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SCLERODERMA (J VARGA, SECTION EDITOR)

Erectile Dysfunction in Systemic Sclerosis

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Abstract Erectile dysfunction (ED) is a major issue in systemic sclerosis (SSc) as it is observed in around 80 to 90 % of men with this connective tissue disease. ED greatly impacts the quality of life and should be actively addressed as a common complication. Whereas ED in the general population is usually associated with risk factors for atherosclerosis as well as cardiovascular disease, the main aetiology of ED in SSc is microangiopathic. In SSc, the blood flow is reduced in the small penile arteries due to corporal fibrosis and myointimal proliferation. There are no data on the prevention of ED in SSc. On-demand phosphodiesterase-5 inhibitors have little effect in improving erectile function, but daily or alternate day regimens of long-acting phosphodiesterase-5 inhibitors provide a measurable, although often limited, benefit. When intracavernous prostaglandin E1 injections are also ineffective, the implantation of a penile prosthesis should be considered as an option.

Keywords Erectile dysfunction · Systemic sclerosis · Prevalence · Risk factors · Causes · Treatment

Introduction

Systemic sclerosis (SSc) is an immune-mediated connective tissue disorder characterised by fibrosis, endothelial damage, and progressive microangiopathic dysfunction of various organs. Vascular complications of SSc such as pulmonary arterial hypertension, digital ulcers, and scleroderma renal crisis are frequent targets of diagnostic and treatments efforts. Erectile dysfunction (ED) is another vascular complication and common in male SSc patients. Despite this fact, ED is only infrequently addressed by studies, by patients and their physicians. This review focuses on the prevalence and causes of ED in SSc as well as treatment options.

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Prevalence and Risk Factors for Erectile Dysfunction

ED in the Non-SSc Population

Sexual activity is an important component of the quality of life, and sexual dysfunction has a considerable psychological and social effect on the affected men, as well as their partners [1–3]. ED is defined as the persistent inability to attain or maintain a penile erection sufficient for successful sexual intercourse that lasts for a minimum of 6 months [4].

ED is common in the general population, i.e. in men without SSc, especially with advanced age. A systematic review assessing the prevalence of ED reported prevalences of around 1 to 10 % in men below the age of 40 years, increasing to 20 to 40 % in men aged 60 to 69 years [5, 6]. An even higher ED prevalence rate of 50 to 100 % was reported for men in their 70s and 80s [5].

Conditions associated with the development of ED in men without SSc include diabetes mellitus, arterial hypertension, hyperlipidaemia, hyperplasia of the prostatic glands and lower urinary tract infections, as well as depression [6–11]. Several studies have demonstrated that ED can be regarded a harbinger of cardiovascular disease and that ED is significantly and independently associated with an increased risk of cardiovascular diseases such as coronary heart disease, stroke and even

all-cause mortality [8, 12–14]. Environmental and lifestyle factors that are linked to the development of ED include obesity, limited physical activity and smoking [15–17]. Medications and drugs that have been linked with favouring or triggering ED include thiazide diuretics, spironolactone, beta-blockers, H_2 antagonists, antidepressants, cyclophosphamide, alcohol and cocaine [11, 18].

ED in Patients with SSc

The association between SSc and ED was first described by Lally and Jimenez in 1981 [19]. ED is now regarded as a widespread problem in SSc, as the prevalence of ED in the sexually active male SSc population has been reported to be over 80 % [20, 21, 22••, 23••]. ED is far more prevalent in men with SSc than in men with rheumatoid arthritis, an inflammatory rheumatic disorder linked with cardiovascular risk (84 vs. 59 %) [21].

In the prospective, multicentre study of the European Scleroderma Trials and Research (EUSTAR) database, 130 men with SSc were assessed for ED using the International Index for Erectile Function-5 (IIEF-5) questionnaire [22••]. The IIEF-5 is a linguistically validated score available in various languages. The self-administered questionnaire has high retest reliability and was shown to be specific and sensitive for detecting change [24]. The IIEF-5 includes questions on erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall sexual satisfaction with each item being scored from 1 to 5. The overall score ranges from 5 to 25 and is classified into five categories: no ED (22 to 25), mild ED (17 to 21), mild to moderate ED (12 to 16), moderate ED (8 to 11) and severe ED (5 to 7). In the EUSTAR study, the median age of the 130 men with SSc was 52.3 years (IQR 45.1 to 61.5) and the median IIEF-5 score was 13 (IQR 6 to 19) [22••]. Further, 82.3 % of men with SSc reported any ED and 31 % severe ED. These figures were similar to another series of SSc patients in which the average IIEF-5 score was 13.3 (SD 6.3) [25]. For comparison, in the general middle-aged population (mean age 45.8, SD 12.5), the mean IIEF-5 score was found to be much higher (mean 21.9; SD 4.9) [7] and a considerably lower proportion of non-SSc men reported ED (32.2 % reported any ED; only 1.3 % of non-SSc men reported severe ED) [7, 22••].

