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Review

Role of altered coagulation-fibrinolytic system in the pathophysiology of diabetic retinopathy

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ABSTRACT

The implications of altered coagulation-fibrinolytic system in the pathophysiology of several vascular disorders, such as stroke and myocardial infarction, have been well researched upon and established. However, its role in the progression of diabetic retinopathy has not been explored much. Since a decade, it is known that hyperglycemia is associated with a hypercoagulated state and the various impairments it causes are well acknowledged as independent risk factors for the development of cardiovascular diseases. But recent studies suggest that the hypercoagulative state and diminished fibrinolytic responses might also alter retinal homeostasis and induce several deleterious molecular changes in retinal cells which aggravate the already existing hyperglycemia-induced pathological conditions and thereby lead to the progression of diabetic retinopathy. The major mediators of coagulation-fibrinolytic system whose concentration or activity get altered during hyperglycemia include fibrinogen, antithrombin-III (AT-III), plasminogen activator inhibitor-1 (PAI-1) and von Willebrand factor (vWF). Inhibiting the pathways by which these altered mediators get involved in the pathophysiology of diabetic retinopathy can serve as potential targets for the development of an adjuvant novel alternative therapy for diabetic retinopathy.

1. Introduction

Coagulation-fibrinolytic system is an integral part of the normal hematopoietic physiology of human body. Blood clot formation post the activation of coagulation cascade serves as a protective mechanism of the body against injury and mainly fulfills two prime purposes – (i) preventing excessive blood loss, (ii) shielding the wounded tissues from microbes and infections. However, during pathological conditions, alterations induced in this system might lead to excessive blood clot formation, which may block narrow vasculature and lead to the progression of several cardiovascular disorders [1]. Besides recent studies show that hyperglycemia-induced pathological molecular changes shift the equilibrium of coagulation-fibrinolytic system towards a hypercoagulant state. This pathological state adversely affects retinal tissue and aggravates the progression of diabetic retinopathy [2].

Diabetic retinopathy, a neuro-microvascular complication associated with diabetes mellitus, is associated with sight jeopardizing consequences. It is one of the leading causes of potentially preventable disease-acquired blindness globally. It is particularly initiated by a series of pathological vascular changes in the retinal blood vessels which are attributed to the molecular alterations induced by hyperglycemia and its effects on the endothelial cells via various downstream pathways such as increased flux of the polyol pathway [3], accumulation of advanced glycation end-products [4], activation of various isoforms of protein kinase C [5], hypertension [6] and overactivation of Renin-Angiotensin-Aldosterone system [7], upregulated generation of reactive oxygen species [8], activation of major inflammatory mediators, like COX-2 (cyclooxygenase-2) [9], cellular adhesion molecules, NF-κB (nuclear factor-kappa B) [10] and cytokines such as TNF-α (tumor necrosis factor-alpha) and interleukins [11], and stimulation of various growth factors such as fibroblast growth factor-2 (FGF2) [12], insulin-like growth factor-1 (IGF-1) [13], angiopoietin-2 [14], transforming growth factor-beta 2 (TGF-beta 2) [15], platelet derived growth factors (PDGFs) [16] and vascular endothelial growth factor (VEGF) [17]. Although all the above mentioned factors are confirmed to be involved in the pathophysiology of this disorder, the exact pathways leading to the progression of this complication are not known. Its pathological progression is highly complex and involves a webbed interplay between several pathways involving retinal endothelial dysfunction [18], inflammation [19], oxidative stress [20] and hemodynamic changes [21], amongst various other factors accounting

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for apoptosis and degeneration of retinal cells. These events alter ocular anatomy and physiology, resulting in characteristic pathological conditions such as formation of microaneurysms (small dilatations in the retinal blood vessels), neovascularization, retinal hemorrhages and macular edema, marking the disease progression through the exhibition of two distinct clinical stages – namely non-proliferative diabetic retinopathy (also known as background retinopathy) and proliferative diabetic retinopathy [22]. The former is characterized by the formation of microaneurysms, while the latter involves retinal neovascularization (de novo synthesis of new immature blood vessels on the pre-existing vasculature). The former stage, if not treated well on time, consequently progresses to the latter advanced stage, and ultimately leads to retinal detachment, which is the eventual reason of vision loss in this diabetic complication [23].

2. Coagulation-Fibrinolytic system during hyperglycemia and its role in advancement of diabetic retinopathy

Hyperglycemia induces several molecular changes which disturb the homeostasis of numerous physiological pathways of the body, and subsequently impair coagulation-fibrinolytic system. These impairments further lead to various pathological alterations in the microvasculature of retina, resulting in the progression of diabetic retinopathy. These hyperglycemia-induced pathological alterations and their subsequent effects on retina are discussed, in detail, as follows:

3. Increased levels of fibrinogen

Various studies conducted in the past prove that hyperglycemia causes hyperfibrinogenemia. Diabetes mellitus, especially Type II, is associated with increased blood fibrinogen levels. Since fibrinogen is critically involved in blood clot formation, its elevated levels cause hyper-coagulation in diabetic patients, thus increasing their blood viscosity [24,25]. Although the exact mechanism by which hyperglycemia increases fibrinogen production is not known, several hypothetical mechanisms have been proposed to explain the same. According to a study, hyperglucagonemia might be one of the reasons of hyperfibrinogenemia. Excessive secretion of glucagon during Type II diabetes mellitus is due to the loss of beta-cell mass which causes an imbalance in the homeostasis of beta-cell to alpha-cell ratio, leading to decreased ratio of insulin-to-glucagon secretion. Hence, the relatively upregulated secretion of glucagon also contributes to hyperglycemia by stimulating hepatic glucose production [26]. Also, this elevation in the glucagon plasma concentration stimulates fibrinogen synthesis via the same pathway. Hyperglycemia, produced in response to glucagon, further stimulates fibrinogen degradation products, thereby upregulating hepatic fibrinogen synthesis. Besides, insulin resistance has been related to increased fibrinogen production. However, the molecular events behind this event are not fully elucidated [27,28].

