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EDITORIAL

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MINIREVIEWS

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ORIGINAL ARTICLE**Retrospective Study**

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CASE REPORT

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LETTER TO THE EDITOR

Liu SQ, Wang D, Tang CC. Association between age at diagnosis of diabetes and ocular disease: Insights from a recent article. *World J Diabetes* 2025; 16(1): 94846 [DOI: 10.4239/wjd.v16.i1.94846]

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The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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Association between age at diagnosis of diabetes and ocular disease: Insights from a recent article

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Abstract

In this article, we discuss Ye *et al*'s recent article on the association between age at diabetes diagnosis and subsequent risk of age-related ocular diseases. The study, which utilized United Kingdom Biobank data, highlighted a strong link between early diabetes onset and major eye conditions, such as cataracts, glaucoma, age-related macular degeneration, and vision loss, independent of glycemic control and disease duration. This finding challenges the previous belief that diabetic eye disease primarily correlates with hyperglycemia. As lifestyles evolve and the age of diabetes diagnosis decreases, understanding this relationship may reveal the complex pathogenesis underlying diabetes-related complications. This editorial summarizes potential mechanisms connecting the age of diabetes onset with four types of ocular diseases, emphasizing the significance of early diagnosis.

Key Words: Diabetes; Age at diagnosis; Cataract; Glaucoma; Age-related macular disease; Vision acuity

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Core Tip: The risk of eye diseases, including cataracts, glaucoma, age-related macular degeneration and vision loss, may be greater among patients who are younger at the time of diabetes diagnosis. Younger patients at the time of diabetes diagnosis may have more severe pathogenicity and refractoriness, which provides some guidance for screening diabetic patients for eye disease. This article reviews the mechanism underlying the occurrence and development of diabetes and eye diseases and the role of age at the time of diabetes diagnosis.

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TO THE EDITOR

Patients with diabetes are more susceptible to ocular disorders, and they present at an earlier age than patients without diabetes[1,2]. Cataracts, glaucoma, and age-related macular degeneration (AMD) are the primary causes of blindness in individuals aged 50 years and older[3]. Hyperglycemia, insulin resistance, and glucose and lipid metabolism disorders in the course of diabetes contribute to lens fiber and protein metabolism disorders, retinal vascular endothelial injury, and optic nerve axonal injury, leading to eye disease and abnormal vision loss. Ye *et al*'s article[4] analyzed the association between age at the time of diabetes diagnosis and ocular disease. This novel and instructive article highlights the potential impact of public health strategies for the prevention and screening of diabetic eye disease.

AGE OF ONSET OF DIABETES

The age of onset of type 2 diabetes gradually increases as socioeconomic status increases and lifestyles changes. Young patients often have an unhealthy lifestyle, combined with hyperlipidemia, hypertension, high body mass index and other metabolic syndromes[5]. In addition, young individuals with diabetes often have higher glycosylated hemoglobin levels and generally poor glycemic control, even if they are more likely to follow directions and adhere to rigorous treatment regimens than older individuals[6,7]. It has been suggested that early-onset diabetes is more difficult to treat and that the cumulative effect of these high glycemic levels may persist for years after diagnosis. Sattar *et al*[8] also investigated the life expectancy and cardiovascular-related mortality of patients with diabetes at different ages of onset and reported that all risks were highest in early-onset patients. The risk decreased rapidly with increasing age of onset and was minimal in those with onset after the age of 80 years[8]. Furthermore, patients with early-onset diabetes experienced more severe insulin deficiency and faster beta-cell degeneration than those with late-onset diabetes[9,10]. Research has shown that early-onset patients experience a 20%-35% decrease in β -cell function during the oral glucose tolerance test compared to only 7% in older patients[11].

In patients with type 1 diabetes, this trend may be even more pronounced. In the research of Cho *et al*[12], patients with early onset disease had a greater incidence of complications such as nephropathy, retinopathy, neuropathy, and carotid plaques than those with late-onset diabetes, but a longer duration of diabetes attenuated this effect[13]. With a longer duration of diabetes, long-term exposure to hyperglycemia can lead to oxidative stress, vascular injury, and beta-cell depletion[10], leading to various microvascular and macrovascular complications[14].

These studies suggest that age at diagnosis of diabetes may be an important clinical parameter representing different degrees of immune and metabolic dysfunction, which determine the pathophysiology, disease course, and complications, together with the disease course and blood glucose levels.