In the vast majority of men with SSc (77 to 90 %), ED had started after the onset of SSc [21, 22••]. The median time interval from the onset of the first non-Raynaud's phenomenon manifestation of SSc to the onset of ED was around 4 years [22••]. It therefore appears that ED is a relatively early complication of SSc.

Although the presence of ED in SSc was associated with risk factors also known in men without SSc (older age and alcohol consumption) [22••, 25], ED in SSc was also associated with factors linked with more severe disease in terms of more severe skin involvement, elevated pulmonary arterial pressures, the presence of restrictive lung disease and of muscular or renal involvement [22••]. Although a positive correlation was found between penile and digital Doppler indices [26], the presence of capillary abnormalities at nail fold capillaroscopy, however, was not predictive of ED in SSc [27].

Causes of ED

Despite comprehensive investigations, the causes of ED in SSc have not yet been entirely clarified. Studies analysing a possible hormonal cause of ED did not find abnormalities in follicle-stimulating hormone, luteinizing hormone, serum testosterone, prolactin, estradiol and thyroid hormones [20, 21, 28] and conclude that there is no endocrine basis for ED in SSc [29]. Several studies have ruled out neurological causes for ED in SSc [20, 30].

In contrast, a combination of fibrotic and vasculopathic abnormalities has been hypothesised [31, 32]. Penile blood pressure in comparison to ankle blood pressure indices were found to be diminished in men with SSc [28]. Duplex sonography measurements in male SSc patients showed impaired peak systolic and diastolic blood flow velocities in the penile arteries [26], as well as the presence of veno-occlusive dysfunction [3, 25]. In contrast, the intimal medial thickness of the carotid artery of SSc patients with ED as an index of atherosclerosis was normal [25]. Penile temperatures were reduced in SSc patients with ED, and compared to healthy controls, the thermal recovery after cold exposure was significantly impaired [33]. Altogether, these data indicate an altered penile blood flow without the presence of atherosclerotic macroangiopathy as a cause of ED in SSc.

As a possible correlate of fibrotic changes in SSc, duplex sonography identified a thickening of the tunica albuginea and diffuse hyperechogenic spots within the corpora cavernosa [25]. Histological studies of penile tissues, gained during an insertion of a penile prosthesis, confirmed the presence of severe corporal fibrosis, increased collagen synthesis by smooth muscle cells and an enhanced accumulation of extracellular matrix [34].

It is known that various hypoxic conditions are able to induce an overexpression of platelet-derived growth factor (PDGF), transforming growth factor (TGF)-β_1 and TGF-β_1 receptors in the corpora cavernosa [35, 36]. Both PDGF and TGF-β_1 have been recognised as important profibrotic regulators of collagen synthesis and extracellular matrix production by smooth muscle cells and are known to also act as smooth muscle mitogens [25, 36]. Under hypoxic conditions, human penile smooth muscle cells also release endothelin (ET)-1 and induce ET-B receptor expression; these processes are further stimulated by ET-1 and TGF-β_1 [37].