Upregulated levels of fibrinogen causes numerous pathological alterations which mediate the progression of diabetic retinopathy. Increased fibrinogen, as already stated, increases the blood viscosity. This event acts as an initial precursor for hyperglycemia-induced ischemia. The fibrinogen-mediated blood coagulation decreases tissue perfusion, as measured by decreased transcutaneous oxygen tension (TcPO2) levels, thereby inducing ischemia [29]. Although it is known that fibrinogen is not normally present in healthy human retina, studies have shown that hyperglycemia-induced pathological alterations (such as overexpression of VEGF) induce abnormal expression of fibrinogen in diabetic retina [30]. Interestingly, VEGF is itself overactivated during hyperglycemia-induced ischemia (and hypoxia) caused due to the reduced production of nitric oxide. Hence a cyclic process is initiated by hyperglycemia whereby nitric oxide deficiency-induced ischemia overactivates VEGF, which upon upregulating fibrinogen expression in retina, further aggravates retinal ischemia [31]. Since retina requires high oxygen supply, fibrinogen-induced ischemia leads to deprivation of oxygen in retinal cells, causing their necrosis [29]. Also, retinal ischemia causes breakdown of blood-retinal barrier (BRB), thereby increasing edema and inducing a robust inflammatory response (by activating leukocytes) in the retina which further damages retinal endothelial cells [32]. Besides, fibrinogen plays several other detrimental roles in retinal cells. Elevated level of fibrinogen stimulates its binding to the retinal endothelium through its interaction with cellular adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1) and α5β1 integrin, which are already upregulated during hyperglycemia-induced retinal inflammation. These interactions increase the production of F-actin (filamentous actin), a contractile protein which regulates the rigidity and contractility of blood vessels. Upregulated expression of F-actin induces contraction, stiffening of cells and actin filament retraction. Endothelial tight junction proteins also get downregulated due to elevated expression of fibrinogen. Both the above mentioned events cause endothelial dysfunction, resulting in its increased permeability which causes vascular leakage, ultimately leading to macular edema. Besides, fibrinogen also causes vasoconstriction via stimulating production of endothelin-1, further aggravating ischemic conditions [30]. Elevated fibrinogen levels also increase the susceptibility of retina towards retinal detachment by altering the adhesion properties of retinal tissue and retinal pigment epithelium. This may partially be attributed to fibrinogen-induced breakdown of blood-retinal barrier, and remaining to fibrinogen-induced upregulation of unstable fibrin formation, which splits into fibrin degradation products. These products being mitogenic in nature induce pathological proliferation of retinal endothelial cells, retinal pigment epithelium and cause photoreceptor degeneration [32,33]. Hence, the above mentioned damages induced by elevated fibrinogen in diabetic retina substantially present sufficient proof of its involvement in the progression of diabetic retinopathy.

4. Impairment of anticoagulant activity of antithrombin-III (AT-III)

Hyperglycemia induces hypercoagulative state due to its prothrombotic properties. Several hyperglycemia-induced pathological alterations such as induction of gene transcription of coagulation factors via oxidative stress pathway and endothelial glycocalyx layer depletion cause this prothrombotic shift [34]. Subsequent studies proposed some additional pathways for hyperglycemia-facilitated prothrombotic state such as impediment of the anticoagulant activity of antithrombin-III (in response to hyperglycemia-induced increased flux of polyol pathway and oxidative stress), leading to thrombin hyperactivity [35]. Fructose (the end product of polyol pathway), as well as its metabolites such as glyceraldehyde and dihydroxyacetone (produced during glycolysis cycle), get auto-oxidized in the presence of reactive oxygen species (produced via mitochondrial dysfunction during hyperglycemia) and lead to the production of methylglyoxal, a highly reactive carbonyl compound [36]. Methylglyoxal reduces the activity of antithrombin-III by covalently binding to its active site (Arg-393 residue), forming an adduct which renders antithrombin-III incapable of activation, thus reducing antithrombin-III-mediated inhibition of thrombin and factor Xa. This event leads to unchecked overexpression of both these coagulation factors, hence explaining hyperglycemia-induced prothrombotic state [37].

This overexpressed thrombin further aggravates several pathological conditions which lead to the progression of diabetic retinopathy. Thrombin is a critical upregulator of oxidative stress and inflammation. It induces the mRNA levels of Nox4 subtype of NADPH (nicotinamide adenine dinucleotide phosphate) oxidase, an enzyme involved in the production of superoxide radical from molecular oxygen, hence increasing oxidative stress [38]. The pro-inflammatory effects of thrombin include induction of nuclear factor-kappa B (NF-κB) via a scaffold protein, caspase-recruitment domain (CARD)-containing protein 10 (CARD10), which activates a G-protein coupled receptor named