PATHOPHYSIOLOGY AND MECHANISM OF OCULAR DISEASE ASSOCIATED WITH DIABETES

In diabetic patients, cataracts develop earlier and progress faster, and the risk is 2 to 4 times greater than in nondiabetic individuals. Type 1 diabetes patients, especially younger patients, may present with aggressive "snowflake" cataracts. Diabetic cataracts are classified into true diabetic cataracts and diabetic senile cataracts, with the latter being more common[15,16]. Various pathological mechanisms, such as the hexosamine pathway, oxidative stress, abnormal polyol metabolism, advanced glycation end products (AGE) aggregation, protein kinase C activation, and vascular endothelial growth factor (VEGF)-related inflammation, contribute to cataract development[17-19]. Typically, 80% of lens glucose is metabolized through anaerobic glycolysis, whereas only 4% is metabolized through the sorbitol pathway. In diabetic cataracts, heightened aldose reductase (AR) activity in the sorbitol pathway leads to excess sorbitol accumulation. Excessive sorbitol accumulates in the lens, and the hypertonic response to sorbitol leads to liquefaction and swelling of lens fibers, which is also a key factor in the pathogenesis of diabetic cataracts[17]. Snow *et al*[20] demonstrated that increased AR gene expression may increase the risk of cataract development in diabetic patients[20]. On the other hand, the sorbitol pathway can also result in an increase in the generation of reactive oxygen species, leading to further

oxidative stress, protein damage, and cataract formation. Proteins in the lens are glycosylated to form AGEs which also cause lens opacity[17,21]. In previous studies, the risk of cataracts in diabetic patients was shown to be influenced by diabetes duration, blood glucose control, and metabolic factors[22]. Notably, type 1 diabetes patients have a greater incidence of early cataracts, with the risk decreasing as the disease progresses[23]. Early cataracts in patients with type 1 diabetes suggest that critical damage to the lens that can threaten vision begins at the onset of diabetes and that hyperglycemia-induced osmotic stress and inadequate blood sugar control over the course of the disease contribute to cataract development[24,25].

Glaucoma is an irreversible optic neuropathy that can lead to blindness. Diabetes and high fasting blood glucose levels are linked to increased intraocular pressure (IOP), a key risk factor for glaucoma[26]. The Bonovas study revealed an increased prevalence of open-angle glaucoma in patients with diabetes compared to those without diabetes (odds ratio = 2.12)[27]. A meta-analysis revealed that patients with diabetes had a 48% greater likelihood of developing glaucoma and a 52% greater likelihood of experiencing ocular hypertension than controls[28]. Consistent with this, the authors demonstrated in a large prospective cohort study that diabetes was associated with an increased incidence of glaucoma. After adjusting for the course of diabetes in the regression equation, the risk of glaucoma was no longer associated with diabetes, which may indicate that the course of diabetes may influence the occurrence of glaucoma. According to some studies, the risk of glaucoma increases by 5% annually with increasing duration of diabetes, and individuals with diabetes for more than 5 years are 3.9 times more likely to develop glaucoma[29]. However, some studies have come to the opposite conclusion; that is, diabetes is not a predictor of glaucoma, and diabetes may even have a protective effect against glaucoma[30-32]. Although mixed results have been reported, some studies have suggested that diabetic retinopathy may indirectly cause glaucomatous optic neuropathy or direct damage to the optic nerve by increasing IOP or vasculopathy, including regulation of the trabecular meshwork, cellular dysfunction and failure, obstruction of aqueous humor drainage, impaired vascular regulation, and endothelial cell dysfunction[33].

AMD is one of the leading causes of severe vision loss in elderly individuals, and its incidence is positively related to age. In this study, the relationship between AMD and diabetes was not significant according to a univariate analysis, but the risk of diabetes was significantly greater than that of normal individuals after adjusting for confounding factors. Additionally, research has shown that the incidence of moderate dry and wet AMD is much greater in diabetic patients with longer disease durations and older ages than in nondiabetic patients[34]. Hyperglycemia is thought to cause retinal pigment epithelium and chorionic membrane dysfunction through the accumulation of highly stable AGEs and hemodynamic disturbances caused by the inflammatory response. Injury to the retinal vascular endothelium leads to hypoxia in energy-requiring photoreceptor cells, which releases VEGF, and chronic VEGF signaling exacerbates hypoxia by leading to pathological neovascularization and fibrosis[35], whereas hypoxia-induced mitochondrial hypoxic damage activates the cyclic GMP-AMP synthase-stimulator of interferon genes pathway, leading to disease progression[21].

