; VF, visual field; DM, diabetes mellitus; POAG, primary open-angle glaucoma.

for prevention of glaucoma. Recent oculomics-based big data analyses have shown that the eyes can provide not only vision but also a window to various systemic conditions (18). Chronic systemic diseases, such as cardiovascular diseases, are closely related to changes in the ocular vessels and retinal layers in several big data studies (19). We also observed that DM influences IOP and the incidence of glaucoma through various pathways. Since chronic diseases interact with each other and affect factors related to glaucoma, its progression can be predicted more accurately based on the large data collection of various ophthalmic data and DM-related biochemical measurements.

In summary, Jiang *et al.* (7) demonstrated the contribution of big data analysis to a better understanding of glaucoma and DM. In the future, big data analysis will support patient outcome prediction and help uncover hidden patterns of diseases to improve healthcare systems.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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