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Diabetes mellitus: The linkage between oxidative stress, inflammation, hypercoagulability and vascular complications

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ABSTRACT

Background: Vascular complications are the leading cause of morbidity and mortality among patients with type 1 and type 2 diabetes mellitus. These vascular abnormalities result of a chronic hyperglycemic state, which leads to an increase in oxidative stress and inflammatory responses.
Aim: This review addresses the relationships among endothelial dysfunction, hypercoagulability and inflammation and their biomarkers in the development of vascular complications in type 1 and type 2 diabetes.
Results: Inflammation, endothelial dysfunction, and hypercoagulability are correlated to each other, playing an important role in the development of vascular complications in diabetic patients. Moreover, it has been observed that several endothelial, inflammatory and pro-coagulant biomarkers, such as VWF, IL-6, TNF-α, D-dimer and PAI-1, are increased in diabetic patients who have microvascular and macrovascular complications, including nephropathy or cardiovascular disease.
Conclusion: It is promising the clinical and laboratory use of endothelial, inflammatory and pro-coagulant biomarkers for predicting the risk of cardiovascular and renal complications in diabetic patients and for monitoring these patients.

1. Introduction

Diabetes mellitus (DM) is a metabolic disorder which affect about 383 million adults, accounting for 8.3% of adult population worldwide, projected to reach 592 million in 2035, or 10.1% of adults, which is equivalent to the appearance of about more than three people with diabetes once every 10 seconds. Approximately 50% of affected individuals are unaware of the diagnosis (International Diabetes Federation, 2013).

DM is the fifth leading cause of death worldwide, accounting for 5.2% of all deaths. Its chronic nature, severity of complications and the means necessary to control them become diabetes a disease very costly not only for affected individuals and their families, but also for the health system. Costs directly related to diabetes range from 2.5% to 15% of the annual health budget, depending on their prevalence and the sophistication of the treatment available (American Diabetes Association, 2013).

This disorder is one of the main risk factors for the development of myocardial infarction, stroke and peripheral vascular disease (Knudson, Weinstock, & Henry, 2008; Aguiar, 1998). Diabetic patients are four to five times more likely to develop heart disease and stroke than individuals without DM, and cardiovascular complications are the leading cause of morbidity and mortality among patients with type 1 (DM1) and type 2 diabetes (DM2) (Knudson et al., 2008; Domingueti, Dusse, Carvalho, et al., 2013; Giannini, Mohn, Chiarelli, et al., 2011; Lerario, 1998). As DM1 arises predominantly during childhood, DM1 patients have a higher risk of developing coronary events earlier. It was observed that the rate of cardiovascular events in DM1 patients exceeds 1% per year after 45 years old and more than 3% per year after 55 years old (Giannini et al., 2011).

DM is also one of the main risk factors for developing chronic kidney disease (CKD). The risk of developing nephropathy is about 30% and 20% in DM1 and DM2, respectively (Romão Junior, 2004). Diabetic nephropathy is the most common cause of end stage renal disease (ESRD), contributing to approximately 45% of new cases, and is also an independent risk factor for cardiovascular disease (Domingueti et al., 2013; Karnib & Zivadeh, 2010).

Conflicts of Interest: None.

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Recent studies have shown that an interrelation between inflammation and metabolic abnormalities in diabetes leads to endothelial injury and the development of vascular complications. It has been suggested that the early indicator of these effects is endothelial dysfunction together with the development of a pro-coagulant state (Goldberg, 2009).

Therefore, the aim of this review was to explore the relationship between endothelial dysfunction, inflammation and hypercoagulability in the development of vascular complications in DM1 and DM2 through the association between endothelial (VWF — von Willebrand factor), inflammatory (IL-6 — interleukin-6 and TNF-α — tumor necrosis factor-alpha) and pro-coagulant (D-dimer and PAI-1 — plasminogen activator inhibitor-1) factors and the development of these complications.

2. Vascular Complications in Diabetes Mellitus

Vascular complications of DM are derived from a chronic hyperglycemic state and can occur both in large blood vessels, characterizing diabetic macroangiopathy, as in small blood vessels, consisting of diabetic microangiopathy. These vascular abnormalities are the result of irreversible non-enzymatic glycation of proteins, alteration in cellular redox potential, increase of oxidative stress and inflammatory state, and the development of endothelial dysfunction and a hypercoagulability state (Fig. 1) (Goldberg, 2009; Oliveira & Guillausseau, 1998).

Vascular endothelial cells exhibit a particular risk of developing intracellular hyperglycemia, since glucose can penetrates these cells by passive diffusion, not being necessary the action of insulin. Thus, the accumulation of intracellular glucose leads to the activation of a secondary metabolic pathway, the aldose reductase, wherein the aldose reductase and sorbitol dehydrogenase catalyze the metabolism of glucose to sorbitol and sorbitol to fructose, respectively. These reactions go together with oxidation of NADPH to $NADP^+$ and reduction of NAD^+ to NADH. The excessive flow of glucose through this pathway leads to a change in redox potential due to depletion of cellular NADPH and an increase in NADH/NAD^+ cytosolic rate (Fig. 2) (Giannini et al., 2011).

