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BRIEF REPORT

Males and females with scleroderma: A comparative study in a Brazilian sample

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ABSTRACT

Objectives: This study aimed to evaluate the clinical and serological profile in systemic sclerosis (SSc) by comparing females and males.

Patients and methods: This retrospective study was conducted with 215 SSc patients (193 females, 22 males; mean age: 50.1±14.5 years; range, 16 to 88 years) between September 2005 and September 2020. Disease severity was calculated by the Medsger severity score. Males and females were compared for clinical and serological markers.

Results: Females more frequently had esophageal involvement (p=0.003), telangiectasias (p=0.03), and antinuclear antibodies (p=0.04). Males more frequently had fingertip scars (p=0.03), digital ulcers (p=0.006), and a worse median Medsger severity score (6 in males *vs.* 4 in females, p=0.05).

Conclusion: In the studied sample, males had more severe disease than females with greater repercussions in periferic circulatory system.

Keywords: Limited, scleroderma, systemic.

Systemic sclerosis (SSc) is an autoimmune disorder of unknown etiology characterized by production of autoantibody against intracellular antigens, inflammation, and fibrosis.[1] As in other connective tissue diseases, SSc has a female predominance, with a female-to-male ratio ranging from 3:1 to 14:1.[1,2] The reasons for this distribution are not completely understood, but estrogens are considered to play a role; estrogens seem to modulate the function of several immune cells, including lymphocytes.[2] Estradiol has been considered to have profibrotic effects, and postmenopausal female diffuse cutaneous SSc patients have significantly higher levels of serum estrogens compared to age-matched healthy controls.[3] Furthermore, estrogen levels are elevated in older men with the diffuse form of the disease, which is associated with heart involvement, and in those that were anti-Scl-70 antibody positive, linked with worse survival.[4]

Few studies address the phenotypic differences of SSc between males and females, and such studies may suffer influence of the sample ethnic background as genetic and epigenetic modifications caused by environmental exposures play an important role in the disease development.[5-7] Herein, a sample of Brazilian patients with scleroderma was studied, aiming to establish the clinical and serological differences between males and females.

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PATIENTS AND METHODS

This retrospective study analyzed 215 SSc patients (193 females, 22 males; mean age: 50.1±14.5 years; range, 16 to 88 years) from a single rheumatology unit of the Mackenzie Evangelical School of Medicine Hospital. This sample represented all the SSc patients that presented to this institution in the last 15 years, from September 2005 to September 2020. Patients fulfilled at least nine points of the 2013 classification criteria of American College of Rheumatology (ACR)/The European Alliance of Associations for Rheumatology (EULAR) for scleroderma.[8,9]

Epidemiological data (age, age at disease onset, tobacco exposure, and ethnic background), clinical data (scleroderma subset; cardiovascular, respiratory, renal, and digestive system; skin and subcutaneous tissue), autoantibody profile (antinuclear antibody [ANA], anti-Scl-70 antibody, and anti-centromere antibody) were obtained through charts review. The presence of organ involvement was evaluated in a cumulative way and classified according to the ACR definition.[10] Disease duration was considered according to the time of the first symptom, not Raynaud's phenomenon. The skin involvement was measured by the modified Rodnan index,[11] and disease severity was evaluated by the Medsger severity score.[12] The modified Rodnan index results was calculated from the sum of the skin evaluation in 17 anatomical sites. Each site was scored as follows: 0, normal skin; 1, mild thickening (the skin is thickened but can still be pinched); 2, moderate thickening (the skin is thickened and cannot be pinched but is not yet completely adhered to the deep planes, and a slight slip of the skin can still be made); 3, intense thickening (very thickened skin, not able to be pinched, adhered to deep planes, not able to be slipped). The Medsger severity score evaluates nine organ systems (skin, lungs, gastrointestinal system, kidneys, muscles, heart, peripheral vascular system, articular symptoms, and general symptoms), each scored separately depending on the level of involvement (no, mild, moderate, severe, or end stage). Pulmonary hypertension was initially accessed through echocardiography; all patients with pulmonary pressure values >35 mm or tricuspid regurgitation velocity >2.8 m/sec underwent right heart catheterization for further analysis. They were considered to have pulmonary artery hypertension if the mean pulmonary artery pressures were >25 mmHg at rest in the setting of a normal pulmonary capillary wedge pressure. Patients with incomplete data were excluded.

Statistical analysis

Analyses were done with the MedCalc® Statistical Software version 19.6 (MedCalc Software Ltd., Ostend, Belgium). Data on male and females were compared through the chi-square test and Fisher exact test if data was nominal, and the Mann-Whitney U test was used if the data was numerical. Data normality was judged by the Shapiro-Wilk test, and central tendency was expressed in median and interquartile range (IQR) as all numerical data were nonparametric.

RESULTS

In the female sample, the median disease duration was of 7 (IQR: 3-12) years, and in the male sample, it was 6 (IQR: 1-9) years. Males had a tendency to be more exposed to tobacco (current and ex-smokers) compared to females (52.8% *vs.* 32.1%, p=0.06). Regarding self-declared ethnic background, no differences were found between sexes (males with 65% European descendants *vs.* females with 67% of European descendants, p=0.86).

