MACROVASCULAR INVOLVEMENT IN SYSTEMIC SCLEROSIS: INFLUENCE OF DISEASE SUBTYPE AND TRADITIONAL RISK FACTORS

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Abstract

Objective. The present study aimed on one hand to test the hypothesis that patients with limited systemic sclerosis (LSSc) have a higher incidence of large vessel disease than patients with diffuse systemic sclerosis (DSSc) and to correlate it with traditional cardiovascular risk factors. On the other hand, we aimed to measure the extent of subclinical atherosclerosis in these patients, evaluating any potential clinical and laboratory vascular risk factor.
Methods. We randomly included in the study 59 systemic sclerosis patients hospitalized in 2013 in two rheumatology centers (Cairo University Hospitals Rheumatology Department and Research Center of the Pathology and Treatment of Systemic Rheumatic Diseases, Bucharest). Non-invasive vascular tests were done: internal and common carotid arteries intima-media thickness (IMT) using Doppler ultrasound, and ankle brachial index (ABI). Traditional vascular risk factors were assessed.
Results. Dividing the study sample into DSSc and LSSc produced several notable observations. The subgroups did not differ significantly by age, sex and disease duration, but ethnicity mattered: 83.3% of Egyptian patients had LSSc (25/30), while only 48.3% of Romanian patients had LSSc (14/29; p = 0.004). Generally, patients with LSSc had significantly higher values of erythrocyte sedimentation rate, alanin aminotransferase, lCIMT and significantly lower HDL levels. There were no significant differences in ABI among subgroups.
Conclusion. The limited phenotype of systemic sclerosis is associated with a more adverse cardiovascular risk profile compared to the diffuse phenotype.

Keywords: systemic sclerosis, ankle-brachial index, carotid duplex, cardiovascular risk

INTRODUCTION

Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by vasculopathy and organ fibrosis. Vasculopathy is triggered by endothelial damage, which occurs early in SSc (1). Atherosclerosis nowadays is considered an inflammatory disease in which endothelial cell dysfunction plays a very important pathogenic role (2,3). Although the detrimental effects of SSc on the small arteries and capillaries are well known, increasing evidence shows that atherosclerosis is also present in SSc, and the rate of atherosclerosis may be increased in SSc patients compared to healthy individuals (1). There are two major disease subtypes, defined according to the extent of skin involvement: limited cutaneous (LCSSc) and diffuse cutaneous SSc (DCSSc) (4). Statistically, fibrosis (for example of the skin and lungs) is more pronounced in DCSSc than in LCSSc, whereas vascular abnormalities are more pronounced in patients with LCSSc who often develop severe Raynaud's phenomenon, telangiectasia and primary type pulmonary hypertension in later disease (5). The carotid artery intima-media thickness (cIMT), as measured non-invasively using B-mode ultrasound, has been proposed as an early manifestation of atherosclerosis (6). The role of duplex scanning in the investigation of carotid artery disease is well established and there is evidence to suggest that it has

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a predictive role in identifying those patients with greater than normal risk of stroke (7). Another well-established predictive marker of cardiovascular mortality is the ankle brachial pressure index (ABPI) which was shown in previous studies in selected groups of patients to have a directly proportional association with survival (8). It is used in the investigation of atherosclerotic peripheral obstructive disease, with the severity of arterial disease being inversely proportional to the ABPI (9). The objective of the present study was to test the hypothesis that patients with LSSc have a higher incidence of large vessel disease than patients with DSSc and to correlate it with traditional cardiovascular risk factors (smoking, systolic blood pressure, adverse lipid profile, blood sugar level and steroid intake) using good surrogate markers of cardiovascular morbidity and mortality (cIMT, ABPI).

The objective of the present study was to test the hypothesis that patients with LSSc have a higher incidence of large vessel disease than patients with DSSc and to correlate it with traditional cardiovascular risk factors (smoking, systolic blood pressure, adverse lipid profile, blood sugar level and steroid intake).