This increase in NADH/NAD^+ rate caused by hyperglycemia imitates the effects of hypoxia, causing an acceleration of glycolysis, leading to increased "de novo" synthesis of diacylglycerol from glycolytic intermediates and subsequent activation of protein kinase C (PKC). Activation of PKC interferes with the synthesis of nitric oxide, promotes increased vascular permeability and contractility, stimulates synthesis of extracellular matrix and thickening of basement membrane, and promotes an inflammatory response through activation of cytokines and adhesion molecules. The alteration in NADH/NAD^+ rate also results in an increased production of superoxide due to activation of oxidases NADH dependent, which oxidize low-density-lipoprotein (LDL), have cytotoxic effects on endothelial cells and promote a reduction in the availability of nitric oxide, leading to endothelial dysfunction (Giannini et al., 2011; Kessler, Wiesel, Attali, et al., 1998). When damaged, endothelial cells release pro-coagulant molecules, such as VWF, PAI-1 and tromboxan A2, and express on their surfaces tissue factor (TF) and adhesion molecules, such as P-selectin, E-selectin, vascular adhesion molecular-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1), which mediate the interaction between neutrophils and platelets with endothelium. Therefore, endothelial dysfunction can promote both a pro-inflammatory state and a pro-coagulant state (Margetic, 2012).

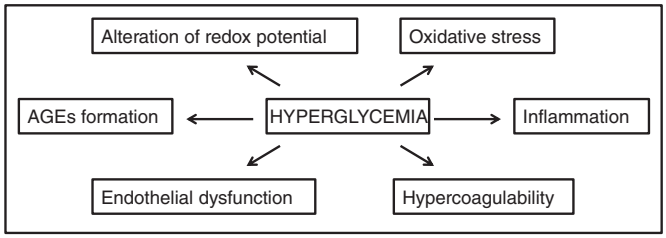

Fig. 1. Mechanisms involved in the development of vascular complications in diabetes mellitus.

When exposed to aldoses, proteins are submitted to glycation and oxidation. Initially, the reaction consists of condensation of glucose with amino groups of proteins to form an instable and reversible Schiff bases product, which may undergo rearrangements to form more stable products called Amadori products (such as glycated hemoglobin). After molecular rearrangements, such products may form the advanced glycation end-products (AGEs), which are irreversible. The molecules linked to AGEs acquire new properties and become oxidants. This process leads to the production of reactive oxygen species, which promote an increase in oxidative stress and prevent the release of nitric oxide, resulting in appearance of vascular lesions. AGEs may also reduce the bioavailability and activity of endothelium-derived nitric oxide, further compromising vascular activity (Fig. 3) (Oliveira & Guillausseau, 1998; Yamagishi & Matsui, 2010).

AGEs can bind to its receptor (RAGE receptors for advanced glycation end-products) present on the surface of endothelial cells, smooth muscle cells, fibroblasts, lymphocytes, monocytes and macrophages, resulting in the activation of nuclear transcription factor NF-κB (nuclear factor-kappaB) (Giannini et al., 2011; Yamagishi & Matsui, 2010). After this activation, NF-κB induces the transcription of various genes, such as endothelin-1, VCAM-1, ICAM-1, E-selectin, thrombomodulin, TF, vascular endothelial growth factor (VEGF), IL-1, IL-6, TNF-α and RAGE, triggering an inflammatory and pro-coagulant state, which causes endothelial activation (Giannini et al., 2011; Sena, Pereira, & Seiça, 1832).

The increased expression of inflammatory cytokines and adhesion molecules can amplify the inflammatory responses, leading to an aggravation of diabetic vascular complications. Also, pro-inflammatory cytokines TNF-α, IL-1 and IL-6 are important to mediate the pro-coagulant effect of damaged endothelial cells, since these cytokines can stimulate the release and expression of pro-coagulant molecules, such as VWF, PAI-1 and TF, and inhibit the expression of anti-coagulant molecules, such as thrombomodulin, by endothelial cells (Margetic, 2012). Reduced expression of thrombomodulin associated with induction of TF expression alters the surface of the endothelium of an anti-coagulant state to a pro-coagulant state. Besides, increased production of growth factors, such as VEGF and fibroblast growth factor (FGF), can stimulate the remodeling of blood vessel wall, resulting in a thickening of the basement membrane, which favors local deposition of proteins and lipids, and promotes sclerosis and an impaired vasodilation (Giannini et al., 2011; Oliveira & Guillausseau, 1998).

Vascular injury, oxidative stress, inflammation and chronic alterations in the hemodynamic balance deriving from alterations underlying hyperglycemia may initiate a process of atherosclerosis and the formation of arterial thrombus (Annichino-Bizzacchi, 2004). During the early atherosclerotic process, matrix proteoglycans sequester circulating LDL and induce its oxidation. These oxidized lipoproteins consist of highly pro-inflammatory molecules that stimulate the expression of several adhesion molecules by endothelial cells, such as VCAM-1, ICAM-1 and selectins, and the secretion of growth factors, such as VEGF, FGF, insulin-like growth factor-1 (IGF-1) and platelet-derived growth factor (PDGF), inflammatory cytokines, such as IL-1 and TNF-α, and chemokines, such as monocyte chemoattractant protein-1 (MCP-1) (Giannini et al., 2011; Libby, 2012).

The expression of adhesion molecules by injured endothelium promotes the selective binding of leukocytes and their transmigration into vascular wall. Furthermore, circulating monocytes are recruited and activated, differentiating into macrophages, which phagocyte the