The comparison of clinical and serological profiles in males and females is presented in Table 1. Females had more esophageal involvement, telangiectasias, and ANA positivity while males had more fingertip scars and digital ulcers. The comparison of Medsger severity score is presented in Figure 1, which shows that males had a worse disease severity than females. Table 2 analyzes the comparison of Medsger domains between males and females and shows that males scored worse in the peripheral vascular and heart domains.

DISCUSSION

Our results have shown that females have more esophageal involvement, telangiectasias, and ANA positivity, while males had more

Table 1. Comparative study of clinical and serological profile in males and females with scleroderma

	Total (n=215)				Males (n=22)				Females (n=193)				
	n	%	Median	IQR	n	%	Median	IQR	n	%	Median	IQR	*p*
Scleroderma subtype													0.55
Limited	120	55.8			11	50			109	56.4			
Diffuse	60	27.9			8	36.3			53	27.4			
Overlap	24	11.1			3	13.6			21	10.8			
Sine-esclero	11	5.1			0	0			11	5.6			
Median disease duration years			7	3-12			7	3-12			6	1-9	0.21
Median age at diagnosis years			44.0	34.0-53.0			42.5	27.7-53.7			45.0	34.0-53.0	0.62
Raynaud's phenomena	196/206	95.1			21/21	100			175/185	94.5			0.60
Esophageal involvement	124/195	63.5			9/21	42.8			115/174	66.0			**0.003**§
Myositis	19/202	9.4			3/21	14.2			16/181	8.8			0.42
Pneumonitis	98/200	49.0			8/22	32.3			90/178	50.5			0.20
Fingertip scars	104/195	53.3			16/21	76.1			88/174	50.5			**0.03**‡
Digital ulcers	22/181	12.1			6/19	31.5			16/162	9.8			**0.006**#
Telangiectasis	96/188	51.0			4/20	20			92/168	54.7			**0.03**##
Calcinosis	27/163	16.5			3/21	14.2			24/162	14.8			0.74
Pericarditis	11/199	5.5			1/22	4.5			10/177	5.6			1.00
Pleuritis	13/192	6.7			3/22	13.6			10/172	5.8			0.15
Articular involvement	69/186	37.0			11/20	50			58/166	34.8			0.07
Pulmonary hypertension	37/189	19.5			5/20	25			32/169	18.9			0.55
Renal crisis	5/187				0	0			5/168	7.3			1.00
Median Rodnan			10	3-19			13.0	4.5-20			10.0	3.0-18.5	0.35
Median Medsger severity scale			5	3-7			6	5-8			4	3-6.7	**0.05**
Antinuclear antibodies	196/211	92.8			17/21	80.9			179/190	94.2			**0.04**†
Anti-topoisomerase	31/194	16.4			3/21	14.2			28/173	16.1			1.00
Anti-centromere	59/187	31.5			2/18	11.1			57/169	33.7			0.06

IQR: Interquartile range; * Refers to comparison between males and females; § OR= 4.8; 95% CI (1.5-15.1); ‡ OR=3.1 (1.0 to 8.9); # OR=4.2 (1.4-12.6); ## OR=4.8 (1.5-15.1); † OR=3.8 (1.09-13.3).

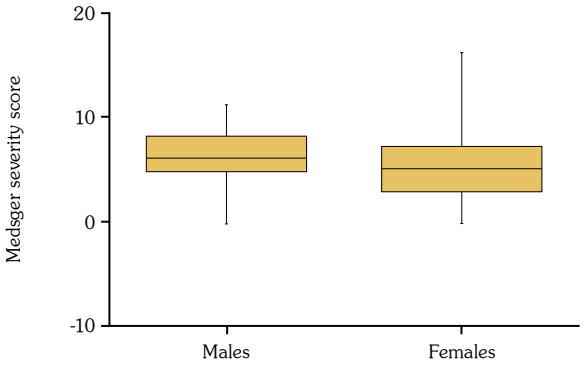

Figure 1. Comparison of Medsger severity score between sexes showing worse disease severity in males compared to females.

digital ulcers, fingertip scars, and worse Medsger severity score. The present findings differ from previous studies. Wangkaew et al.,[6] studying 113 patients from Thailand, found that males had more interstitial pneumonitis and right ventricular dysfunction. Peoples et al.,[5] studying SSc patients with new onset, found that females were younger at disease onset and more likely to have the limited cutaneous subtype with anti-centromere antibody and improved survival. They also found that males were more exposed to tobacco, had a more diffuse form, increased anti-Scl-70 antibodies, and worse survival than females. However, Nguyen et al.,[13] studying 381 scleroderma patients from France, found that females had more calcinosis and self-reported symptoms of anxiety. This diversity of results probably reflects not only the differences in study design but also the peculiarities of the studied sample. Scleroderma has important genetic influences. A multicentric study by Gourh et al.[14] on scleroderma genetic background found that the immunodominant peptides of topoisomerase-1, fibrillarin, and centromere protein A in African Americans are homologous to viral protein sequences from the Mimiviridae and Phycodnaviridae families, stressing the importance of environmental factors in this disease's autoantibody profile and, consequently, in the disease phenotype. These aspects highlight the importance of local studies in understanding the disease and its phenotypical variability.

