Concise report

Clitoral blood flow in systemic sclerosis women: correlation with disease clinical variables and female sexual dysfunction

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Abstract

Objectives. The objectives of this study were to investigate clitoral blood flow in SSc women compared with healthy controls and to correlate it with microvascular damage and disease clinical variables. We also evaluated the correlation between clitoral blood flow and sexual dysfunction.

Methods. Twenty-two SSc women and 20 healthy controls matched for sex and age were enrolled in this study. Baseline Doppler indices of the clitoral artery were measured. Peak systolic velocity, end diastolic velocity, resistive index (RI), pulsatile index (PI) and systolic/diastolic (S/D) ratio were measured. The female sexual function index (FSFI) was used to assess sexual function.

Results. The RI and S/D ratio were higher ($P < 0.0001$) in SSc women compared with healthy controls. The PI, RI and S/D ratio increased with progression of capillaroscopic damage. The RI and S/D ratio were higher ($P < 0.01$) in women with digital ulcers than in women without digital ulcers. No correlation exists between Doppler indices of the clitoral artery and age or clinical variables of disease. The FSFI was reduced in 7 (32%) of 22 SSc women. A negative correlation was observed between both the FSFI and RI ($R = -0.74$, $P < 0.0001$) and the S/D ratio ($R = -0.68$, $P < 0.0001$). A negative correlation exists between the RI and all domains of the FSFI score except for desire.

Conclusion. Clitoral blood flow was reduced in SSc women compared with healthy controls. Clitoral blood flow was reduced in SSc women with digital ulcers and it correlated with capillaroscopic damage progression. A negative correlation exists between the RI and S/D ratio and all domains of the FSFI score except for desire.

Key words: systemic sclerosis, clitoral blood flow, female sexual dysfunction.

Introduction

SSc is a connective tissue disease characterized by endothelial dysfunction and fibrosis of the skin and internal organs [1]. SSc may affect all aspects of life including sexual function. Female sexual dysfunction (FSD) is multifactorial and depends not only on disease-related or therapy-associated aspects, but also on non-disease-related aspects such as marital status and general psychological/pyschiatric health [2–4]. In women with SSc, factors that influence FSD include vaginal tightness, dryness, ulcerations or fissures, constricted introitus, small-sized uterus, menstrual changes, dyspareunia, marked decline in orgasmic function and desire [5].

Many of the severe internal organ complications of SSc are vascular, including pulmonary arterial hypertension, scleroderma renal crisis, cardiac and gastrointestinal complications and erectile dysfunction [6]. In men with SSc, erectile dysfunction due to impairment of flow inside the cavernous arteries is correlated with vascular damage of the hands [7]. Until now no study has investigated clitoral blood flow in women with SSc and its correlation with FSD. In diabetic women, FSD is due to
reduced inflow of the clitoral cavernous arteries. Baseline clitoral blood flow is reduced in diabetic women compared with healthy controls. Sildenafil seems to improve the clitoral blood flow of premenopausal women with type 1 diabetes [8, 9]. The aim of this study was to investigate clitoral blood flow in women with SSc compared with healthy controls and to correlate it with microvascular damage and clinical variables of disease. We also evaluated the correlation between clitoral blood flow and sexual dysfunction.

Materials and methods

Subjects

Twenty-two Caucasian women [median age 39 (range 25–47) years] fulfilling the ACR preliminary criteria for the classification of SSc were enrolled in this study [10]. Nine patients had limited cutaneous SSc and 13 had diffuse cutaneous SSc as defined by LeRoy et al. [11]. Median disease and RP duration were 7 (1–17) and 8.5 (2–18) years, respectively.

Inclusion criteria were diagnosis of SSc by at least 12 months before study enrolment, minimum age of 18 years and sexually active. Exclusion criteria were menopausal status, pregnancy, nursing, psychiatric diseases, use of psychoactive drugs, congenital or iatrogenic female genital tract diseases, endocrine dysfunction not related to SSc (e.g. hypogonadism, hypopituitarism), pulmonary arterial hypertension, scleroderma renal crisis, systemic hypertension, hyperlipidaemia, intima media thickness >0.65 mm, cardiac and hepatic failure, diabetes, peripheral vascular diseases and coagulopathy. Smokers and subjects unable to give written informed consent were also excluded. SSc patients underwent therapeutic treatment with calcium channel blockers (nifedipine 30 mg/day). The median duration of therapy was 8.5 (2–18) years. Therapy was discontinued 48 h before the examination.

