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TOPIC HIGHLIGHT

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Prognostic value of endothelial dysfunction in type 1 diabetes mellitus

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Abstract

Patients with diabetes mellitus are at high risk of developing atherosclerosis, associated with higher rates of micro and macro vascular involvement such as coronary artery disease and renal disease. The role of hyperglycemia to induce synthesis of reactive oxygen species by the oxidation of glucose, leading to an increased production of advanced glycosylation end products, as well as inflammation and oxidative stress has been proposed as a possible mechanism in the pathogenesis of endothelial dysfunction (ED). The interaction between C-peptide - the connecting segment of pro-insulin-and nitric oxide in vasodilation is also discussed. Therefore, endothelial dysfunction has been identified as an early marker of vascular disorder in type 1 and type 2 diabetes mellitus. In some other diseases, ED has been considered an independent predictor of vascular disease, regardless of the method used. Studies have demonstrated the importance of endothelial dysfunction as an useful tool for identifying the risk of vascular complications in patients with type 1 diabetes mellitus, particularly as regards to renal impairment. The aim of this review is to clarify the prognostic value of endothelial dysfunction as a marker of vascular disease in these subjects.

Key words: Endothelial dysfunction; Type1 diabetes; Prognostic; Cardiovascular disease; Pathogenesis

Core tip: This review is divided into two parts: first we discuss aspects related to the pathogenesis of endothelial dysfunction in type 1 diabetes mellitus. In the second, are pointed out and critically discussed the scientific evidence about the important role of endothelial dysfunction, independent of the method used for its diagnosis, as an early marker of cardiovascular and renal complications in this population.

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INTRODUCTION

Diabetes mellitus patients have a high risk to develop atherosclerotic disease[1]. The macro- and microvascular complications are the main cause of morbidity and mortality, especially in those with more than five years of disease[2-4]. Endothelial dysfunction (ED) has been identified as an early marker of vascular disease in type 1 diabetes mellitus (T1DM)[5]. In some other conditions, ED has been an independent predictor of cardiovascular risk[6].

This review aims to evaluate the endothelial dysfunc-

tion role as a prognostic factor of vascular complication in patients with T1DM.

PATHOGENESIS OF ENDOTHELIAL DYSFUNCTION IN T1DM

The role of vascular endothelium on the pathogenesis of vascular disease has been better known in the last 30 years. Adequate endothelial function depends on the healthy balance between vasoconstrictor and vasodilator substances that interact in the endovascular environment[7,8]. Nitric oxide (NO), identified by Furchgott *et al*[9], is synthetized from L-arginine by nitric oxide synthase (eNOS) in the presence of oxygen, nicotinamide adenine dinucleotide phosphate and BH4 (tetrahydrobiopterin). This substance produced on endothelial cells diffuses itself into smooth muscle cells and platelets, where it stimulates the activity of the soluble guanylate cyclase and hence production of cyclic GMP promoting, in turn, relaxation of the muscle layer of the vessel and reduces platelet aggregation. On the other hand, NO reduction is associated with increased vascular injury, because it enhances platelet aggregation and increases monocyte adhesion to vascular endothelium; as well it stimulates proliferation of smooth muscle cells[10].

In pathologic situations, as diabetes, numerous mechanisms as: (1) decreased synthesis or inactivation of NO; and (2) increased production and release of vasoconstrictor substances have been proposed to explain the ED. In addition, metabolic changes favoring increased production of free radicals as well as advanced glycosylation end products (AGEs) are able to accelerate the nitric oxide inactivation[10].

Considering that the major metabolic disturbance in diabetes is hyperglycemia, it has been suggested that it may induce the synthesis of reactive oxigen species, by the oxidation of glucose[11], leading to an increased production of AGEs[12], among other mechanisms. On the other hand, a recent study demonstrates that hypoglycemia is also associated with ED, oxidative stress and inflammation. Moreover, worsening of endothelial function was greater in those who went from hypoglycemia to hyperglycemia than those recovered to a state of normoglycemia[13].