In the current study, females had a higher prevalence of esophageal dysfunction compared to males. Classic esophageal involvement in SSc is defined as no or decreased peristalsis in the distal esophagus and hypotensive lower esophageal sphincter pressure.[15] This is one of the clinical features that has known ethnic variations, being less common in East Asians than in the White population.[16] The role of estrogen in the gastrointestinal tract has been widely studied. In the general population, estrogen increases nitric oxide, which relaxes lower esophageal sphincter, allowing reflux. In females, with estrogen replacement therapy, the gastroesophageal reflux symptoms are

Table 2. Values of the Medsger severity score domains in the total scleroderma sample according to sex

	Total			Males			Females			
	Range	Median	IQR	Range	Median	IQR	Range	Median	IQR	*p**
General symptoms	0-3	0	0-0	0-2	0	0-1	0-3	0	0-0	0.63
Peripheral vascular	0-4	1	1-2	0-4	2	1-3		1	1-2	**0.003**
Skin	0-4	1	1-2	0-3	1	1-2	0-4	1	1-2	0.64
Articular/tendons	0-3	0	0-0	0-2	0	0-0	0-3	0	0-0	0.65
Muscles	0-3	0	0-0	0-1	0	0-0	0-3	0	0-0	0.62
Gastrointestinal tract	-	1	0-1	0-2	1	0-1	0-3	1	0-1	0.97
Lungs	0-3	0	0-1	0-2	1	0-2	0-3	1	0-1	0.61
Heart	0-4	0	0-0	0-4	0	0-0	0-3	0	0-0	**0.05**
Renal										

IQR: Interquartile range; * P refers to comparison between males and females.

increased by 32% according to Nordenstedt et al.[17] Likewise, during pregnancy, symptoms of gastroesophageal reflux increase, reaching a prevalence of 30 to 80%.[18-20] Nevertheless, this hormone has a complex function in the gastrointestinal tract. It also seems to play an anti-inflammatory role as it upregulates the occludin protein, which is a component of the tight junction of mucosal cells.[20] Kang et al.[20] observed that females have more symptoms of gastrointestinal reflux than males but that men have more erosive mucosal lesions resulting from the reflux than women.

Telangiectasias were also more common in females in this study. Although these manifestations do not have any severe consequences for the patients, they do affect aesthetical aspects that may have significance for the patient's quality of life. Moreover, body disfigurement in SSc is consistently related to anxiety and depression, leading to social discomfort, especially for younger individuals.[21]

The present study also showed that the male sample had a higher proportion of ANA negativity. This result agrees with those from Salazar et al.,[22] who studied a sample of 3,249 scleroderma patients, finding 9.6% ANA negativity. They also reported that 19% of males and 13% of females had ANA negativity. Circulating autoantibodies help not only to diagnose the disease but also to classify it. In SSc, anti-Scl-70 has been more commonly found in generalized form, and anti-centromere antibody is more common in the limited scleroderma.[1] Anti-centromere autoantibodies have been linked to telangiectasis and esophageal involvement through the CREST syndrome.[1] Nevertheless, although involvement of esophagus and telangiectasias were currently seen more commonly in females, only anti-centromere antibodies were found to be more prevalent in females.

Males had higher prevalence of peripheral arterial complications and scored worse in this domain in the Medsger severity score compared to females. Moreover, they had higher values in the heart domain of the Medsger severity score. Estrogens are linked to cardiovascular protection in premenopausal women. Among other properties, estradiol stimulates the endothelial nitric oxide synthase to induce production of nitric oxide, which has an important vasculoprotective role through its vasodilating and antiaggregating properties.[23] Additionally, its arterial remodeling properties concurs to the protective actions against ischemia and the damage of ischemia/reperfusion injuries in many tissues, such as the myocardium, limbs, brain, and skin.[23] All these beneficial vascular properties of estrogen may support the worse outcome of arterial damage in males.

Finally, a higher Medsger severity score, implicating a worse disease's prognosis, was found in males compared to females with the same range of disease duration. A worse prognosis in males agrees with previous observations,[5,6] suggesting that they should be watched more carefully and treated more aggressively.

This study has several limitations. One limitation is the retrospective design. Another limitation is the low number of patients, mainly in the male sample. Capillaroscopy findings, required medications, and environmental exposure were not compared. Studies from different ethnic backgrounds and highlights are needed for a better understanding of genetic and environmental influences in SSc phenotype.

In conclusion, in this sample of Brazilian individuals with SSC, peripheral artery disease complications were more frequent in males, whereas females had more frequent esophageal involvement, telangiectasis, and ANA positivity. The disease severity, measured by the Medsger severity score, was worse in males.

Ethics Committee Approval: The study protocol was approved by the Evangelic Mackenzie School of Medicine Ethics Committee (date: 01.09.2020, no: 98305418.0.0000.0103). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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