Visual impairment in diabetic patients results from neurodegeneration of the retina and optic nerve caused by chronic hyperglycemia. Reduction of the blood supply and oxygen delivery to retinal tissue, glycosylation of proteins in the lens and retina, and persistent inflammation lead to tissue damage and loss of function.

HIGHLIGHTS OF THE CHOSEN ARTICLE

This is the first report to demonstrate the association between age at diagnosis of diabetes and ocular diseases in more than 20000 participants. The sample size of this prospective cohort study is large and the conclusions are reliable. Most predisposing factors for diabetic ocular diseases, including average blood glucose control level, blood lipids, hypertension, smoking and drinking, obesity, exercise time, sleep time, and income level, were excluded. The highlight of this study is that diabetic ocular disease is independent of the level of glycemic control and the duration of diabetes. The incidence of ocular and visual lesions continues to increase in patients with a younger age at the time of diabetes diagnosis, especially those with type 1 diabetes. These findings suggest that the risk of diabetic eye disease may be related to insulin resistance, β -cell destruction, or the presence of autoantibodies[36]. In addition, diabetes in young people is mostly associated with obesity, hyperlipidemia and other factors, suggesting that poor living habits or physical damage caused by the metabolic syndrome may be irreversible and decisive, even affecting the occurrence of diseases in elderly individuals. This study emphasizes the importance of considering the age of diagnosis of diabetes when assessing the risk of eye health, which provides guidance for the prevention and screening of diabetic eye diseases. This inspired us to reconsider the risk factors for diabetic eye diseases and include the age of diagnosis of diabetes in the criteria.

There are several potential drawbacks. First, the time of diagnosis of diabetes in some patients is not consistent with the time of onset. In some cases, early hyperglycemia is often not detected until some acute or chronic complications occur. Second, this study used a rigorous propensity score matching procedure to match diabetic patients with the control group, and Cox proportional hazard regression models were used to process the data. However, the present study demonstrated that patients with an earlier diagnosis of diabetes were more likely to develop eye disease and vision problems than were those without diabetes, rather than comparing the differences between different groups of diabetes patients. Third, most factors associated with diabetic eye disease have been ruled out, but UV exposure and the use of some medications, such as hormones, GLP-1 agonists and statins, have also been shown to affect the incidence of diabetic retinopathy. Moreover, there was a significant difference in the sex distribution of diabetic eye lesions. Some studies have shown that the prevalence of cataracts in women is greater than in men[37,38]. Therefore, it is recommended that a stratified analysis be conducted according to sex. Fourth, different types of glaucoma and cataracts may have different relationships with diabetes. For example, the most common cataract in diabetic patients is a cortical cataract, and studies have shown that a posterior subcapsular cataract, rather than cortical cataract, is associated with poor blood sugar control

[39,40]. It is recommended that authors classify the different types of cataracts and other eye diseases so that people can better understand the correlation.

CONCLUSION

Diabetes is a chronic disease that can lead to many complications. However, few studies have investigated the correlation between the age of onset of diabetes and various complications. Diabetes in young individuals is associated with a greater risk of ocular disease and vision loss. This relationship is more pronounced in type 1 diabetes patients. Studies have suggested that the age at diagnosis of diabetes may be an important clinical parameter, which may represent the different degrees of immune and metabolic dysfunction in patients, and may determine the pathophysiology, course of diabetes, and some metabolic risk factors. Future research should conduct animal studies on relevant mechanisms to explore the effects of early-onset diabetes on ocular diseases in terms of insulin resistance, beta-cell depletion, glucose and lipid metabolism imbalance, and genetic abnormalities.

FOOTNOTES

Author contributions: Liu SQ, Wang D, and Tang CC conceived, designed, and refined this review; Liu SQ drafted the manuscript; Wang D and Tang CC contributed equally to this work as co-corresponding authors. The reasons for designating Wang D and Tang CC as co-corresponding authors are as follows. First, they both participated in choosing the idea of the study. Second, they both revised the manuscript. Third, they are both responsible for the study. In summary, we believe that designating Wang D and Tang CC as co-corresponding authors of is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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