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Current aspects on diabetes retinopathy

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Abstract
Diabetic retinopathy (DR) is a complication of long-term diabetes mellitus (DM). Diabetic retinopathy is the major ocular complication associated with diabetes, and represents the leading cause of legal blindness in the working-age population of developed countries. Although classically diagnosed based on abnormalities of the retinal microvasculature, diabetic retinopathy is now widely recognized as a neurovascular disease. Systemic management of diabetes by combined control of glycemia, blood pressure, and serum lipid levels remains the most important method of preventing diabetic retinopathy onset and progression. To relieve ER stress, the cell activates an adaptive mechanism known as the unfolded protein response (UPR). The UPR coordinates the processes of protein synthesis, protein folding, and degradation to ensure proteostasis, which is vital for cell survival and activity. Ant vascular endothelial growth factors are now extensively used to treat diabetic retinopathy and macular edema with promising results.

Keywords: Diabetes retinopathy, Diabetes mellitus, Non proliferative diabetes retinopathy and proliferative diabetes retinopathy

1. Introduction

1.1. Diabetes Mellitus

Diabetes is a metabolic disease resulting from the body's insufficient production or use of insulin, a peptide hormone responsible for regulating glucose levels in the blood and tissues. Especially when improperly managed, diabetes results in a number of complications over time, affecting nearly every organ system, including the ocular tissue. In addition to increased risk for glaucoma and cataracts, the most threatening ocular implication of diabetes is diabetic retinopathy, an aggressive disorder historically clinically associated with a variety of retinal microvascular abnormalities. Diabetic macular edema (DME), another manifestation of diabetic retinopathy involving macular thickening due to fluid accumulation, is accountable for a great proportion of diabetes-related vision loss. [1] While advanced stages of PDR (proliferative DR) have classically been regarded as the most threatening to sight, visual dysfunction at all stages, even those deemed mild by clinical evaluation, is now apparent. As the leading cause of blindness in US working-age adults, [2] diabetic retinopathy has many economic implications for healthcare systems and the overall population,[3] as well as a variety of personal consequences on patient quality of life [4, 5].

1.2. Diabetic Retinopathy

Diabetic retinopathy (DR) refers to diabetes-induced pathology of the retinal capillaries, arterioles and venules, and the subsequent effects of leakage from or occlusion of the small vessels. Changes within the retinal capillaries include thickening of the basement membrane, epithelial cell dysfunction due to loss of epithelial tight junctions, loss of pericytes, endothelial and smooth muscle cells, weakening, increased permeability and occlusion of capillaries, and microaneurysm formation. The microaneurysm is the hallmark of retinal microvascular disease in diabetic patients [6]. A haemorrhage was defined as a red spot with irregular margins and/or uneven density, particularly when surrounding a central lesion considered a microaneurysm.

1.2.1. Characteristics of Human DR

Clinically, DR is mainly classified in two groups, non-proliferative DR (NPDR) and proliferative DR (PDR). PDR is judged by the presence of retinal neovascularization, [7] which is usually confirmed with fluorescence fundus angiography imaging. PDR is the more advanced stage of DR. In PDR, proliferating neovasculature contributes to severe complications, e.g., vitreous hemorrhage, retinal scars, and tractional retinal detachment, all of which often need vitreoretinal surgery. However, the endpoint of PDR is variable, and

irreversible vision loss is attributed to retinal structure damage and layer thinning. Thus, the Early Treatment of Diabetes Retinopathy Study (ETDRS) has staged NPDR with mild, moderate, and severe grades, aimed to screen risk factors and to detect the earlier stages of DR for nonsurgical treatment, e.g., retinal photocoagulation or antiangiogenic therapy. [8, 9] Histologically, retinal vascular lesions are considered to be the hallmark and the grading criterion of DR. The first visible alteration in retinal vasculature is the formation of microaneurysms. The further changes are intraretinal focal hemorrhage, venous beading, and intraretinal microvascular abnormalities (IRMAs) showing with microvascular torsion and regional capillary nonperfusion on fluorescence fundus angiography imaging. IRMA is associated with "cotton wool" spots observed with funduscopy, which are focal infarcts of nerve fibers in essence. Following the progression of vascular damage, diabetic macular edema appears, which is one of the major causes of vision loss in DR, linking with lesions at the blood–retinal barrier [10, 11].