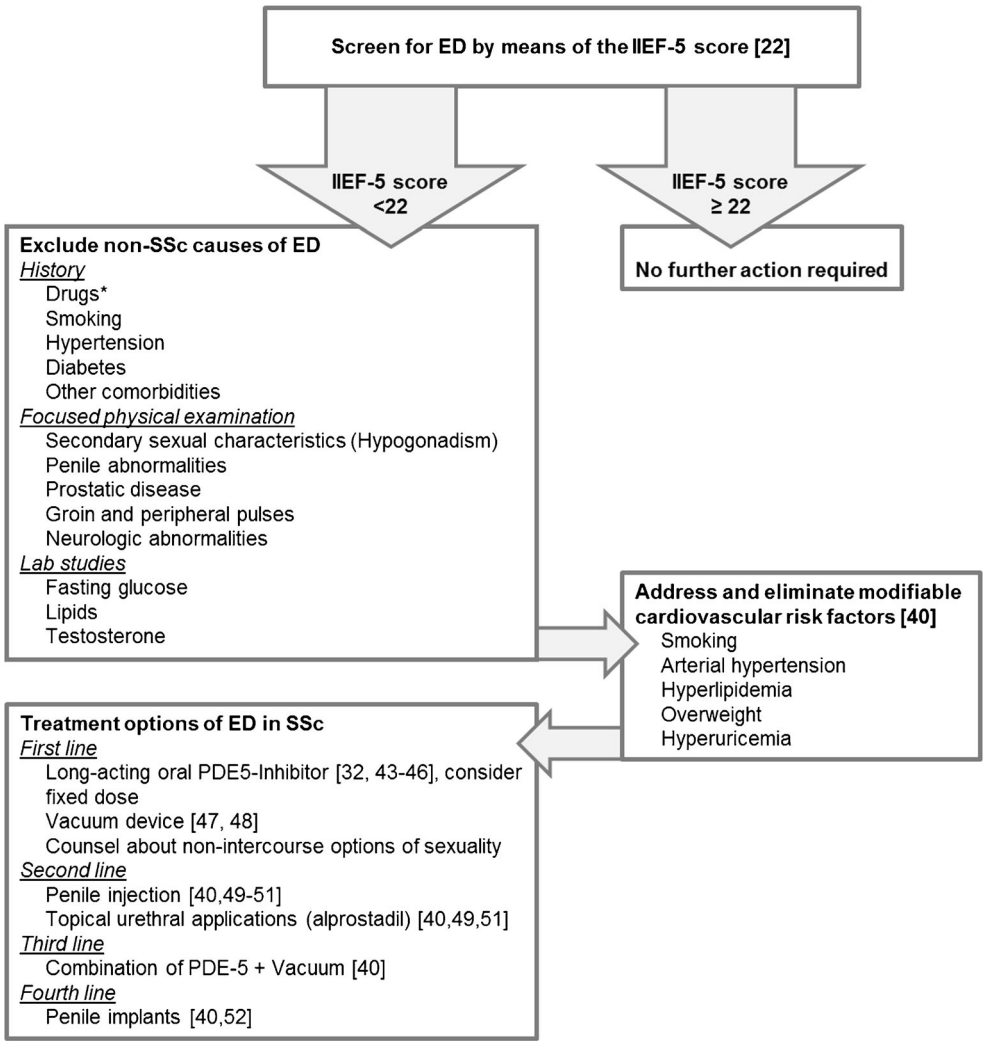

Fig. 1 Practical approach to men with SSc. *e.g. diuretics (thiazides, spironolactone), antihypertensive drugs (calcium-channel blockers, beta-blockers, methyldopa, clonidine, reserpine, guanethidine), cardiac or cholesterol drugs (digoxin, gemfibrozil, clofibrate), antidepressants (selective serotonin-reuptake inhibitors, tricyclic antidepressants, lithium, monoamine oxidase inhibitors), tranquilisers (butyrophenones, phenothiazines), H_2 antagonists (ranitidine, cimetidine), hormones (progesterone, estrogens, corticosteroids, luteinizing hormone-releasing hormone antagonists, 5α-reductase inhibitors, cyproterone acetate), cytotoxic agents (methotrexate), immunomodulators (interferon-α), anticholinergic agents (disopyramide, anticonvulsants), recreational drugs (alcohol, cocaine) [11]

Taken together, these results indicate that the molecular mechanisms by which penile hypoxia induces the advent of penile fibrosis may be self-perpetuating and that the profibrotic mechanisms operating in SSc could, once initiated, ultimately be similar to those also implicated in the non-SSc population [38].

Treatments for ED

As ED in the general population shares modifiable risk factors with cardiovascular disease, the modification of lifestyle, psychological or drug-related risk factors that target superimposed cardiovascular risk may also be beneficial in ED. A systematic review looking at the effect of lifestyle modification and cardiovascular risk factor reduction on ED concluded that risk factor reduction also had a beneficial influence on erectile function in the general population [39]. Current guidelines suggest that these modifiable risk factors for ED be addressed prior to, or in parallel with, specific therapeutic options [40].