Other substances involved in the pathogenesis of endothelial dysfunction in T1DM are insulin and C-peptide. Several studies have shown that the vasodilator effects of insulin depends on the synthesis of nitric oxide, since the use of substances that block eNOS, inhibits the increase of blood flow mediated through the action of insulin[14-16]. Moreover, acute administration of C-peptide-a connecting segment of pro-insulin-is able to increase blood flow in subjects with T1DM after exercise or at rest, but not in normal subjects[17,18]. As well, a prolonged infusion of C-peptide in type 1 diabetic subjects improves kidney function[19] by a mechanism that involves the interaction between nitric oxide activity, and Na^+K^+ATPase[20,21]. So, it is important to understand that the pathogenesis of endothelial dysfunction in T1DM is complex and involves metabolic and hormonal changes; in particular, the role of insulin deficiency that leads to a decreased production of nitric oxide, increased oxidative stress in the vascular milieu with consequent decreased in the ability to promote vessels dilation. Furthermore, it is suggested that a better control of metabolic changes by insulin replacement can decrease the aggression of endothelial cells.

Other aspects of the pathogenesis of vascular abnormalities in diabetic subjects deserve attention. T1DM and T2DM are associated with a reduction in the number of endothelial progenitor cells (EPCs)[22-24]. It is interesting to note that this reduction is related to the severity of peripheral vascular disease which reinforces the importance of EPCs as a marker of vasculopathy in diabetic patients[25]. Moreover, potent vasoconstrictor such as angiotensin II and endothelin promote endothelial dysfunction in the metabolically altered environment of diabetes[26]. This knowledge is relevant since it may allow the emergence of new therapeutic perspectives. It is noteworthy that it has already been demonstrated that oral treatment with bosentan, endothelin receptor antagonist, for 4 wk, improves endothelial function in T2DM[27].

PROGNOSTIC VALUE OF ENDOTHELIAL DYSFUNCTION

The literature clearly suggests that metabolic and hormonal disorders present in T1DM injure the endothelial cells favoring endothelial dysfunction and initiation of the atherogenic process. A longitudinal study published recently suggests that flow-mediated vasodilation is an useful tool to stratify T1DM children according to cardiovascular risk, as well as for the long term follow-up[28]. However, the prognostic value of endothelial dysfunction as a marker of vascular complications should be further analyzed.

A 10-year follow-up prospective cohort study involving young T1DM adults with a mean disease duration of 19 years, evaluated the ability of adhesion molecules in predicting coronary artery disease (CAD) defined by angina, confirmed myocardial infarction, stenosis > 50%, ischemic electrocardiogram, or revascularization. With this purpose, a nested case-control study involving 60 patients who developed CAD and 72 patients without the disease was performed. Dosages of vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 and E-selectin were performed from stored samples prior to the cardiovascular event. Although there was a correlation between adhesion molecules and lipid variables, considered an unquestionable cardiovascular risk factor in type 1 diabetes, only E-selectin was an independent predictor of CAD (HR = 1.07, 95%CI: 1.01-1.15, $P < 0.03$)[29].

Another cross-sectional study that included patients with T1DM without cardiovascular disease and a comparison group of healthy subjects, sought to identify association between endothelial dysfunction [flow-mediated vasodilation (FMD)] and subclinical cardiovascular dis-

ease. It was then observed a strong inverse correlation between FMD and systolic dysfunction (r = -0.70, P < 0.0001), diastolic dysfunction (r = -0.77) and duration of T1DM (r = -0.61,) P < 0.0001 for the three variables[30]. The association between ED and other markers of subclinical CAD, as the carotid intima-media thickness (IMT), was evaluated in a study that included T1DM patients and non-diabetic children-without significant differences in weight, age, blood pressure and gender. This study demonstrated that the T1DM group had lower peaks of FMD response and higher IMT when compared to controls (P < 0.001). Moreover, in the multivariate analysis, there was a strong association between increased IMT and decreased FMD in the group of children with diabetes (P < 0.03). However, the data in the literature are still conflicting. A study involving patients with T1DM and healthy subjects showed no difference between the IMT of the two groups, although endothelial function had been worse in T1DM group and correlated with glycemic control[31].

On the other hand, a recent study that evaluated endothelial function, IMT and ventricular function in 30 children and adolescents with T1DM compared with 30 healthy subjects matched by gender, age, and body mass index, found a lower FMD response, increased IMT and impaired diastolic function with lower early peak flow velocity, decreased E/A ratio, increased early filling deceleration time in T1DM patients. Furthermore, these changes were more evident in patients with poor glycemic control[32].

