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MINIREVIEWS

Current evidence of pathophysiology of diabetic macular edema: A review

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Abstract

Diabetic macular edema (DME) is an important cause of vision loss in patients with diabetes mellitus. The pathophysiology of DME can be described as a process whereby hyperglycaemia leads to overlapping and inter-related pathways that play a role not only in the initial vascular events, but also in the events that cause the edema to become chronic. On a macrocellular level, DME is believed to be in part caused by alterations in hydrostatic and oncotic pressures and shear stress. Angiogenic factor expression, inflammation and oxidative stress constitute the key components of microvascular pathways. The interactions, signalling events and feedback loops between the various molecules are complicated and are not completely understood. These molecular mediators, acting in conjunction with macrocellular factors, which are all stimulated in part by the hyperglycaemia and hypoxia, can have a direct endothelial effect leading to hyperpermeability, disruption of vascular endothelial cell junctions, and leukostasis. Macular edema is thought to be caused as a result of these consequences.

Key words: Diabetes mellitus; Macular edema; Pathophysiology; Vascular endothelial growth factor; Inflammation

Core tip: Diabetic macular edema (DME) is an important cause of vision loss in patients with diabetes mellitus. The pathophysiology of DME can be described as a process whereby hyperglycaemia leads to overlapping and inter-related pathways that play a role not only in the initial vascular events, but also in the events that cause the edema to become chronic. On a macrocellular level, DME is believed to be in part caused by alterations in hydrostatic and oncotic pressures and shear stress. Angiogenic factor expression, inflammation and oxidative stress constitute the key components of microvascular pathways. The interactions, signalling events and feedback loops between the various molecules are complicated and are not completely understood. These molecular mediators, acting in conjunction with macrocellular factors, which are all stimulated in part by the hyperglycaemia and hypoxia, can have a direct endothelial effect leading to hyperpermeability, disruption of vascular endothelial cell junctions, and leukostasis. Macular edema is thought to be caused as a result of these consequences.

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INTRODUCTION

Most common reason of visual loss in diabetes mellitus (DM) is diabetic macular edema (DME)[1,2]. Macular edema can develop in any stage of the disease but the risk increases as the disease progresses[3]. The role of hyper-

glycemia on development of DME has been investigated in a population based study, Wisconsin Epidemiologic Study of Diabetic Retinopathy (DR). In this study, the risk of developing DME in 10 years is reported as 20.1% in type I DM, 13.9% in noninsulin-dependent type Ⅱ DM and 25.4% in insulin-dependent DM patients[4].

The classification of DME has changed over time as new imaging techniques have evolved. DME is classified as clinically significant according to visible retinal thickening and hard exudates in relation to distance from macula in Early Treatment Diabetic Retinopathy Study. In Global Diabetic Retinopathy Project, mild, intermediate or severe DME have been described according to the severity of involvement of macular center in light of ocular coherence tomographic findings[5,6].

Since the macular edema in presence the of DM may lead to permanent visual loss, it is of great importance to understand the pathophysiology of DME in order to prevent this complication and to develop new treatment strategies. The factors leading to development and progression of DME and the macrovascular and microvascular changes induced by DM are summarised in this review.

GENERAL INFORMATION

Why is the macula involved?

Even though there is a generalized micro vascular damage and vascular leakage throughout the retina, there are some predisposing histological and metabolic properties of the macula that render it prone to edema: (1) high cellular concentration; (2) high metabolic activity; (3) the oblique-horizontal course of Henle fibers toward periphery; (4) weak intercellular junctions in the external plexiform layer; and (5) presence of central avascular zone.

Normal retinal circulation and blood-retinal barrier

Among the tissues in the body, retina is one of the tissues with highest oxygen requirement and is supplied by two different circulations. Inner 2/3 of retina is supplied by retinal circulation and outer 1/3 is supplied by choroidal vessels. Endothelial cells on vascular wall and the surrounding pericytes and astrocytes constitute the inner blood retinal barrier. Outer blood retinal barrier is formed by tight junctions between the cells of retinal pigment epithelial (RPE) layer.

