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Update in the epidemiology, risk factors, screening, and treatment of diabetic retinopathy

EPIDEMIOLOGY

Diabetic retinopathy (DR) is a common microvascular complication of diabetes mellitus and is the leading cause of visual loss in the elderly. Hyperglycemia and altered metabolic pathways lead to oxidative stress and the development of neurodegeneration in the initial stage of diabetic retinopathy[1]. Vascular endothelial damage, the development of microaneurysms, and dot intraretinal hemorrhage are early hallmarks of nonproliferative diabetic retinopathy (NPDR). Disruption of the blood–retinal barrier and leakage of multiple inflammatory cytokines and plasma proteins lead to the hard exudates observed under fundoscopy. As disease progresses, vasoconstriction and capillary occlusions lead to tortured capillaries and retinal ischemia. The presence of 'cotton wool spots' can be seen during this stage. At the end stage of diabetic retinopathy, severe hypoxia leads to neovascularization, vitreous hemorrhage, and retinal detachment[1].

In Taiwan, the prevalence of diabetic eye disease ranged from 3.75 to 3.95%, and the prevalence of poor vision and blindness ranged from 0.29 to 0.35% during 2005 to 2014[2]. In Korea, the prevalence of diabetic retinopathy increased from 14.3% in 2006 to 15.9% in 2013[3]. Both studies revealed that women with type 2 diabetes had a higher prevalence of diabetic retinopathy than men, but men suffered from more severe retinopathy, poor vision, or blindness. The severity of diabetic retinopathy not only impacted the quality of life, but also predicted all-cause, vascular, and non-cancer mortality[4]. Another study found that diabetic retinopathy is associated with prolonged QT interval, which may play a role in life-threatening arrhythmia[5].

RISK FACTORS, PREVENTIVE FACTORS, AND BIOMARKERS

The development of diabetic retinopathy strongly correlates with a longer duration of diabetes, greater hyperglycemia, and hypertension. A higher HbA1c level is significantly associated with the progression of diabetic retinopathy[6,7] and intensive glycemic control reduces the incidence and deterioration of retinopathy[8]. In recent studies, glycemic variability was found to be strongly associated with diabetic retinopathy in type 2 diabetes[9]. Therefore, correcting postprandial hyperglycemia is also important for the prevention of diabetic retinopathy[10]. Moreover, there is clear evidence regarding the relationship between hypertension and diabetic retinopathy. Tight blood pressure control reduces the deterioration of retinopathy[11]. Other risk factors include nephropathy, dyslipidemia, smoking, and higher body mass index, which are also modifiable to prevent the progression of diabetic retinopathy[12,13,14].

Despite the above mentioned risk factors, studies revealed a substantial variation in the development and severity of diabetic retinopathy that could not be fully explained by the known risk factors. Thus, identifying more biomarkers to stratify the risk or to evaluate the therapeutic response of diabetic retinopathy is important.

Systemic biomarkers include markers of inflammation such as C-reactive protein (CRP)[15] and homocysteine[16], and the advanced glycation end products (AGE)[17] are related to the pathogenic process and the risk of diabetic retinopathy. Many more biomarkers have been identified by plasma proteomic approach. For example, retinol-binding protein 1 (RBP1), diphosphoinositol polyphosphohydrolase 3 alpha, neuroglobin (NGB) were downregulated and hemoglobin subunit gamma 2 (HBG2) and CD 160 antigen[18] were upregulated in diabetic retinopathy. Among the above mentioned five proteins, the plasma level of neuroglobin may be a potential biomarker for diabetic retinopathy due to the significant difference between the control and the diabetic retinopathy group[18]. Furthermore, metabolomics[19], micro RNA[20], and genetic biomarkers are also under extensive investigation.

Ocular biomarkers include sampling the vitreous and tears as well as ocular imaging. Increases in angiogenic factors, such as vascular endothelial growth factor (VEGF)[21] and platelet-derived growth factor (PDGF)[22], and decreases in antiangiogenic factors, e.g., pigment epithelium-derived factor (PEDF)[23], were detected in the vitreous in diabetic retinopathy. Also, an increased microaneurysm turnover rate[24] and larger retinal vessel diameters[25] detected by retinal fundus photos and retinal neurodegeneration recognized by optical coherence tomography (OCT)[26] were associated with the development of diabetic retinopathy. However, most of the novel biomarkers have yet to be applied in clinical practice and require more validation studies for predicting diabetic retinopathy and its clinical outcomes.

SCREENING

As diabetic retinopathy remains the leading cause of visual impairment, screening for diabetic retinopathy is important to

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early detect preventable blindness. Most patients with developed diabetic retinopathy have no symptoms until macular edema (ME) or proliferative diabetic retinopathy (PDR) presents. Although panretinal laser photocoagulation (PRP) and intraocular VEGF inhibitor injection are effective for ME or PDR related visual impairment, they benefit more in preventing visual loss than in reversing deteriorated visual acuity. Therefore, a timely screening program for diabetic retinopathy could assist individuals with diabetes to preserve their vision.

