ORIGINAL RESEARCH—ERECTILE DYSFUNCTION

Imbalanced Low-Grade Inflammation and Endothelial Activation in Patients with Type 2 Diabetes Mellitus and Erectile Dysfunction

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ABSTRACT

Introduction. Erectile dysfunction (ED) is highly prevalent among type 2 diabetes mellitus patients (T2DM). Although a link among systemic inflammation, endothelial dysfunction, and ED is described in clinical situations mainly related with coronary heart disease (CHD) risk, evidences of this link in T2DM patients are rather limited.
Aims. To evaluate the association between endothelial dysfunction and balance of pro-/anti-inflammatory mediators with ED presence and severity in T2DM.
Methods. We conducted a cross-sectional study of 190 T2DM patients without symptomatic CHD, 150 out of them with ED and 40 without ED. Serum levels of E-selectin, intercellular adhesion molecule-1, tumor necrosis factor-α (TNF-α), and interleukin (IL)-10 were measured using specific enzyme-linked immunosorbent assays (ELISAs). ED presence and severity were tested by the five-item version of the International Index of Erectile Function questionnaire.
Main Outcome Measures. Differences in circulating levels of endothelial dysfunction (ICAM-1, E-selectin) and inflammatory/anti-inflammatory (TNF-α, IL-10, TNF-α : IL-10 ratio) markers between T2DM patients with and without ED, and assessment of biomarkers ED predictive value while adjusting for other known ED risk factors.
Results. Patients with ED were older and had longer duration of diabetes than patients without ED. E-selectin serum levels were significantly increased, while IL-10 were lower in patients with ED; because TNF-α levels tend to be higher, TNF-α : IL-10 ratio was more elevated in ED patients. No significant differences of ICAM-1 levels were observed between study groups. Endothelial activation markers and TNF-α, as well as diabetes duration, were negatively correlated with erectile function. On multivariate analysis including age, duration of diabetes, insulin treatment, hypertension, insulin resistance, fair-to-poor glycemic control, and metabolic syndrome, increments in E-selectin levels and TNF-α : IL-10 ratio predicted independently ED presence, while IL-10 increases were associated with lower risk of ED in T2DM patients.
Conclusions. ED in T2DM patients without symptomatic CHD is associated with systemic endothelial dysfunction and a predominant, imbalanced low-grade inflammatory response. **Araña Rosaínz MDJ, Ojeda Ojeda M, Rodriguez Acosta J, Castelo Elías-Calles L, Orlandi González N, Torres Herrera O, García Álvarez CT, Maciquez Rodríguez E, Estevez Báez M, Álvarez Seijas E, and Fragas Valdés R. Imbalanced low-grade inflammation and endothelial activation in patients with type 2 diabetes mellitus and erectile dysfunction. J Sex Med 2011;8:2017–2030.**

Key Words. Erectile Dysfunction; Type 2 Diabetes Mellitus; Inflammation; Endothelial Dysfunction

Introduction

Erectile dysfunction (ED) is highly prevalent in men with diabetes mellitus (DM). Estimates range from 25 to 75%, a variability probably due to differences in ED definitions or severity, or type and duration of diabetes between study samples. Indeed, among other factors, it is recognized that men with type 2 DM (T2DM) have an increasingly greater risk of ED with increased duration of diabetes [1,2] and with poor glycemic control [3].

The etiology of ED in patients with T2DM is multifactorial [4]. Several mechanisms commonly accepted as involved in ED development in T2DM patients are linked to a disturbed vascular function or response. Major underlying phenomena are endothelial dysfunction and impaired insulin vascular response in insulin-resistant individuals [5,6]. A similar role is ascribed to both of these factors in the pathogenesis of ED among men with metabolic syndrome (MetS) and obesity [7,8], two comorbidities frequently present in T2DM patients. Endothelial dysfunction is currently viewed as an initiating event of atherosclerosis, and several recent studies suggest close associations among ED, endothelial dysfunction, and atherosclerosis. Consequently, ED diagnosis is approached as a sentinel event for coronary heart disease (CHD) in asymptomatic men with diabetes or MetS. In these clinical settings, endothelial dysfunction may be detected by determining plasma levels of circulating soluble markers of endothelial activation [9]. Increased levels of soluble intercellular adhesion molecule-1 (sICAM-1), vascular cell adhesion molecule-1, and P-selectin were observed in patients with ED with or without conventional CVD risk factors [10], like MetS or T2DM. Also, plasma circulating levels of sICAM-1, soluble E-selectin (sE-selectin), and P-selectin are reported to be higher in acute hyperglycemia, in individuals at risk of T2DM, and in diabetic patients with poor glycemic control [11,12]. Among subjects with T2DM, the levels of these soluble markers of endothelial activation are also associated with macroangiopathic and microangiopathic complications, including CVD, diabetic nephropathy, and retinopathy, as well as with the presence of ED, signaling endothelial dysfunction as a common contributing mechanism to T2DM and its complications [13]. However, the relationship of ED severity in T2DM patients with endothelial dysfunction, and the influence of potential confounders on this link, has not been clearly established.

Likewise, several recent findings suggest that ED could be a disease of low-grade systemic inflammation [14]. A close relationship among subclinical inflammation, endothelial dysfunction, and ED is recognized. Chronic inflammation contributes centrally to atherosclerosis, and subclinical inflammation is present in diverse clinical scenarios associated with accelerated atherosclerosis, including insulin resistance, impaired glucose tolerance, overt T2DM, MetS, and obesity [15–17]. Indeed, T2DM is described as a disease of the innate immune system [18], where proinflammatory cytokines like tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) disturb insulin sensitivity and β-cell function [19]. In a recent study of 141 patients with or without ED and CVD, including less than 30% diabetic patients, ED was significantly associated with high blood concentrations of C-reactive protein, TNF-α, IL-6, IL-1β, and markers of prothrombotic activation, independently of the presence or absence of CVD [20]. However, in the particular setting of patients with T2DM, the link between ED and low-grade inflammation has been scarcely explored, and knowledge about the influence of anti-inflammatory compensatory responses is especially limited. IL-10 is an anti-inflammatory cytokine playing a crucial role in the regulation of the innate immune system. This cytokine acts in a feedback loop to inhibit the production of proinflammatory cytokines and downregulates macrophage functions. IL-10 attenuates progression of atherosclerosis in various animal models and alleviates peripheral insulin resistance in vivo. Circulating levels of IL-10 have been shown to be elevated in obese women but diminished in MetS and T2DM patients [21]. These findings suggest that IL-10 could function as a regulating molecule intending the balance in clinical conditions involving low-grade inflammation, a role that is evidenced in acute and chronic inflammatory diseases like sepsis and rheumatoid arthritis. In these disorders, the uneven total sum of the complex interactions among cytokines orchestrating and downmodulating inflammatory responses, like TNF-α and IL-10, which are interrelated in a mutual feedback loop, could basically contribute to the final pathophysiological events [22,23].

The aim of the present study is to evaluate the association between endothelial dysfunction and low-grade systemic inflammation with ED presence and severity in patients with T2DM, stressing the influence of counterregulatory anti-inflammatory mechanisms, while adjusting for