Oral pharmacotherapy with phosphodiesterase-5 (PDE-5) inhibitors should then be considered as a first-line option. Treatment with PDE-5 inhibitors increases the level of penile cGMP, which governs the relaxation of smooth muscle cells and consecutively increases the penile arterial blood flow temporarily. This class of drugs must not be regarded as an initiator of erection, as sexual stimulation is required as a prerequisite.

Three different PDE-5 inhibitors are commonly available for the treatment of ED, sildenafil, tadalafil and vardenafil. Recently, new molecules of the PDE-5 inhibitor family are available (mirodenafil, udenafil and avanafil). All PDE-5 inhibitors are similarly effective and safe for the treatment of ED in non-SSc patients [41]. Even though the different PDE-5 inhibitors share many pharmacological and clinical characteristics, their half-lives differ. The plasma elimination half-life of tadalafil is about 3 to 5 times longer than that of sildenafil and vardenafil [40, 42]; in non-SSc men, the efficacy of

tadalafil is maintained for up to 36 h compared to only up to 12 h in sildenafil [40].

Data on the efficacy of PDE-5 inhibitors in SSc are limited. A small case series described a low efficacy of on-demand sildenafil when given in doses of 20 to 50 mg [32]; the efficacy of tadalafil on SSc-related ED has been studied in slightly more depth [43, 44]. A randomised study compared the efficacy of on-demand tadalafil (20 mg) with tadalafil dosed in a fixed alternate dose regimen. Flow-mediated dilation and peak systolic velocities of cavernous arteries at penile duplex sonography increased significantly with the alternate day regimen, but not with the on-demand tadalafil administration [43]. Unlike the on-demand treatment, the alternate day regimen also considerably reduced ET-1 plasma levels and the circulating vascular cell adhesion molecule (VCAM) as markers of endothelial function [43]. Therefore, a constant plasma level of the PDE-5 inhibitor seems to have a beneficial role in the treatment of SSc-related ED. A lower, daily dose of tadalafil (10 mg) was also studied, and after 12 weeks of treatment, it was found to result in an improvement of IIEF-5 scores and morning erections, together with an objective enhancement of penile arterial inflow [44]. Long-acting PDE-5 inhibitors may also be considered as the first-line treatment of ED because this drug class improves the frequency and severity of Raynaud's phenomenon and promotes the healing of coexisting digital ulcers [45•, 46].

Patients not tolerating or not responding to PDE-5 inhibitors may benefit from vacuum constriction devices which induce penile rigidity by means of a vacuum and then trapping blood in the penis by an elastic bondage around the penis base [40]. Such devices were reported to improve significantly the erectile function as well as the men's and their partners' sexual satisfaction [47, 48].

Alternatively, prostaglandin analogues may be administered via intracavernous injection or intra-urethral applications [40, 49••]. Alprostadil is an analogue of prostaglandin E1 that increases the concentration of cAMP and decreases the intracellular calcium concentration, resulting in the relaxation of smooth muscle cells. Several randomised clinical trials supported its effectiveness in men without SSc. Alprostadil was more effective in the case of intracavernosal compared to intra-urethral administration [50, 51].

The implantation of a penile prosthesis is considered as a third-line option in case of pharmacological treatment failure. The choice of the device, malleable or inflatable, is dependent on the preference of the patient and the patient's ability to manipulate the device. Prosthesis implantation has a high satisfaction rate of over 70 % in non-SSc patients [40]. The main complications are mechanical failure of the device and infections. Although penile prostheses are considered a safe and permanent solution for ED in the non-SSc population [40, 52], the data on their use in the SSc population are limited.

A practical approach to the screening and treatment of ED in men with SSc is presented in Fig. 1.

Conclusions

A high prevalence of ED is observed in men with SSc. In SSc, ED results from cavernosal fibrosis and an impaired blood flow through small penile arterioles. Symptoms of ED can be easily quantified by the IIEF-5 questionnaire. These should be routinely administered in clinical practice, and men should be counselled consequently. Even though only few data are available on the effectiveness of treatment options for ED in SSc, physicians should consider PDE-5 inhibitors after addressing modifiable risk factors for ED. Second- and third-line treatment decisions should involve urology.

Compliance with Ethical Standards

Conflicts of Interest VKJ and UAW declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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