· Review ·

Association of systemic cardio-vasculature status with retinal vascular endothelium in diabetes

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心血管状况与糖尿病视网膜血管内皮细胞的相关性

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摘要

糖尿病视网膜病变及其并发大血管病变表明两者之间致病存在相关性。血管内皮细胞是糖尿病血管损伤的主要部位。糖尿病视网膜病变能并发全身动脉硬化和改变血管内皮的功能及结构。在黄斑,动静脉交叉处和在筛板区视神经中的视网膜血管内皮细胞不同与其余视网膜血管中内皮细胞。中央视网膜在视神经中动脉和静脉非常接近且共用同一外膜;因此,增加动脉壁的硬度和厚度可以影响该区域中的相邻中央视网膜静脉中的血流量。此外,小动脉床中的动脉硬化加剧与视网膜微血管扩张有关;这表明筛板中视网膜中央动脉压迫视网膜中央静脉的可能性,从而损害糖尿病患者视网膜中的小静脉流出。经观察发现糖尿病视网膜病变患者在后层流区的视网膜中央静脉中的血流量发生改变。在视网膜中央静脉中增加静水压可能在糖尿病视网膜病变的病情进展过程中起重要作用。这篇综述文章的主旨是强调这种常常被忽视的发病机制。

关键词:糖尿病视网膜病变;微脉管;心血管疾病;视网膜中央动脉;视网膜中央静脉;内皮;发病机理

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Abstract

• The relationship between diabetic retinopathy and macro-vascular complications in diabetes suggests a pathogenic association between these conditions. Vascular endothelium has been identified as a main site of blood vessel injury in diabetes. Diabetic retinopathy is associated with systemic arterial stiffness and altered vascular endothelium function and structure. Retinal vasculature endothelium at the macula, arterio-venous crossings, and in the optic nerve at the lamina cribrosa region is reported to differ from the endothelium in the rest of the retinal blood vessels. The central retinal artery and vein are in close proximity in the optic nerve where they share a common adventitia; thus, increased arterial wall stiffness and thickness may affect blood flow in the neighboring central retinal vein in this region. Moreover, increased arterial stiffness in small arterial beds is associated with retinal venular widening; it suggests the possibility of central retinal artery compressing the central retinal vein at the lamina cribrosa, thereby compromising venular outflow in the retina of diabetic patients. Altered blood flow in the central retinal vein in the postlaminar region has been detected in patients who experience progression of diabetic retinopathy. Increased hydrostatic pressure in the central retinal vein may play a major role in the pathogenesis of diabetic retinopathy. The aim of this review article is to emphasize this pathogenetic mechanism that has often been overlooked.

• KEYWORDS: diabetic retinopathy; microvasculature; cardio-vascular disease; central retinal artery; central retinal vein; endothelium; pathogenesis
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INTRODUCTION

Diabetes mellitus is a metabolic diseasethat causes micro-vascular and macro-vascular complications that significantly affect patients' life expectancy and quality of life. Microangiopathy (diabetic retinopathy, diabetic neuropathy, and diabetic nephropathy) and macroangiopathy (coronary artery disease, stroke, and peripheral artery disease) often coexist in diabetic patients.

Many reports have studied the relationship between diabetic micro-vascular and macro-vascular disease[1-9]. Diabetic retinopathy is evaluated using retinal fundus examination, which has often been used as a biomarker for systemic cardio-vascular disease (CVD). Although there is speculation regarding the usefulness of fundus examination for risk stratification in CVD, there are many studies providing evidence for links between retinal micro-vascular signs and specific CVDs[10-17]. Large multicenter studies have reported that arterial narrowing is associated with the incidence of

diabetes, while venular widening is associated with diabetic retinopathy incidence and progression[12]. Moreover, there is evidence that the presence of diabetic retinopathy is associated with CVD morbidity and mortality in patients with diabetes[17-20].

Although ocular fundus examination may prove to be a useful method for risk stratification in CVD, physicians must be aware of several characteristics of the ocular microcirculation that distinguish it from the microcirculation in other parts of the body. These specifics necessitate caution when making general conclusions regarding micro-vascular alteration in CVD, because retinal microvasculature changes in CVD may not correspond to those in the systemic microvasculature. Retinal microvasculature is an end-organ vasculature that does not form anastomoses with other ocular or orbital tissues. The non-fenestrated retinal endothelium has a strong inner retinal barrier that allows for high control of the fluid and nutrients transport through the vascular wall. The retinal vasculature is auto-regulated without any autonomic innervations and the retina lacks lymphatic vessels. Furthermore, the retinal microcirculation has been developed to comply with the specific ocular configuration and function so that the angioarchitecture of the arteries and veins inside the eyeball at some locations are unique in the body.