Twenty healthy controls matched for sex and age [median age 35 (range 26–44) years] were also enrolled. The healthy controls were not matched for marital status. The subjects’ written consent was obtained according to the Declaration of Helsinki and the study was approved by the ethics committee of Sapienza University, Rome, Italy.

Echo colour Doppler examination

All subjects underwent colour Doppler ultrasound to measure clitoral blood flow. Ultrasound was performed using an Apio Ultrasound System (SSA-790; Toshiba, Tokyo, Japan) equipped with a convex 7.5 MHz probe. The echo colour Doppler examination was performed in each patient by one independent investigator blinded to the status of the SSc women.

Each woman was scanned in the gynaecological position. The Doppler translabial probe was placed sagittally on the clitoris at an angle of <20°, without exerting any significant pressure on the tissues. After identifying the clitoral artery using colour flow mapping, the Doppler probe was positioned over the vessel and at least three sequential Doppler waveforms were obtained. The following parameters were analysed: peak systolic velocity (PSV), end diastolic velocity (EDV), resistive index (RI), pulsatility index (PI) and systolic/diastolic (S/D) ratio. The RI was calculated as (peak systolic frequency shift – minimum diastolic frequency shift)/peak systolic frequency shift and the PI as (peak systolic frequency shift – minimum diastolic frequency shift)/mean frequency shift. The PSV and EDV are expressed as centimetres per second [12].

In both groups gonadal ultrasonography was performed to verify ovulation. The Doppler parameters were evaluated in the follicular phase of the menstrual cycle [13]. We have previously determined the reproducibility of these parameters in five patients with SSc. The coefficient of variation for measurement of the RI by the same observer on different days was 1.2%.

The female sexual function index

The female sexual function index (FSFI) was used to assess sexual function. It is a self-reported measure of sexual function that has been validated on a clinically diagnosed sample of women with female sexual arousal disorder. The questionnaire is composed of 19 items divided into six domains: desire, arousal, lubrication, orgasm, satisfaction and pain. This questionnaire gives separate scores on a five-point scale in six domains (desire, arousal, lubrication, orgasm, satisfaction and pain) and a composite full-scale score (ranging from 2 to 36). Higher scores indicate better function and a domain score of zero indicates no sexual activity during the past month. Women who scored <19 were classified as having sexual dysfunction, while those who scored >19 were classified as not having sexual dysfunction [14].

Clinical assessments

We systematically collected the following data: age, disease duration (date of the first non-RP symptom), duration of RP, digital ulcers history, modified Rodnan skin score (mRSS), marital status and parity.

Nailfold videocapillaroscopy

Nailfold videocapillaroscopy was performed with a videocapillroscope (Pinnacle Studio Version 8, Corel Corp.) equipped with a 500× optical probe. The nailfolds of the second, third, fourth and fifth fingers were examined in each patient. According to Cutolo et al. [15], the patterns identified within the ‘SSc pattern’ include early, active and late.

Statistical analysis

All the results are expressed as median and range. Commercially available software (SPSS version 18.0; SPSS Inc., Chicago, IL, USA) was used. The coefficient of skewness and the coefficient of kurtosis were used to evaluate the normal distribution of data. The assumptions of normality cannot be assumed within the data set, particularly due to the small sample size, therefore non-parametric tests were used throughout. The Kruskal–Wallis test was
used to test differences between study groups. The Bonferroni test was used in the post hoc analysis. The Spearman’s rank correlation coefficient (\( r \)) was used to measure the association between two measured quantities. \( P \)-values < 0.05 were considered significant.

