



Diabetes mellitus and diabetic nephropathy: a review of the literature on hemostatic changes in coagulation and thrombosis

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Abstract

Vascular complications lead to morbidity and mortality in patients with diabetes. Diabetic nephropathy (DN) is one of the main life-threatening problems for these patients, as it is the main cause of end-stage renal disease. This study aimed to measure the clinical effects of diabetes in patients with diabetes and in patients with diabetic nephropathy. Improved hypoglycemic control in patients with diabetes could impressively reduce platelet hyperreactivity, and oxidative stress alters the levels of many coagulation and thrombosis factors, resulting in an abnormal hemostasis and impaired levels of numerous serum markers. Most studies have revealed that coagulation factor levels are high in patients with diabetes and nephrodiabetes. Serum inflammatory factors, and coagulation and endothelial functions are good predictors of diabetic nephropathy. This literature review was conducted with access to scholarly databases and Google Scholar through Qassim University, and it analyzes studies from early 2010 until November 2020. Many studies have inferred that diabetes severely affects hemostasis and increases the risk of cardiovascular disease.

Key Words Diabetes, Coagulation, Thrombosis, Nephropathy

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder that is defined as the presence of hyperglycemia that emanates from a fault in insulin action, a shortage in insulin secretion, or both [1]. The anabolic characteristics of insulin result in abnormalities in the metabolism of micronutrients (lipids, carbohydrates, and proteins). These metabolic abnormalities are due to the low levels of insulin to fulfill an adequate response and/or insulin resistance of target tissues, mainly skeletal muscles and adipose tissue, and to a lesser extent in the liver, at the level of insulin receptors, signal transduction systems, and/or effector enzymes or genes. Type 1 diabetes is a common form of diabetes and presents as a complete deficiency of insulin due to the impairment of pancreatic beta cells. In contrast, hyperglycemia in type 2 diabetes occurs because of insulin resistance [2]. In May 2017, there were approximately 451 million patients with diabetes worldwide aged between 18 and 99 years, and by 2045, this number is expected to increase to 693 million [3], which will put a lot of pressure onto health facilities worldwide. Therefore, this study aimed to identify the effect

of diabetes on vascular complications, specifically diabetic nephropathy (DN), as reported in studies available on Google search engines between 2010 and 2020. It also explores homeostatic changes in coagulation and thrombosis factors [fibrinogen, Von Willebrand factor (VWF), and ADAMTS13] in patients with diabetes and DN.

Diabetes is significantly associated with vascular disease. As the rate of progression of vascular complications in patients with diabetes is much faster than that in individuals without diabetes [4], microvascular and macrovascular complications from diabetes are linked with alterations in the coagulation system, boosted platelet activation, and abnormal functioning of the endothelium [5]. Today, diabetes today has formed into a global medical condition, and the continually increasing incidence of diabetes is an indication of an increase in the incidence of vascular complications likely to burden medical systems.

Nephropathy develops in 30% of patients with type 1 diabetes and 40% of patients with type 2 diabetes [6]. Renal failure is another serious complication of diabetes [7]. Although kidney diseases develop in patients with diabetes, they may also be caused by hypertensive nephrosclerosis, and unresolved acute kidney failure may contribute to a

reduced level of kidney function. DN refers to alterations in the kidneys in patients with diabetes (both type 1 and type 2 patients) and specific pathologic structures and functions that result from the effect of diabetes on the kidneys. Clinically, hypertension, proteinuria, and a progressive reduction in kidney function are consequences of diabetes vicissitudes on the kidneys. The occurrence of DN is also linked to a genetic element that is likely polygenetic, with differences being observed in various racial and ethnic groups. European Americans and African Americans (potentially by APOL1 gene variants) exhibited a higher risk for DN than Native Americans and Mexican Americans [8]. Sobczak and Stewart [9] concluded that diabetes is a complex disease that seriously affects hemostasis and increases the risk of cardiovascular diseases.

The underlying mechanisms that are responsible for the higher thrombosis risk in diabetes are complicated, and they involve multiple pathways. Patients with diabetes exhibit premature atherosclerosis and more-extensive vascular disease, rendering them more susceptible to plaque rupture and thrombus formation [10]. Furthermore, patients with diabetes showed a higher thrombotic tendency due to the hyper-reactivity of platelets and increased activation of prothrombotic coagulation factors along with reduced fibrinolysis [11]. Pan *et al.* (2018) [12] demonstrated that, as a predictor of DN, the value of fibrinogen is much higher than that of hemostatic parameters.