DISCUSSION

Systemic Vascular Endothelial Dysfunctionand Diabetic Retinopathy The vascular endothelium has been identified as a main site of blood vessel injury in diabetes[21-22]. Atherosclerotic changes in blood vessels that occur in diabetes can vary from functional changes with minimal structural changes to severe vascular damage that affects the vascular media and may stimulate severe thrombosis. Endothelial damage increases the permeability of the vascular endothelium to lipoproteins, decreases production of nitric oxide (NO), increases migration and adhesion of leucocytes, stimulates vascular growth, and causes prothrombotic dominance and release of vasoactive substances[22].

Patients with diabetic retinopathy have significantly decreased flow-mediated dilation than patients without diabetic microangiopathy, which is suggestive of generalized endothelial dysfunction in these patients[3,5,23]. Subclinical CVD measurements and early structural atherosclerotic changes in the carotid artery are reported to be associated with diabetic retinopathy[1-2,6-8,19,23]; however, some studies did not find an association between carotid artery intima-media thickness and diabetic retinopathy[2-3,5,24].

Increased systemic arterial stiffness has been reported in patients with diabetic retinopathy[3,25]. Plasma urotensin-Ⅱ, a potent vasoconstrictor that is associated with CVD, was also independently associated with diabetic retinopathy in type 2 diabetes[6]. Finally, diabetic retinopathy is associated with hypertension[26], heart failure[27], coronary heart disease[17,19] and stroke[19].

Cardio-vascular Disease and Non-Diabetic Retinopathy Retinopathy in the absence of diabetes mellitus (non-diabetic retinopathy) is characterized by the presence of microaneurysms, hemorrhages, hard exudate, cotton wool spots, venous beading, intraretinal micro-vascular abnormalities, and neovascularisation with a prevalence ranging between 4.8% and 12.5%[7,28]. Non-diabetic retinopathy is associated with hypertension, increased IMT, and smoking[28]. The presence of non-diabetic retinopathy signs and symptoms is also associated with three fold higher risk of stroke[16]. Moreover, a significant association exists between retinopathy and coronary artery calcification in subjects with and without diabetes and hypertension[15].

The above-mentioned studies on non-diabetic retinopathy suggest a link between the pathogenetic mechanisms in micro-vascular and macro-vascular diseases. Retinal blood vessel changes were also associated with vascular endothelial dysfunction and with several markers of atherosclerosis[11,13,28]. Wider retinal venular caliber was associated with decreased brachial flow-mediated dilation, independent of traditional cardio-vascular risk factors[11]. Venular diameter was also linearly related to several markers of atherosclerosis, including decreased ankle-arm index, increased plaques score, increased aortic calcification, and increased carotid artery intima-media thickness[13]. Furthermore, increased arterial stiffness in large arterial beds is associated with retinal arterial narrowing, while increased arterial stiffness in small arterial beds is associated with retinal venular widening[29].

However, diabetic retinopathy is more prevalent than non-diabetic retinopathy and involvesa greater risk for vision loss[28]. Therefore, an additional factor attributed to diabetes is expected to be involved in diabetic retinopathy. Hemorheological and inflammatory mechanisms have also been suggested to contribute to diabetic retinopathy[30-31]. Plasma levels of thrombomodulin and other blood coagulation factors are significantly increased in patients with proliferative diabetic retinopathy compared to healthy individuals or in patients with simple diabetic retinopathy[30]. Thrombomodulin, thrombin antithrombin Ⅲ complexes, and plasmin-alpha 2-plasmin inhibitor complexes are independent predictors of diabetic retinopathy[30]. Similarly, inflammatory markers, such as C reactive protein and soluble intercellular adhesion molecule-1, are positively associated with retinopathy[31-32]. Increased blood viscosity, hypercoagulability, increased stickiness, and deformability of erythrocytes have also been reported in diabetes[33-34]. These factors may increase the shear stress on retinal vascular endothelium and in co-action with pro-inflammatory mechanisms and hyperglycemia may aggravate endothelial dysfunction. One of the first histopathological findings in diabetic retinopathy is pericyte loss that has also been regarded as a cause of micro-vascular abnormalities in diabetic retinopathy[35]. Pericytes are reported to be highly sensitive to metabolic changes in diabetes and are strongly inter-related with endothelial cells by ligand-receptor systems[36].