**Results**

No significant differences in the PSV [7.45 (4.2–15.7) vs 9.55 (7.30–12.6), \( P > 0.05 \)] and PI [1.64 (1–4) vs 1.48 (1.15–2.30), \( P > 0.05 \)] median values exist between SSc women and healthy controls. Conversely, the EDV [1.96 (0.5–4) vs 3.2 (2.4–4.9), \( P < 0.0001 \)] was significantly reduced, while the RI [0.71 (0.67–0.80) vs 0.64 (0.61–0.68), \( P < 0.0001 \)] and S/D ratio [3.60 (3.04–5.06) vs 2.79 (2.57–3.26), \( P < 0.0001 \)] were significantly increased in SSc women compared with healthy controls (Fig. 1). No correlation \( (P > 0.05) \) exists between clitoral blood flow (PSV, EDV, PI, RI and S/D) and age, RP, disease duration or mRSS. Fifteen (68.2%) women are married and 6 (27.3%) are nulliparous. Disease subset, marital status and parity did not influence clitoral blood flow.

Nine patients had an early capillaroscopic pattern (40.9%), seven had an active capillaroscopic pattern (31.8%) and six had a late capillaroscopic pattern (27.3%). No significant differences of PSV and EDV were observed in the three capillaroscopic patterns. Conversely, the PI, RI and S/D ratio were significantly different in the three capillaroscopic patterns. The PI \( (P < 0.05) \), RI \( (P < 0.001) \) and S/D ratio \( (P < 0.01) \) increased with progression of capillaroscopic damage (Table 1).

Eleven (50%) of 22 SSc patients have a history of digital ulcers. The PSV [7 (4.2–15.7) vs 7.9 (5.10–10.8)], EDV [1.7 (1–4) vs 2.03 (1.6–3.4)] and PI [1.71 (1.29–2.71) vs 1.62 (1.28–2.21)] were not significantly \( (P > 0.05) \) different in women with or without a digital ulcer history. Conversely, the RI [0.74 (0.69–0.80) vs 0.7 (0.67–0.77)] and S/D ratio [3.98 (3.23–5.06) vs 3.43 (3.04–4.51)] were significantly \( (P < 0.01) \) different in women with or without a digital ulcer history (Fig. 1).

The FSFI was reduced in 7 (32%) of 22 SSc women. The median FSFI score was 23 (10.8, 31.6). A negative correlation was observed between the FSFI and RI \( (R = -0.74, P < 0.0001) \) or S/D ratio \( (R = -0.68, \)
All parameters are expressed as median and range.

<table>
<thead>
<tr>
<th></th>
<th>Early</th>
<th>Active</th>
<th>Late</th>
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<tr>
<td>PSV, cm/s</td>
<td>7.9 (5.1–12.9)</td>
<td>9.03 (4.9–12.7)</td>
<td>6.7 (4.2–15.7)</td>
<td>&gt; 0.05</td>
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<tr>
<td>EDV, cm/s</td>
<td>2.2 (1.6–4)</td>
<td>2.2 (1.4–3.7)</td>
<td>1.7 (1–3.1)</td>
<td>&gt; 0.05</td>
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<td>PI</td>
<td>1.57 (1.28–2.05)</td>
<td>1.62 (1.38–2.71)</td>
<td>1.83 (1.71–2.38)</td>
<td>&lt; 0.05</td>
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<td>RI</td>
<td>0.69 (0.67–0.71)</td>
<td>0.73 (0.71–0.78)</td>
<td>0.77 (0.70–0.80)</td>
<td>&lt; 0.001</td>
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<td>S/D ratio</td>
<td>3.23 (3.04–3.8)</td>
<td>3.6 (3.43–4.65)</td>
<td>4.26 (3.73–5.06)</td>
<td>&lt; 0.01</td>
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A negative correlation exists between the RI and arousal (R = −0.71, P < 0.0001), lubrication (R = −0.67, P < 0.001), orgasm (R = −0.67, P < 0.001), satisfaction (R = −0.63, P < 0.01) and pain (R = −0.61, P < 0.01). No correlation was observed between the RI and desire (R = −24, P > 0.05).