Hyperglycemia in DM boosts the impairment of antioxidant systems and decreases reduced glutathione (GSH) levels [13]. Oxidative stress is involved in the pathogenesis of endothelial dysfunction (ED), which is characterized by increased vascular stiffness and tone and the presence of a prothrombotic state [14]. Oxidative stress and the formation of reactive oxygen species (ROS) and nitric oxide synthase (NOS) species in these proteins cause modifications in the formation of amino acids, such as 3-nitrotyrosine (3-N-Tyr) and sulfoxymethionine (Met-SO). The presence of the previously mentioned oxidized amino acids can affect the functional properties of these proteins. Oxidized fibrinogen and VWF exhibit prothrombotic tendencies [15, 16]. In addition, oxidative stress may promote the buildup of high-molecular-weight VWF multimers (UL-VWF), although to a lesser extent than in thrombotic microangiopathies where ADAMTS-13 is strongly reduced or absent, the proteolytic processing of UL-VWF multimers is severely flawed. Remarkably, UL-VWF multimers had the highest ability to recruit and activate platelets in the circulation. Severe resistance to proteolysis by ADAMTS-13 is mainly due to the formation of Met-SO at position 1606 in the A2 domain of VWF [15, 17], thus favoring an accumulation of UL-VWF multimers [15]. Sun and Liu [18] demonstrated that serum inflammatory factors, coagulation, and endothelial functions are good predictors of DN.

Hyperglycemia may promote the non-enzymatic glycation of platelet membrane proteins with alterations in protein conformation and structure, in addition to changes in membrane lipid dynamics [19]. These consequences could, in

turn, lead to improved receptor expression, which is crucial for platelet function, for instance, P-selectin and GpIIb/IIIa, rendering platelets much more susceptible to potential ligands [20]. In those with diabetes, compared with those without diabetes, a higher expression of platelet activation markers (CD31, CD62P, and CD63) and platelet surface receptors (GP Ib and GP IIb/IIIa) is seen, which facilitates binding to VWF [21]. Fasting glucose and HbA1c levels have been correlated with P-selectin expression in patients with diabetes undergoing coronary angioplasty, suggesting that platelet hyperreactivity could be reduced by improving glycemic control [22].

FIBRINOGEN (FACTOR I)

Fibrinogen a 340-kD plasma glycoprotein that circulates at 2–4 mg/m. It consists of two sets of α , β , and γ chains that are aligned as rod-like proteins. At the beginning of the coagulation process, thrombin cleaves fibrinopeptides from the N-terminus of the α and β chains, permitting the polymerization of fibrin monomers into an insoluble fibrin network [23]. The formed fibrin network is stabilized by transglutaminase enzyme factor XIIIa (FXIIIa), which in turn crosslinks the γ - γ and γ - α chains within the previously formed network, in addition to antifibrinolytic proteins in the network [24]. The link between fibrinogen and glycemic markers in type 2 diabetes supports the value of emerging markers for early detection of diabetes [25]. Moreover, patients with diabetes are at an increased risk of coronary artery disease. The fibrinogen levels in patients with diabetes are higher than in those without diabetes [26].

Genetic interactions with environmental factors are the main influencers of fluctuations in the plasma fibrinogen levels [27]. Since there is a spike in interleukin (IL)-6 levels in diabetes, Ajjan and Grant [28] related the increased fibrinogen levels associated with low-grade inflammation, which stimulates hepatocytes to produce fibrinogen, representing a major association between inflammation and hypercoagulation. Several studies have reported differences in fibrinogen levels between patients with diabetes and DN (Table 1).

VON WILLEBRAND FACTOR (VWF)

VWF is a huge multimeric protein that plays an important role in platelet-dependent primary hemostasis. After injury to the vessel wall is sustained, plasma VWF binds to the collagen in the subendothelial matrix. In addition, VWF binds coagulation factor VIII (FVIII) and prevents its deactivation in the circulation [29].

Endothelial cells, megakaryocytes, and their platelet derivatives function as stores for newly synthesized VWF multimers. Endothelial cells secrete VWF through a regulated pathway or a constitutive pathway, and the VWF in plasma originates from these pathways because the alpha-granule content of plasma is released only when activated.

Table 1. Changes in the blood levels of coagulation factors.