The estimated crude prevalence rates of diabetic retinopathy (DR) and vision-threatening retinopathy are as much as 40.3% and 8.2%, respectively [12, 13], In recent years, studies have demonstrated that dysfunction of the endoplasmic reticulum (ER), or ER stress, is involved in the pathogenesis of diabetes and its complications [14, 15]. The ER is the central cellular organelle responsible for protein folding and maturation. To ensure the fidelity of protein folding, the ER possesses sophisticated machinery to recognize aberrant proteins and target them for refolding or clearance. This process is known as the unfolded protein response (UPR) [16]. Diabetic retinopathy (DR) is a wellknown long term complication of diabetes mellitus (DM). DR is a significant cause of blindness and ocular morbidity in developed nations. In India, the number of diabetics is increasing and hence the number of DR patients is bound to increase over the next few decades [17, 18].

In patients with DM, the prevalence of any form of DR is about 24% [18]. The Early Treatment Diabetic Retinopathy Study (ETDRS) was a landmark study done between 1980 and 1985, which laid down the principles of classification of DR and provided guidelines for management by retinal laser treatment in cases of advanced disease, that is, proliferative DR (PDR) [19]. The primary outcome in ETDRS was stabilization of vision and prevention of further loss. However, vision improvement was seen in only 3% of patients. Laser photocoagulation was the main intervention in ETDRS apart from systemic control of sugars and other metabolic parameters [20]. The pathogenesis of early DR revolves around damage to the retinal capillary bed caused by persisting high blood glucose levels and high advance glycation end (AGE) products resulting in retinal ischemia. Retinal ischemia in turn leads to production of diffusible angiogenic factor which was earlier called as Factor X by Isaac in 1949 [21]. Diabetic retinopathy (DR) is the most common complication of diabetes mellitus (DM) and is a leading cause of blindness among working-age people worldwide [22]. Globally, it has been estimated that about 30% of people with DM have DR [23].

Park *et al.* reported that overall prevalence of any DR was 19%, and the prevalence of vision-threatening DR was 5%. participants with duration of 10 years or greater, retinopathy was found in 55.2% compared with 12.6% in those with diabetes for a duration of 10 years or less [24] Recent study results showed that the prevalence and incidence of severe DR may be decreasing in people with recently diagnosed with type 1 diabetes [25, 26]. However, while the number of persons with diabetes reporting visual impairment grew, the age-adjusted percentage of adults with diagnosed diabetes who reported visual impairment declined significantly, These findings are likely related to changes in medical management of type 2 diabetes [27, 28] In NHANES, there was increased use of more than 1 oral hypoglycemic agent from the predominant use of 1 type of oral agent [28, 29]. This resulted decrease of the mean glycated hemoglobin (HbA1c) levels and increase of maintaining HbA1c levels of less than 7.0% in 41% and 58% of those with type 2 in 1999 to 2000 and 2005 to 2006, respectively [30] Patients with a lower concentration of insulin or with insulin resistance have been reported to have less DR after adjustment for age, gender, duration of diabetes, blood pressure, and blood glucose concentration [24] The possible mechanisms of insulin resistance and β-cell function in the development of DR in type 2 diabetic patients have been explained by a delay in insulin reaching extravascular target sites. Lower pancreatic β-cell insulin secretory capacity may be a risk factor for severe DR [31] Better β-cell function may promote better long-term metabolic control with lower and more physiological peripheral insulin concentrations. This in turn may result in delayed or reduced development of DR. An increase in body mass index (BMI) also correlated significantly with the deterioration of HbA1c, a decrease in high density lipoprotein cholesterol, an increase in triglycerides as well as a higher prevalence of hypertension [32, 33]. Both metabolic syndrome and increased oxidative stress due to their association with obesity and DR have also been suggested as possible pathophysiological mechanisms. Most studies have reported a significant association between high BMI and obesity with DR [33, 34] Observational study done in Japanese type 2 diabetic patients showed that increased fruit intake was associated with reduced incident DR among patients with a low-fat energy-restricted diet [35] The mechanisms whereby fruits exert preventive effects on DR are not clear, but a high fruit-vegetable intervention is known to increase carotene and vitamin C levels in plasma. Another possibility is that the preventive effects of fruits are mediated through glycemic control. Fruits are low glycemic index foods rich in dietary fiber, which can slow glucose response after ingestion [36]. In this review, we focus a summary of the most common and important problems for consideration on the appropriate study of DR. The current research focuses in clinical and basic science are summarized for researchers to consider and compare with their own experimental achievement.

2. Conclusion

DR remains the leading cause of blindness in working-age adults in the US. Better understanding of the cellular and molecular mechanisms underlying diabetes-related vascular and neuronal damage is important to identify therapeutic targets to protect the retina and reduce vision loss in diabetic patients. Emerging evidence suggests that increased ER stress and activation of the UPR in retinal cells promote the main pathophysiological events in DR, such as oxidative stress, inflammation, apoptosis, vascular leakage, and angiogenesis.

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