In retinal circulation, arteries branch into precapillary arterioles which are surrounded by smooth muscle cells controlled by autonomic nervous system. Beyond this level, in the capillary layer, pericytes take place of smooth muscle cells and the flow rate is determined by autoregulation. Under normal circumstances, capillaries and venules are primary sites of fluid passage and the flow changes according to local metabolic needs, oxygen and carbon dioxide partial pressures. In the early stages of diabetic retinopathy, there is damage to inner blood retinal barrier and the increased filtration of fluid from capillaries and venules result in macular edema.

PATHOPHYSIOLOGY

There are numerous pathophysiologic mechanisms that have been proposed as the role of diabetes on development of DME. But, the exact mechanism of the damage to the blood-retinal barrier caused by hyperglycemia is not known. Several pathways involving angiogenic and inflamatory factors and oxidative stress are considered to take role.

Macrovascular effects of diabetes

In all tissues including retina, the movement of fluid and particles across vascular wall depend on intravascular and extravascular hydrostatic and oncotic pressures. According to Starling's Law, equilibrium is reached when the differences between intra and extravascular the oncotic and hydrostatic pressures are equal. In retina, capillary hydrostatic pressure is related with systemic blood pressure, and the oncotic pressure is related with the albumin level that constitute majority of serum proteins. Tissue hydrostatic pressure is equal to intraocular pressure and tissue oncotic pressure is related with interstitial protein content. This equilibrium is disrupted in case of diabetes by several factors. Increased transluminal hydrostatic pressure due to hypertension and increased tissue oncotic pressure due to blood- retinal barrier damage and leakage of intravascular proteins into the interstitial space result in retinal edema. If a there is coexistent diabetic nephropathy, the decreased serum albumin levels lower intravascular oncotic pressure which contribute to edema[7].

There are animal models which show increased ocular blood flow in case of increase in blood glucose levels. It is also reported that acute increases in plasma glucose levels cause increase in ocular blood flow in human studies. Increased thromboctye aggregation, decreased erythrocyte deformability and increased blood flow cause an increase in shear stress on the vascular endothelial cells. The resulting secretion of vasoactive and inflammatory factors contribute to the pathological process on the molecular level[8,9].

Microvascular effects of diabetes

Pericyte loss is the earliest and most specific sign of diabetic retinopathy. Cogan *et al*[10] have shown the loss of the pericytes as ghost cells surrounding the capillary walls. The mechanism of pericyte loss in diabetes is not clearly known. Pericytes express advanced glycosylation endproducts (AGE) receptors and thus may be susceptible to damaging effects of AGEs. Additionally, it may be indirectly related to the leukocyte adhesion to the vasculature[11].

Pericyte loss is the first sign that can be shown histologically, whereas the first clinical sign of diabetic retinopathy that can be shown by fundus examination and fundus flourescein angiography is microaneurysm formation. Pericytes exert antiproliferative effect on endothelial cells and their loss results in hypercellular microaneurysm formation. Hypocellular aneurysms are thought to be formed by apoptosis of these proliferated endothelial

cells. Pericyte loss also results in loss of support around the vascular wall which leads to focal dilatations at the weak points contributing to microaneurysm formation[10].

Thickening of the capillary basal membrane and accumulation of the extracellular matrix elements are shown in diabetes retinopathy. It is thought that these changes result in abnormal autoregulation of vascular flow and retinal hemodynamic instability.

Endothelial cells have intercellular tight junctions which act as barrier to intravascular components. These junctions are formed by numerous intercellular proteins including occludin, claudin and zonula occludens-1 which are responsible for most of the barrier function. In diabetes, the synthesis and expression of these proteins are affected resulting in weakening of intercellular bonds.

Combined effect of loss of pericytes, microaneurysm formation, basement membrane thickening and loss of intercellular junction proteins result in DME.

Biochemical effects of diabetes

Four pathways have been proposed as the mechanism of microvascular damage as a result of hyperglycemia. These are: (1) polyol pathway (Aldose reductase pathway); (2) advanced glycation end product formation; (3) protein Kinase C activation; and (4) hexosamine pathway.

Until recently, these four pathways were thought to operate separately to form vascular damage. But all these pathways are shown to operate by increasing superoxide formation by the mitochondria and increased superoxide levels play the central role in the combined theory of diabetic retinopathy mechanism[12].