**Discussion**

We demonstrated that in women with SSc, clitoral blood flow was reduced compared with healthy controls. This reduction was associated with capillaroscopic damage and a digital ulcers history. Until now, no study has evaluated clitoral blood flow in women with SSc. In our study we did not observe significant differences in clitoral arterial inflow (PSV and PI) between SSc women and healthy controls. Conversely, in women with SSc, clitoral vascular resistance (RI and S/D ratio) was higher in SSc women than healthy controls. Comparative studies of clitoral blood flow exist in other selected patients. Karatas et al. [12] demonstrated better baseline clitoral blood flow and sexual function in elite female athletes compared with sedentary healthy females. In diabetic women, baseline clitoral blood flow was reduced, and it increased after the 12th week of daily 5 mg tadalafil intake [8, 9].

The RI and S/D ratio are useful parameters to quantify renal blood flow alterations that may occur with renal disease. PSV and PI are indices of reduced inflow; conversely, the RI and S/D ratio are indices of increased resistance due to microvascular and fibrotic changes of the clitoris. In our study group the PSV and PI are not significantly reduced in SSc women compared with healthy controls; conversely, Doppler indices of resistance are increased. We can hypothesize that baseline clitoral blood flow was reduced for fixed (e.g. intimal fibrosis) or reversible (vasospasm) changes of the clitoral artery and/or fibrosis of the clitoris with microvasculature damage. Doss et al. [16] demonstrated in vaginal tissue specimens of SSc women the following specific histopathological features: duplication or disruption of the internal elastica, medial hypertrophy, adventitial changes, connective tissue fibrosis and vasculitis. In diabetic rats the authors demonstrated that diabetes induces vaginal tissue fibrosis and adverse effects on the hemodynamic mechanism of clitoral engorgement [17]. In SSc patients, Doppler indices of cavernous, digital and intrarenal arteries have been related to the severity of target organ damage and to the capillaroscopic pattern [7, 18, 19].

In our study group the clitoral blood flow did not present any correlation with the disease and RP duration and mRSS; conversely, clitoral blood flow was reduced in SSc women with a digital ulcer history and with capillaroscopic damage progression. We can suppose that the impairment of clitoral blood flow, as well as erectile dysfunction, is due to microvascular damage. Rosato et al. [7] demonstrated that in SSc men Doppler indices of erectile dysfunction show a correlation with microvascular damage.

In our study group a negative correlation exists between the clitoral resistive indices (RI and S/D ratio) and FSFI. All domain scores of the FSFI, except for desire, showed a negative correlation with the clitoral RI. We can suppose that clitoral blood flow influences female sexual function. The nitric oxide (NO) cyclic guanosine monophosphate pathway is involved in penile erection and is enhanced by sildenafil. Moreover, NO synthase isoforms have been identified in clitoral tissue and may also have a role in the female sexual genital arousal response [9]. Sildenafil was successfully used to treat genital arousal disorder of premenopausal women with type 1 diabetes [20]. Sildenafil seems to improve subjective sexual aspects (arousal and orgasm) and Doppler indices of clitoral blood flow. Since SSc produces microvascular and macrovascular damage, vasoactive drugs could be used to treat genital dysfunction in SSc women. Therefore no randomized trials have been done in woman with SSc using phosphodiesterase-5 inhibitors.

In conclusion clitoral blood flow was reduced in women with SSc compared with healthy controls. A correlation between reduced clitoral blood flow and a decrease in sexual function was seen in all domains of the FSFI score, except for desire. We can suppose that clitoral blood flow, in association with other known factors of female reproductive organ impairment (vaginal tightness, dryness, ulcerations or fissures, constricted introitus, small-sized uterus, menstrual changes, dyspareunia), may play a key role in the pathogenesis of FSD. The principal limitation of this study was the small number of SSc patients and healthy controls. This report is to be considered an exploratory study that needs confirmation.
Rheumatology key messages

- Clitoral blood flow was reduced in women with SSc compared with healthy controls.
- Clitoral blood flow decreases with capillaroscopic damage progression in women with SSc.
- Clitoral blood flow influences all domains of the FSFI score, except for desire, in women with SSc.

Disclosure statement: The authors have declared no conflicts of interest.

References