According to current guidelines for the screening of diabetic retinopathy, reported by the International Council of Ophthalmology (ICO) and American Diabetes Association (ADA) in 2018, the timing of the first eye examination and minimum screening examinations are required for appropriate referral to an ophthalmologist[27,28]. For type 2 diabetes patients, the first eye examination should be initiated once a diagnosis of diabetes is confirmed, as for type 1 diabetes, the timing being extended to 5 years after the onset of diabetes. Minimum screening, on the other hand, includes visual acuity examination and retinal examination[27]. Both examinations should be performed by well-trained personnel, and retinal imaging could be analyzed either by human-based telemedicine or an automated computer system[29]. Thanks to the advances of artificial intelligence (AI) and a deep learning algorithm, the first automated diabetic retinopathy screening program has been approved by FDA since April 2018[30], achieving a 96.8% sensitivity and 87% specificity for detecting referable diabetic retinopathy[31]. Recently, implementation of a smartphone-based retinal camera in low-resource settings also showed great potential in the detection of diabetic retinopathy when combined with telemedicine[32]. To maximize the cost-effectiveness of diabetic retinopathy screening, several studies introduced an individualized screening schedule based on the patient's risk of proliferative diabetic retinopathy or macular edema[29,33,34]. It was estimated that it would save $1 billion over 20 years, compared with routine annual screening in type 1 diabetes in the USA[33]. However, the individualized screening schedule in type 1 diabetes needs further validation in type 2 diabetes.

Table 1 | Comparison among different treatment modalities in diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR)

	Treatment	Clinical trial results
DME	Anti-vascular endothelial growth factor (VEGF): ranibizumab, evacizumab, aflibercept[35-40]	Aflibercept resulted in better visual acuity than bevacizumab in DME eyes with initial worse visual acuity[41]
PDR	Panretinal laser photocoagulation (PRP)[42-43], Anti-VEGF: ranibizumab, evacizumab, aflibercept	Aflibercept group had better visual acuity than PRP group[46]; Ranibuzumab was non-inferior to PRP group[47,48]

TREATMENTS

In addition to optimal medical control of blood glucose, blood pressure and serum cholesterol level, several intraocular managements have become standard treatments for diabetic retinopathy[27,28]. As for patients with diabetic macular edema (DME), the use of anti-VEGF therapy has reformed its management, including agents such as ranibizumab, bevacizumab, and aflibercept. Since 2010, several large randomized trials have demonstrated the efficacy of all three anti-VEGF agents in the reduction of diabetic macular edema and in the improvement of vision[35–40]. However, in eyes with diabetic macular edema with initial worse visual acuity (20/50 or worse), aflibercept could result in better visual acuity than did bevacizumab at 2 years[41]. Despite the progress in anti-VEGF therapy, the optimal frequency of injections and the duration of the treatment course are still largely unknown. Most patients might require frequent injection of intravitreous anti-VEGF during the first year of treatment, and fewer injections are needed in following years for the maintenance of remission[27].

For patients with proliferative diabetic retinopathy, on the other hand, panretinal laser photocoagulation has been demonstrated to be effective in reducing the risk of vision loss[42,43]. PRP, therefore, is considered the preferred treatment for patients with all stages of PDR and severe NPDR[44,45]. In addition to PRP, recent studies have also provided evidence that intravitreous injection of anti-VEGF may be a safe alternative treatment for PDR. The clinical efficacy and mechanistic evaluation of aflibercept for proliferative diabetic retinopathy (CLARITY) study demonstrated that eyes assigned to anti-VEGF group (aflibercept) had better visual-acuity results than eyes assigned to the PRP group at 1 year[46]. The Diabetic Retinopathy Clinical Research Network randomized trial showed that visual-acuity outcomes in the anti-VEGF group (ranibizumab) were non-inferior to those in the PRP group at both 2 years and 5 years[47,48]. The comparison among different treatment modalities in diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR) is summarized in Table 1. However, adherence to frequent follow-up, treatment burden, and patients' preference must be considered when applying the above mentioned clinical trial results to clinical practice in the real world.

The molecular basis of diabetic retinopathy are still under investigation, such as the involvement of (pro)renin receptor in the retinal renin-angiotensin system (RAS) activation pathway[49]. These studies might help the discovery of novel drug targets and provide more individualized therapies.

CONCLUSION

In summary, despite progress in the treatment of diabetic macular edema and diabetic retinopathy, the lower fundus

examination rate due to the limitation of medical resources delayed the diagnosis and treatment of diabetic retinopathy. Therefore, implementation of an automated diabetic retinopathy screening program and identification of more specific and sensitive biomarkers are important to facilitate the earlier detection of diabetic macular edema and diabetic retinopathy to decrease the prevalence of poor vision and blindness.

DISCLOSURE

The authors declare no conflict of interest.

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