MATERIALS AND METHODS

Patients

The study was cross-sectionally designed to include patients hospitalized in 2013 in two rheumatology centers: Cairo University Hospitals Rheumatology Department and Research center of the Pathology and Treatment of Systemic Rheumatic Diseases, Bucharest, Romania. The inclusion criterion was the diagnosis of SSc, which was further classified as either limited or diffuse according to the LeRoy criteria (4). The exclusion criteria were the presence of mixed connective tissue disease and other auto-immune connective tissue pathologies overlapping SSc. All the patients were over 18 years old, each gave written informed consent and the study was approved by the local ethics committees.

Measurements

Demographic data, smoking status and part of the disease history (duration, articular, extra-articular and organ involvements, treatment regimens) were recorded by means of anamnesis and medical records reviewing. A clinical examination followed to record blood pressure (auscultatory sphygmomanometer; 5 mmHg error), ankle-brachial index (ABI; measured by dividing the systolic blood pressure from both brachial arteries and from both the dorsalispedis and posterior tibial arteries using appropriately sized cuffs for the resting supine patient) and signs of skin, articular and organ involvement. Laboratory workup included the quantification of anti-nuclear antibodies (enzyme linked immunosorbent assay), erythrocyte sedimentation rate (ESR; Westergren method, with normal range according to age) and usual blood tests (Table 1). Chest X-ray and/or computed tomography was performed on patients who did not have these investigations in the last 3 months and all patients underwent carotid Doppler ultrasound examination (Philips HDI 5000 duplex with a 7.5-12 megahertz linear array transducer), performed by a skilled operator. Certain organ or tissue involvements were marked if they were diagnosed at time of the clinical examination or documented by a rheumatologist in the patient's history. Clinical cardiac involvement in SSc was defined by arrhythmias, pericarditis, heart failureand cardiomyopathy.

Statistics

The normal distribution of data was assessed using descriptive statistics, normality and stem-and-leaf plots and the Lillefors corrected Kolmogorov-Smirnov test. Normally distributed data were reported as means with standard deviations and interval and their correlations and differences were assessed with Pearson coefficients and t tests respectively. Non-normally distributed data were reported as medians with intervals and their correlations and differences were assessed with Spearman coefficients and Mann Whitney tests respectively. Qualitative data were expressed as absolute and percent frequency and their differences were assessed using χ^2 tests (or Fisher tests were appropriate). All tests were considered significant if $p < 0.05$ and were done using SPSS v.17 for Windows (SPSS Inc., Chicago, S.U.A., 2008).

RESULTS

General characteristics

A total of 59 SSc patients, with a mean age of 47 years, met the inclusion and exclusion criteria and were included in the study. As it can be seen in Table 1, female and LSSc patients predominated in the sample.

TABLE 1. *General characteristics of the study group (n = 59)*

Demographics		Scleroderma	
age (years)	47.3 (13.3; 19-74)	duration (years)	7 (0.5-36)
Sex	52 female (88.1%)	Rodnan score	15 (3-44)
Egyptian	30 (50.8%)	Medsgerscore (total)	6 (1-15)
Cardiovascular		DSSc	20 (33.9%)
smoking	5 (8.5%)	Raynaud phenomenon	59 (100%)
SBP (mmHg)	117 (17; 80-165)	arthritis	27 (45.8%)
DBP (mmHg)	70 (60-100)	tenosynovitis	11 (18.6%)
ABI	0.98 (0.6-1.25)	myositis	10 (16.9%)
rCIMT (mm)	0.62 (0.18; 0.3-1)	digital ulcers	32 (54.2%)
lCIMT(mm)	0.6 (0.18; 0.3-1)	calcinosis	10 (16.9%)
ATS plaque	8 (13.6%)	acro-osteolysis	16 (27.1%)
Laboratory		telangiectasis	27 (45.8%)
ANA positive	53 (89.8%)	dysphagia	50 (84.7%)
ESR (mm/h)	33 (6-131)	barium abnormality	30 (50.8%)
Hgb (g/dL)	12.4 (1.2; 9.9-15.2)	malabsorption	8 (13.6%)
WBC (10^3/µL)	7.88 (0.25; 4-14)	cardiac involvement	21 (35.6%)
PLT (10^3/µL)	285 (79.9; 115-492)	renal involvement	3 (5.1%)
CPK (U/L)	77 (22-1161; n=43)	sicca symptoms	14 (23.7%)
LDH (U/L)	293 (180-916; n=42)	fibromyalgia syndrome	5 (8.5%)
BUN (mg/dL)	28 (11-56)	dyspnea	29 (49.2%)
CR (mg/dL)	0.77 (0.13; 0.53-1.04; n=58)	X-ray lung reticulations	25 (42.4%)
AST (U/L)	19 (8-68)	CT pulmonary fibrosis	17 (28.8%)
ALT (U/L)	19 (10-57)	entrapment neuropathy	7 (11.9%)
FPG (mg/dL)	95 (75-135)	glucocorticoids	36 (61.1%)
TC (mg/dL)	185.5 (46.6; 99-300)	methotrexate	23 (38.9%)
HDL (mg/dL)	49 (40-140)	cyclophosphamide	17 (28.8%)
LDL (mg/dL)	103.2 (22.5; 39-148)	antihypertensives	30 (50.8%)
TG (mg/dL)	87 (35-198)	hydroxychloroquine	15 (25.4%)