Growth factors and inflamation

Vascular endothelial growth factor (VEGF) is a growth factor that regulates embryologic vasculogenesis and pathologic angiogenesis by stimulating endothelial cell migration and proliferation and increasing survival. Among different members of the VEGF family, VEGF-A plays the key role in ocular angiogenesis and vascular permeability. VEGF-A has 9 isoforms, VEGF-A165 being mostly involved in ocular pathologies[13-15]. VEGF causes DME by the stimulation of the development of neovascularization that are devoid of tight junctions between the endothelial cells[16]. In addition, VEGF has a proinflamatory effect by causing increase in ICAM-1 and VCAM-2 resulting in stimulation of leukocyte chemotaxis and adhesion.

One VEGF family member that has become an important treatment target is Placental Growth Factor (PlGF) which is first isolated from the placental tissue. It causes DME by causing damage to intercellular tight junctions on vascular wall and retinal pigment epithelium. Tissue hypoxia and insulin stimulates PlGF formation which causes subretinal fluid accumulation and increase in retinal edema[17].

There are many evidence that show inflammation plays a role in diabetic retinopathy and DME. The mechanism of intravitreal corticosteroids in decreasing macular edema has not been fully understood but it supports the hypothesis that inflammation is part of the DME process.

The blood retinal barrier does not allow passage of leucocytes under normal conditions. In DM, leucocytes produce toxic superoxide radicals and proteolytic enzymes that weaken the intercellular tight junctions and denature extracellular matrix proteins. This leads to vascular leakage and edema. Leucocytes become rigid and bind strongly to endothelial cells. Combined with rigid erythrocytes and thrombocytes, these leucocytes also cause vascular occlusion. This causes focal retinal ischemia and hypoxia which further leads to increase in inflammatory reaction[18-20].

There are many inflammatory mediators that have been shown to increase in vitreus and systemic circulation in case of diabetes mellitus and diabetic retinopathy. Most studied mediators are tomur necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and intercellular adhesion molecule-1 (ICAM-1). TNF-α is a proinflammatory cytokine and is thought to serve by increasing leucostasis and is related with VEGF and ICAM-1 levels[21]. ICAM-1 is an intracellular protein that is required for the adhesion of leucocytes to endothelial cells. ICAM levels increase with VEGF stimulation and AGE (Advanced glycation products- ileri glukozilasyon ürünleri) products. This also exerts its effect by aiding leucostasis[22]. IL-6 is shown to increase VEGF expression and causes edema by increasing vascular permeability[23,24].

Other factors

Matrix metalloproteinases are cytokines that increase locally with advanced glycation end products, reactive oxygen and direct effects of hyperglycemia. Under normal conditions, they play role in extracellular matrix formation, repair and angiogenesis. They cause protein degradation and weakening of intercellular tight junctions which lead to increase in vascular permeability[25].

Type 1 carbonic anhydrase enzyme has been shown in choroidal endothelium and retina pigment epithelium[26]. CA causes a more profound increase in vascular permeability when compared to VEGF. CA inhibitors are used to treat macular edema caused by other pathologies in which these are thought to inhibit CA in retinal pigment epithelial cells resulting in increased absorbtion of extracellular fluid. But DME patients do not respond well to CA inhibitors. RPE is presumed to be damaged in DM or the abnormal amount of extracellular fluid exceeds the limits of RPE[26-28].

Hypertension is a known risk factor in development and progression of diabetic retinopathy. Angiotensin 2 (Ag-2) increases VEGF and related vascular permeability. Ag-2 is shown to cause pericyte migration and hypertrophy. Angiotensin converting enzyme receptors are found on endothelium, choroid and pericytes. ACE inhibitors decrease blood pressure as well as decreasing retinal blood flow. ACE inhibitors are shown to decrease development of DR in type 1 DM but does not seem to have effect on progression and DR development in type 2 DM patients[22,29,30].

CONCLUSION

In conclusion, as a major cause of visual loss in diabetic patients the pathogenesis of DME is complex, and a variety of factors and biochemical pathways are involved, which provides an opportunity for the development of a number of therapeutic modalities to treat the condition.

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