Retinal Vascular Endotheliumin Diabetic Retinopathy Yu *et al*[21] report that there are four

locations in the eye where vascular endothelium differs significantly from the rest of the ocular microcirculation: the macular region, the vortex veins, the central retinal vein, and retinal artery – vein crossing points. The authors of the aforementioned article reported that the shape of the endothelium in the macula suggests increased blood flow in this region and an increased capability of blood flow redistribution suggested by predominant arterioles and relatively short capillary lengths. It is also known that age has a significant effect on the length of endothelial cells in the veins at arterio – venous crossing points. The vortex vein system was characterized by dramatic differences in the endothelium cytoskeleton and, cell and nuclei shape depending on their location, suggesting differences in hemodynamic forces in different regions. Endothelium shape of vortex veins in the post-ampullar, scleral entrance and the first half of the sclera canal are more similar to arteriolar than venular endothelium. Such arteriole – like endothelium was also detected in the central retinal vein at the level of lamina cribrosa[37]. Similar to the exit site of the vortex veins, the lamina cribrosa is another region where a pressure gradient exists between the intraocular and extraocular tissues. The blood flow in the central retinal vein at the level of lamina cribrosa is affected by the pressure gradient between the intraocular pressure and the intracranial aqueous pressure that is present inside the optic nerve sheath. The central retinal artery and vein are closely related, as they share a common adventitia and as they pass through the lamina cribrosa, the diameter of the central retinal vein is decreased[38]. Increased arterial wall stiffness and thickness may also affect blood flow in the neighbouring central retinal vein and this is hypothesized to be the factor responsible for the predilection of central retinal vein occlusion at the posterior lamina cribrosa.

Blood flow in the central retinal vein is pulsatile and changes simultaneously with the intraocular pulse pressure[39]. The pulsatile nature of blood flow in the central retinal vein may be one of the causes of the characteristic arteriole – like endothelium shape at the level of lamina cribrosa. The greatest endothelium phenotype changes are at the level of the posterior lamina cribrosa, which is identified as the most prevalent site of optic nerve head thrombosis[37]. In contrast, endothelia cells in the central retinal artery are not significantly altered at the different laminar regions[21].

In patients with vascular comorbidities, expression of endothelial f-actin stress fibre is increased in the endothelium of the central retinal vein in the posterior lamina cribrosa and the retrolaminar regions, suggesting increased shear stress at these locations[21,37]. The lamina cribrosa region has also been described as a "throttle" for retinal blood inflow and outflow[38]. Blood flow in the central retinal artery and vein at the lamina cribrosa is affected by blood pressure, intraocular pressure, intracranial pressure, and the hemorheological properties of the blood. The above mentioned studies investigating the relationship between macro – vascular and micro – vascular diabetic complications reported that altered systemic endothelial function and increased arterial stiffness is

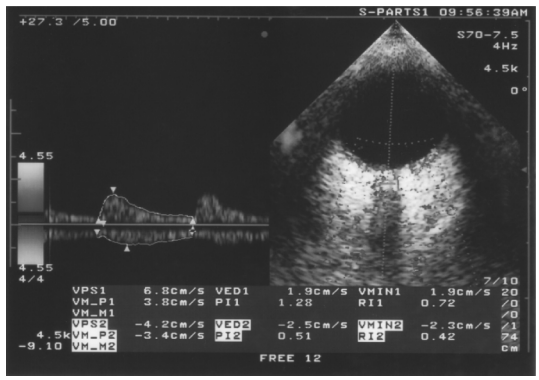

Figure 1 Color Doppler imaging of the central retinal artery (CRA) and central retinal vein (CRV) in the retrobulbar optic nerve of a diabetic patient without diabetic retinopathy (digitally processed image) The left part of the image presents the blood velocity wave of the CRA (above the horizontal green line) and of the CRV (below the horizontal green line). The central retinal venous outflow in this patient causes a moderate pulsatility with a pulsatility index (PI) of 0.51.

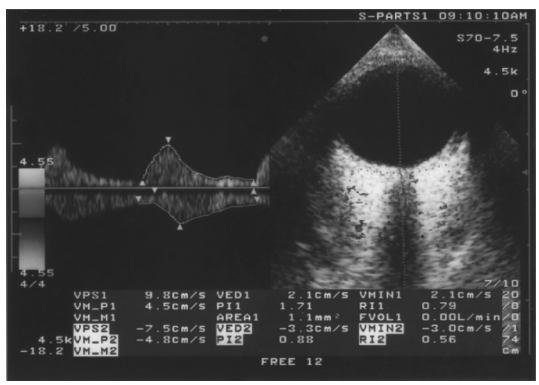

Figure 2 Color Doppler imaging of the central retinal artery (CRA) and central retinal vein (CRV) in the retrobulbar optic nerve of a patient with pre – proliferative diabetic retinopathy (digitally processed image) The blood velocity wave in the central retinal vein shows a markedly increased pulsatility with a pulsatility index (PI) of 0.88.

