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Letter to the Editor

Erectile dysfunction: Imbalance between pro-angiogenic and anti-angiogenic factors in systemic sclerosis

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Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrosis of skin and internal organs, endothelial and microvascular damage. Erectile dysfunction (ED) is a major issue for male with high prevalence and great impact on quality of life [1].

ED is observed in around 80% of men with SSc. ED was associated with age, severe cutaneous, muscular or renal involvement, elevated pulmonary pressures and restrictive lung disease [2].

Whereas ED in the general population is usually associated with risk factors for atherosclerosis as well as cardiovascular disease, the main etiology of ED in SSc is microangiopathic [3]. There were no differences in the prevalence of early, active and late capillaroscopy patterns between men with or without ED [4].

In SSc, color Doppler showed a reduction of cavernous arteries flow and the presence of veno-occlusive dysfunction. The Doppler indices alterations were due to diffuse hyperechogenic “spots” inside the *corpora cavernosa*, thickening of the tunica albuginea and corporal fibrosis. Doppler indices of cavernous arteries showed a negative correlation with microvascular and macrovascular damage. On-demand phosphodiesterase-5 inhibitors were used as ED treatment [5,6].

Angiogenesis is impaired in SSc patients. The balance between pro-angiogenic and anti-angiogenic factors tightly regulates angiogenesis. Tissue ischemia leads usually to the expression of angiogenic growth factors (e.g. VEGF). Conversely, endostatin is a powerful inhibitor of angiogenesis and its high levels correlate with skin sclerosis, digital ulcers, capillaroscopic damage, pulmonary arterial hypertension and scleroderma renal crisis [7,8].

Since ED is a vascular complication of SSc, aim of this study was to demonstrate that in SSc men with ED there is an imbalance between serum pro-angiogenic and anti-angiogenic factors with impaired angiogenesis.

We enrolled five SSc male patients with ED [median age 53 (45–65)] and five SSc patients without ED [median age 47 (41–63)], fulfilling the American College of Rheumatology/European League criteria for classification of SSc. Four patients had limited cutaneous SSc (lcSSc) and 6 diffuse cutaneous SSc (dcSSc).

Patients with hypercholesterolemia, diabetes mellitus, stroke, smoking, peripheral arterial diseases, coronary heart disease and pulmonary arterial hypertension were excluded.

The subjects' written consent was obtained according to the Declaration of Helsinki and the study was conducted in agreement to local ethics committee's directives.

The International Index of Erectile Function-5 (IIEF-5), a self-administered questionnaire, was used to evaluate ED. The IIEF-5 provides a numerical score that is classified into five categories: severe ED (scores 5 to 7), moderate ED (scores 8 to 11), mild to moderate ED (scores 12 to 16), mild ED (scores 17 to 21), and no ED (scores 22 to 25) [2].

Serum VEGF and endostatin levels were measured by commercial ELISA kit (Quantikine ELISA, R&D Systems, Minneapolis MN) according to the instructions provided by the manufacturer.

Median value IIEF-5 of all SSc male is 20 (8–24). Five patients have ED [median IIEF-5 12 (8–18)], five patients do not have ED [median IIEF-5 23 (22–24)]. Digital ulcers (DUs) history was present in 4 (40%) patients. Two patients have an early capillaroscopic pattern, 5 patient an active pattern and three a late pattern. There are no differences of serum level of VEGF or endostatin in three capillaroscopic pattern and in SSc patients with or without DUs.

The serum levels of VEGF (pg/ml) are significantly ($p < 0.05$) lower in male with ED [median value 117.9 (75.4–259)] than in male without ED [median value 395.7 (368.4–486.5)]. The serum levels (ng/ml) of endostatin are significantly ($p < 0.05$) higher in male with ED [median value 135.7 (124.4–176.2)] than in male without ED [median value 98.9 (95.9–117.5)] (Fig. 1). Also DLCO predicted value (%) is significantly lower in male with ED [median value 67 (66–75)] than in male without ED [median value 80 (77–83)]. No significant differences of age [53 (45–65) vs 47 (42–63)], modified Rodnan skin score [10 (4–17) vs 12 (4–20)], intimal media thickness [0.78 (0.75–0.90) vs 0.70 (0.50–0.90)], pulmonary artery systolic pressure [30 (26–32) mmHg vs 30 (27–30) mmHg], disease activity index [3 (1–3.5) vs 2 (1–3)] and disease severity score [5 (3–6) vs 3 (2–8)] were observed between male with ED or without ED.

We can suppose that in SSc male with ED angiogenesis is impaired and it is characterized by low serum level of VEGF and high serum level of endostatin. In SSc male without ED we observed an increase of pro-angiogenic factors (VEGF), conversely in SSc male patients with ED anti-angiogenic factors (endostatin) are higher. VEGF increases in early stage of vascular damage, conversely elevated serum levels of endostatin correlate with skin sclerosis, DUs, giant capillaries in NVC, pulmonary arterial hypertension and scleroderma renal crisis. Because

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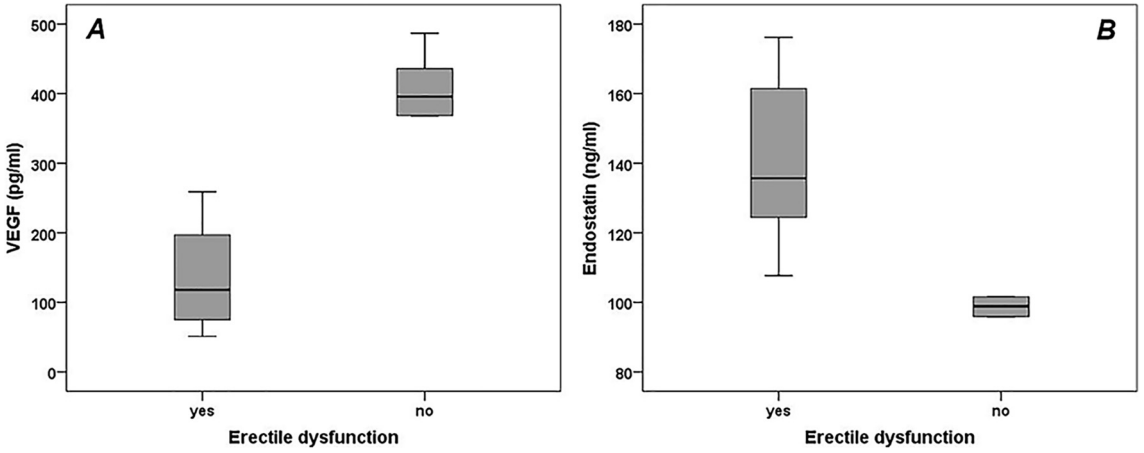

Fig. 1. Serum levels vascular endothelial growth factor (VEGF) and endostatin in SSc male patients with or without erectile dysfunction.

ED is a vascular complication of SSc, we can suppose that it is characterize both microvascular damage of cavernous arteries and impaired angiogenesis.

This study has some limitations: small sample size, absence of healthy controls group and randomization.

Conflict of interest

Authors declare no conflict of interest.

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