Factor	Changes in blood		Mechanism that causes nephropathy
	In DM	In diabetic nephropathy	
Fibrinogen	Increased Kafle <i>et al.</i> [26] ^{a)} Zhao <i>et al.</i> [38] ^{a)} Bembde [39] ^{a)} Sapkota <i>et al.</i> [40] ^{a)}	Increased Sun <i>et al.</i> [18] ^{a)} Mohan <i>et al.</i> [41] ^{a)} Kaur <i>et al.</i> [42] ^{a)}	Higher fibrinogen levels result in changes in the rheological properties of the blood, such as increases in plasma viscosity, platelet thrombogenesis, and erythrocyte aggregation and changes leading to compromises in the endothelial layer integrity and vascular reactivity [43].
VWF	Increased Madan <i>et al.</i> [44] ^{a)} Kubisz <i>et al.</i> [45] Dayer <i>et al.</i> [46] ^{a)} Saboor <i>et al.</i> [47] Oggianu <i>et al.</i> [48] ^{a)}	Increased Kubisz <i>et al.</i> [45] Domingueti <i>et al.</i> [49] ^{b)} Shao <i>et al.</i> [50] ^{a)}	A study hypothesized that low ADAMTS13 levels cause an increase in large-sized VWF multimers, resulting in renal microvascular platelet thrombosis, and that they are therefore relevant to the development and/or progression of diabetic nephropathy [51].
ADAMTS13 antigen	Decreased Oggianu <i>et al.</i> [48] ^{b)}	Increased Domingueti <i>et al.</i> [49] ^{b)} Reduced Taniguchi <i>et al.</i> [51] ^{b)}	
ADAMTS13 activity	Decreased Oggianu <i>et al.</i> [48] ^{b)}	Increased Domingueti <i>et al.</i> [49] ^{b)}	

^{a)}Type 1 DM. ^{b)}All patients in these studies had type 2 DM.
Abbreviations: DM, diabetes mellitus; VWF, von Willebrand factor.

After synthesis is completed, the molecules are released. In the regulated pathway, secretagogues such as histamine, fibrin, and thrombin stimulate the release of stored VWF [30].

VWF performs two functions: primary hemostasis and coagulation, wherein it carries factor VIII, protecting it from degradation by protein C and significantly elongating VWF plasma half-life. VWF is vital for platelet attachment at vascular damage sites, helping form thrombi in special interactions with subendothelial collagen and platelet receptors [31]. In diabetes, the level of VWF increases in the blood (Table 1).

ADAMTS13

Disintegrin and metalloprotease with thrombospondin motif 13 (ADAMTS13) is a metalloprotease that regulates the function of VWF. ADAMTS13 is synthesized in vascular endothelial cells and hepatic stellate cells as a ~180-kDa glycoprotein [32]. ADAMTS13 is a member of the ADAMTS family of Zn²⁺-dependent metalloproteases with disintegrin-like thrombospondin type 1 (TSP) repeats, cysteine-rich, and spacer domains [33]. ADAMTS13 plays an important role in preventing microvascular thrombosis, as it cleaves the most-thrombogenic form of VWF, (UL-VWF) multimers [34]. ADAMTS13 rapidly cleaves the bond between tyrosine 842 and methionine-843 in the A2 domain of VWF multimers. This cleavage results in two fragments of 176-kDa and 140-kDa subunits, thus decreasing the molecular weight and consequently the VWF function [35].

VWF is an acute-phase reactant, and its level increases

in inflammatory and metabolic disorders, such as glucose intolerance, diabetes, and obesity. In contrast, ADAMTS13 activity decreases in patients with systemic inflammation. Consequently, inflammation may activate thrombosis, resulting in an increase in the imbalance between VWF and ADAMTS13. Different mediators of inflammation (cytokines, superoxide anions, histamine, and thrombin) result in increased VWF levels via various mechanisms [36]. IL-8 and TNF- α significantly stimulated the release of UL-VWF by ECs, whereas IL-6 inhibited UL-VWF cleavage by ADAMTS13. An in vivo study revealed an important role of ADAMTS13 in averting redundant spontaneous secretion of the Weibel-Palade body and in the regulation of leukocyte adhesion and extravasation during inflammation [34].

The ADAMTS13 activity and plasma level are decreased in different pathological and physiological settings linked with a higher risk of clotting, such as liver cirrhosis, pregnancy, cardiac surgery, and inflammatory disease (Table 1) [37].

CONCLUSION

Various aspects of normal hemostasis have been demonstrated to be affected by diabetes. Among these are coagulation, thrombotic, and fibrinolytic factors, which can be reliable predictors of both severe nephrological conditions and clinical events. Diabetes mellitus interferes with normal hemostasis; in other words, patients with diabetes exhibit overall hemostatic abnormalities. The oxidation effect of hyperglycemia is manifested through the modulation of the serum levels and activities of coagulation and thrombotic

factors. Diabetic nephropathy, a microvascular complication of diabetes, exhibits further negative effects in patients with diabetes by altering the levels of coagulation factors. In conclusion, we observed a strong relationship between diabetes and biomarkers affecting vascular complications. Lastly, a dysregulated hemostatic balance in patients with type 2 diabetes can lead to cardiovascular issues. Therefore, the assessment of predictors and markers should be mandatory to identify, manage, and clinically prevent and treat these adverse conditions.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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