associated with diabetic retinopathy[3,5,23,25]. This may suggest increased vessel wall stiffness in the central retinal artery that may exert pressure on the central retinal vein via their shared adventitia in the posterior lamina cribrosa. Moreover, decreased vascular lumen in the central retinal vein and altered hemorheological properties of the blood that are present in diabetes may cause altered blood flow at this "throttle" region. We previously reported increased blood velocity and pulsatility index in the retrobulbar central retinal vein in patients who had progression of diabetic retinopathy (Figure 1 and Figure 2)[40-41]. Regarding the fact that blood flow in the central retinal artery is not increased in these patients, we suggested that a local hemodynamic alteration is present in the central retinal vein.

Central Retinal Vein Congestionand Clinical Signs of Diabetic Retinopathy Altered circulation in the central retinal vein at the lamina cribrosa of diabetic patients suggests compromised venous outflow from the retina. This may result in venous congestion and increased intravascular hydrostatic pressure in the retinal veins of diabetic patients. The clinical signs that predict diabetic retinopathy – venous dilation, as

well as the clinical signs of developed diabetic retinopathy – decreased retinal fractal dimension, decreased vessel wall compliance and altered vessel permeability resulting in microaneurisms, hemorrhages, exudates and edema, are in accordance with this hypothesis[34,42]. As mentioned previously, increased arterial stiffness in small arterial beds is associated with retinal venular widening, suggesting the possibility of central retinal artery compression to the central retinal vein at the lamina cribrosa and compromising the venular outflow in diabetic patients' retinas[29]. In favor of this hypothesis are cases of unilateral diabetic retinopathy and diabetic macular edema that are preceded by retinal venular widening in the affected eye, which later develop central retinal vein occlusion[43]. Moreover, optic nerve head configuration may affect the relationship between the central retinal artery and vein in the laminar region, so that unilateral cases of diabetic retinopathy in patients with tilted disks have been reported[44]. Diabetic papillopathy, in which oedematous optic nerve tissue induces pressure on the central retinal vein, is another condition that aggravates diabetic retinopathy and retinopathy regression was reported after papillopathy resolution[45-46]. Furthermore, the neuroretinal rim area increases with the severity of diabetic retinopathy, suggesting that subclinical optic nerve head swelling may also be related to compromised central retinal venous outflow[47]. The Beijing Eye Study 2011 reported that higher prevalence and severity of diabetic retinopathy were associated with higher cerebro – spinal fluid pressure[48]. The authors suggested that higher cerebro – spinal fluid pressure increases central retinal vein pressure that may lead to retinal vein congestion and vascular leakage in the diabetic retina.

Retinal vasodilation in diabetes may be triggered by other mechanisms, such as inflammation, a reaction to local tissue acidosis, altered autoregulation, or in response to increased blood flow. A number of studies have suggested that inflammatory mechanisms are involved in the pathogenesis of diabetic retinopathy[31-32,49]. However, an inflammatory reaction and tissue acidosis would be expected to induce vasodilation in both arterioles and venules, whereas diabetic retinopathy is preceded by only venular dilation[50-51]. Regarding the selective approach to retinal blood flow measurements, there is still a lack of consensus regarding retinal blood flow changes in various stages of diabetic retinopathy and thus we cannot properly address the relationship between retinal blood flow and retinal vasodilation.

The venous vascular endothelium at arterio – venous crossings in the retina and at the posterior lamina cribrosa have distinct features suggesting increased shear stress at these locations. Diabetes and other systemic conditions, such as hypertension, dyslipidemia, and atherosclerosis, may further aggravate blood flow at these regions and increase shear stress on the vascular endothelium. Therefore, therapeutics that act by reducing shear stress and improving blood hemorheological properties may prove beneficial for preventing diabetic retinopathy.

Inconclusion, both the macro – and microvasculature vascular endothelium is affected in diabetes. The specific angioarchitecture of the central retinal artery and vein at the lamina cribrosa renders the venular endothelium at this location exposed to significant changes related to shear stress. Increased arterial vascular wall thickness and altered hemorheological factors in diabetes may further increase the shear stress to the venular endothelium at posterior lamina cribrosa. Retinal venous dilation and altered postlaminar central retinal venous blood flow are associated with progression of diabetic retinopathy, suggesting compromised retinal venous outflow in diabetic retinopathy. We suggest that retinal venous congestion may be a major factor in the pathogenesis of diabetic retinopathy. Further comprehensive studies on retinal circulation and morphometric assessment of the central retinal artery and vein in diabetes are necessary to validate this hypothesis.

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