Note: nominal data are reported as absolute values and percentages. Normally distributed data are reported as "mean (standard deviation; minimum-maximum)", while non-normally distributed data are reported as "median (minimum-maximum). Where there are missing data, the total number of entries is reported (n).

Abbreviations: S/DBP – systolic/diastolic bloodpressure; ABI – ankle-brachial index; r/l CIMT – right/left carotid intima-media thickness; ATS – atherosclerotic; ANA – anti-nuclear antibodies; ESR – erythrocyte sedimentation rate; Hbg – hemoglobin; WBC – white blood cells; PLT – platelets; CPK – creatine phosphokinase; LDH – lactate dehydrogenase; BUN – bloodurea nitrogen; CR – creatinine; AST – aspartateaminotransferase; ALT – alanine aminotransferase; FPG – fasting plasma glucose; TC – total cholesterol; H/LDL – high/low density lipoproteins; TG – triglycerides; DSSc – diffuse systemic sclerosis; CVS – cardiovascular; CT – computer tomography

Limited SSc

Dividing the study sample into diffuse and limited SSc produces several notable observations (Table 2). The subgroups did not differ significantly by age, sex and disease duration, but ethnicity mattered: 83.3% of Egyptian patients had LSSc (25/30), while only 48.3% of Romanian patients had LSSc (14/29; $p = 0.004$). Generally, patients with LSSc were more frequently treated with glucocorticoids and hydroxychloroquine, they had significantly higher values of ESR, ALT, lCIMT and significantly lower HDL levels. The rest of the differences were not statistically significant ($p > 0.09$), meaning that LSSc patients had the same profile when it came to cardiovascular (frequency of involvement, SBP, DBP, smoking, carotid ASC plaque, FPG, ABI, rCIMT, TC, LDL, TG), laboratory (Hgb, WBC, PLT, CPK, LDH, BUN, CR, AST), auto-immune (ANA) and disease (Medsger and Rodnan scores, Raynaud phenomenon, arthritis, myositis, digital ulcers, calcinosis, dysphagia, barium abnormality, malabsorption, renal involvement, fibromyalgia syndrome, MTX, CFM, antihypertensives, domperidon) parameters.

Macro-vascular involvement

The study recorded three major macro-vascular indices: ABI, CIMT and the presence or absence of carotid atherosclerotic plaques. These indices were tightly correlated with each other suggesting the fact that they evaluate the same construct (Table 3).

ABI was negatively correlated with age and lipid profile (Table 4) and it was significantly lower in

TABLE 2. *Comparison of limited and diffuse forms of SSc*

	LSSc (n=39)	DSSc (n=20)	p		LSSc (n=39)	DSSc (n=20)	p
ESR (mm/h)	42	37	0.047	dyspnea	33.3%	80%	0.001
ALT (U/L)	21.7	17.5	0.020	lung reticulations	30.8%	65%	0.012
lCIMT (mm)	0.64	0.53	0.028	pulmonary fibrosis	24.1%	62.5%	0.011
HDL (mg/dL)	53	59	0.002	sicca symptoms	12.8%	45%	0.010
tenosynovitis	10.3%	35%	0.033	entrapment neuropathy	5.1%	25%	0.038
acroosteolysis	17.9%	45%	0.027	glucocorticoids	71.8%	40%	0.018
telangiectasia	35.9%	65%	0.034	hydroxychloroquine	35.9%	5%	0.010

Note: p values represent the significance of tests used to compare differences in means between scale data (ESR, ALT, lCIMT, HDL) or differences in frequency of nominal data (the rest).
Abbreviations: L/DSSc – limited/diffuse systemic sclerosis; ESR – erythrocyte sedimentation rate; ALT – alanine aminotransferase; lCIMT – left carotid intima-media thickness; HDL – highdensity lipoproteins.

