Penile involvement in Systemic Sclerosis: New Diagnostic and Therapeutic Aspects

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Received 10 May 2010; Revised 22 June 2010; Accepted 27 July 2010

Academic Editor: V. D. Steen

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Systemic Sclerosis (SSc) is a connective tissue disorder featuring vascular alterations and an immunological activation leading to a progressive and widespread fibrosis of several organs such as the skin, lung, gastrointestinal tract, heart, and kidney [1, 2]. The typical hallmark of SSc is a microvascular involvement, while macrovascular involvement is not well documented in these patients, but the majority of authors agree that its prevalence is similar to general population [3]. Vascular involvement in SSc has been believed to be limited to digital arteries [4]. It is extremely rare that SSc patients without vascular risk factors have macrovascular lesions above the elbow or knee. However, a relatively high incidence of vascular involvement between the digits and the elbow or knee has been described [5]. Early disease is mediated through microvascular dysfunction secondary to a number of factors including endothelial damage, overexpression of specific adhesion molecules, and perivascular inflammatory cell infiltration [6]. These changes make endothelium unable to carry out its functions in the regulation of vascular tone, coagulation, adhesions and migration of blood cells, transportation of nutrients, achieved through production of a complex array of molecules including vasodilators (e.g., nitric oxide: NO), vasoconstrictors (e.g., endothelin-1: ET-1), and cell adhesion molecules (e.g., selectins and integrins) [7]. The endothelial dysfunction can explain some major clinical symptoms of SSc such as Raynaud’s phenomenon (RP), fingertip ulcers and gangrene, pulmonary arterial hypertension and erectile dysfunction (ED) (Figure 1). Irrespective of the classification of the disease, SSc is typically associated with RP that is characterized by microvascular damage, high plasma adrenomedullin and ET-1 levels, reduced production of NO [8–11].

Similarly, at the penile level, there occurs a consistent vascular damage that almost invariably determines,
as a consequence of both endothelium damage [12–16] and increased fibrogenesis [17], the so-called “sclerodermic penis”. In fact, the prevalence of ED in men with SSc has been reported as high as 80% [18] and it can be considered an end-organ disease involving both macro and microvascular damage.

2. Pathophysiology of Sclerodermic Erectile Dysfunction

Hormonal derangement is a common finding in SSc patients even if a hormonal basis for impotence, that is, abnormalities in serum testosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, and oestradiol, has never been demonstrated. Neurological causes could also be excluded. In contrast, penile blood pressure, but not ankle blood pressure indices, were found to be diminished [19]. Duplex sonography measurements in male SSc patients show impaired peak systolic velocities (PSVs) in penile arteries and also the presence of veno-occlusive dysfunction. The latter is often associated with the identification of diffuse hyperechogenic “spots” inside the corpora cavernosa, along with a thickening of the tunica albuginea and is consistent with the presence of a high degree of corporeal fibrosis [20]. In a recent angiographic study it has been demonstrated that the prevalence of coronary artery disease in SSc patients is not different from a control group [21]. In accordance, our studies found that the intima-media-thickness (IMT) of the common carotid artery of patients with ED in the context of SSc is normal, thus confirming that advanced atherosclerosis occurs late in the course of disease. By contrast, endothelial dysfunction is present early, as we were able to demonstrate with impaired thermal recovery of the penis after cold exposure [22]. Taken together, these data indicate an altered arterial blood flow in the absence of general atherosclerosis as it is common in end-organ disease. Indeed, an increased collagen synthesis by smooth muscle cells and the accumulation of extracellular matrix had been already demonstrated in patients with SSc [23], and it is known that under hypoxic conditions of various origin, transforming growth factor beta (TGFβ), platelet-derived growth factor (PDGF) and its receptors are overexpressed in the corpora cavernosa [24]. TGFβ1 and PDGF have both been identified as important regulators of the collagen and extracellular matrix synthesis by smooth muscle cells and also act as smooth muscle mitogens. Under hypoxic conditions, human penile smooth muscle cells also release ET-1 and induce ET-B receptor expression, processes that in turn are strongly increased by TGFβ1 and ET-1 itself [25]. These results suggest that the molecular mechanisms by which penile hypoxia of any cause induce penile fibrosis are similar to those implicated in the fibrotic transformation of tissues in SSc patients [26]. The hypoxic and the SSc-specific processes may thus contribute to, and even perpetuate, each other in the manifestation of ED.
Contradictory attitudes exist about the mechanisms of the vasospastic arteriolar paroxysms—from hyperactivity of the sympathetic nervous system and “local defect” with receptor and nerve endings’ dysfunctions, endothelial dysregulation and blood cells’ activation to statements of primary central nervous mechanism. The vеноarteriolar reflex is a local mechanism protecting the capillary bed against high hydrostatic pressure and therefore the tissue against edema. The underlying mechanism of the vеноarteriolar reflex is still debated, although it is commonly believed to depend on an intact innervations of the arterioles by sympathetic vasoconstrictor fibers [27]. The modulating role of endothelium with its influence on the contractile control processes of the penis in SSc patients are altered could confirm such a hypothesis since SSc patients counteract to high hydrostatic pressure and therefore the tissue against edema. There-
of endothelial damage leading to vascular disease in SSC. In a recent study, we demonstrated that once-daily tadalafil is able to decrease the mean number of Raynaud’s attacks by reducing surrogate markers of vascular damage such as adrenomedullin and ET-1 plasma levels. The results of that study lead us to postulate the beneficial effect of adding daily long-term PDE5 inhibitors to the medical treatment of SSC [37]. The use of endothelin-receptor antagonists (ERAs) in SSC is actually deserved to patients with severe pulmonary arterial hypertension. The possibility of an add-on effect of ERAs to PDE5i is to be considered in future studies. At the moment, no proof-of-fact that the use of ERAs alone may improve ED is present.

In the era of PDE5 inhibitors, we believe that the implantation of a penile prosthesis may be considered only in patients who fail pharmacotherapy or who prefer a permanent solution of their problem. The choice of prosthesis is depends from patients’ preference and his manual dexterity. This solution may have a high satisfaction rate as in the non-SSc population but must take into account that it is not reversible. Finally, mechanical failures and infection has the same occurrence (1%–3%) than the general population [38].

5. Conclusion

Long-standing SSC is almost always associated with the presence of some degree of ED, because of micro and macrovascular disseminated damage through cavernosal penile arteries and capillaries and subsequent cavernosal fibrosis. As a consequence, ED should be systematically questioned and counselled in any patient presenting with SSC by a specialized team. Although robust data on treatment options for ED in the SSC population are not yet available, empirical treatment should be started with a daily or alternate day regimen of a long-acting PDE5i after addressing modifiable risk factors for ED. Second-line treatment decisions require the cooperation between expert specialists in order to maximize medical therapy benefits for underlying conditions.

References


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