Several studies have shown the importance of endothelial dysfunction as a marker of renal impairment. In 2005, we demonstrated that FMD had an inverse correlation with microalbuminuria (r = -0.50, P = 0.049) in children and adolescents with a short duration diabetes (2.9 + 1.2 years) calling attention to the value of the endothelial dysfunction as a very early marker of vascular complications[4]. This association was also demonstrated in patients with disease duration > 10 years, with the following features: individuals with proteinuria and chronic renal failure (CRF) had FMD 7% and 4% respectively, while those with normal albumin excretion or microalbuminuria showed FMD > 8%, considered the lower limit of normality for flow-mediated vasodilation in adults[33]. In this study, there was a continuous, progressive and significant increase in the levels of endothelin-1 and C-reactive protein in individuals (1) without microalbuminuria; (2) with microalbuminuria; (3) with proteinuria; and (4) CRF. In addition, the sensitivity coefficient to shear stress endothelium was inversely correlated with glomerular filtration rate (GFR) (r = -0.48, P = 0.03). This aspect can be somewhat reinforced by another recent study that demonstrated that pulse pressure was associated with a decline in estimated GFR (r = 0.26, P = 0.003, adjusted), as well as the higher pressure pulse predicted an increased risk to develop end-stage renal disease: adjusted HR of 1.2 (95%CI: 1.1-1.4, P = 0.011)[34]. In addition, a cohort study of 18 T1DM patients followed for 8 years has shown an association between the expansion of the cortical interstitial volume fraction and PA1-activity and VCAM levels[35].

It is worth noting that changes in endothelial function can be identified regardless of the method used. A sustained hyperaemic stimulation induced by the hand skin heating method, as well as FMD vasodilation, were used to evaluate endothelial dysfunction in T1DM patients with and without microangiopathy and also in healthy controls matched for gender, age and body mass index. It was observed that FMD was lower in the diabetes group compared to controls. Furthermore, the presence of clinical complications was significantly associated with lower FMD and creatinine levels were also negatively correlated with the magnitude of FMD. With regard to the hand skin heating method, it was shown that the radial flow shear stress increased vascular diameter in all groups, however, the amplitude of FMD in diabetic patients were significantly lower than in the control group[36]. This dataset demonstrate the importance of endothelial aggression factors as potential markers of vascular injury.

More recently, longitudinal studies have sought to identify markers of endothelial dysfunction as predictors of long-term cardiovascular events. In a prospective study, T1DM patients with persistent normoalbuminuria and nephropathy, without previous cardiovascular events, were followed for a mean period of 12.3 years. The plasma levels of soluble receptor for advanced glycation end products (sRAGE) and other biomarkers were measured at baseline. High levels of sRAGE as a reflection of RAGE expression, was associated with greater incidence of fatal or nonfatal cardiovascular disease, as well as all-cause mortality. Furthermore, there was a significant association between levels of sRAGE and GRF in patients with nephropathy[37]. These authors, in a prospective study with a similar sample, showed that higher plasma levels of the pro-inflammatory cytokine high -mobility group box 1 was an independent predictor of fatal and non-fatal cardiovascular events and also a high-risk marker for all causes of mortality[38].

According to a recently published review, the mechanisms of endothelial dysfunction and ischemic response in diabetes mellitus is complex, involving inflammation, intercellular signaling peptides and proteins, cell angiogenic potential, among others[39]. It is noteworthy that a prospective study demonstrated a decrease of EPCs in children with T1DM, as well as the association between better glycemic control and increased EPCs after an one-year follow-up, suggesting that knowledge of this mechanism may be a way of mediating the high cardiovascular risk in these patients[40]. Therefore, more knowledge on the balance between vascular homeostasis and cardiometabolic risk factors will certainly improve the monitoring of diabetic patients and reduce vascular complications and consequently morbidity.

CONCLUSION

In summary, the pathogenesis of endothelial dysfunction

in T1DM is complex and involves several mechanisms such as inflammation, oxidative stress, interaction between insulin and C peptide, decreased number of endothelial progenitor cells among others. The prognostic value of assessing endothelial function as a marker of cardiovascular morbidity and risk has been demonstrated by cross-sectional and prospective studies with long follow-up, using various methods to identify subclinical atherosclerosis and endothelial dysfunction. The dataset demonstrate that regardless of the method used, impairment of endothelial function is a predictor of risk for cardiovascular disease and nephropathy. This knowledge suggests that new preventive and therapeutic interventions should be recommended early in order to decrease morbidity in this high-risk population.

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