TABLE 3. *Macro-vascular involvementindices in SSc*

	ASC plaque		
	Absent	Present	p
ABI	0.94	0.86	0.038
rCIMT (mm)	0.59	0.83	0.001
lCIMT (mm)	0.58	0.75	0.014
	ABI	rCIMT	lCIMT
ABI	-	r = -0.397 p = 0.002	r = -0.390 p = 0.002
rCIMT	r = -0.397 p = 0.002	-	r = -0.827 p < 0.001

Note: p values in the upper part of the table represent the significance of Mann-Whitney tests, while in the lower part they represent the significance of Spearman correlation coefficients.
Abbreviations: SSc – systemic sclerosis; ABI – ankle-brachial index; r/l CIMT – right/left carotid intima-media thickness; ATS – atherosclerotic.

smoking patients (0.79 compared to 0.95; p = 0.028). There were no significant differences in ABI among subgroups divided neither byother cardiovascular factors (sex, cardiac involvement, GC, antihypertensive treatment; p > 0.3) nor by SSc vascular involvement (digital ulcers, acroosteolysis, teleangiectasia; p > 0.1). CIMT was positively correlated with cardiovascular scale variables (age, blood pressure, ESR, FPG, lipid profile), but also with SSc scale data (Rodnan and Medsger scores), but without significant differences among subgroups divided neither by cardiovascular factors, including smoking (p > 0.2) nor by SSc vascular involvement (p > 0.2). SSc patients with carotid atherosclerotic plaque had longer disease duration and an adverse cardiovascular profile (Table 4), without significantly different frequencies among the aforementioned subgroups.

DISCUSSION

Main study findings

Through its findings, the study met its main objective: we found that LSSc patients had a significantly higher lCIMT and a significantly lower HDL compared to DSSc, both strong surrogate markers

TABLE 4. *Correlations and differences of macro-vascular indices and risk factors in SSc*

	ABI		rCIMT		lCIMT		ASC plaque		
	r	p	r	p	r	p	no	yes	p
age (years)	*-0.453*	*<0.001*	*0.465*	*<0.001*	*0.431*	*0.001*	45.6	58.1	*0.011*
SBP (mmHg)	-0.086	0.519	*0.505*	*<0.001*	*0.449*	*<0.001*	119	135	*0.008*
DBP (mmHg)	0.056	0.674	*0.492*	*<0.001*	*0.422*	*0.001*	74	84	*0.006*
ESR (mm/h)	-0.174	0.192	*0.389*	*0.003*	*0.424*	*0.001*	40.8	39.4	0.830
FPG (mg/dL)	-0.015	0.910	*0.275*	*0.035*	*0.281*	*0.035*	93.7	103	*0.038*
DD (years)	-0.147	0.271	*0.452*	*<0.001*	*0.466*	*<0.001*	8.3	18.9	*0.006*
Medsger	-0.188	0.154	*0.264*	*0.043*	0.208	0.114	7	7	0.982
Rodnan	-0.071	0.595	*0.314*	*0.016*	*0.344*	*0.008*	15	18	0.633
TC (mg/dL)	*-0.416*	*0.001*	*0.515*	*<0.001*	*0.389*	*0.002*	179	227	*0.015*
LDL (mg/dL)	*-0.399*	*0.002*	*0.484*	*<0.001*	*0.400*	*0.002*	101	116	0.086
HDL (mg/dL)	-0.116	0.382	-0.068	0.611	-0.105	0.430	54.6	59.9	0.640
TG (mg/dL)	*-0.293*	*0.025*	*0.335*	*0.010*	*0.270*	*0.039*	90.7	122	0.097

Note: p values in the right part of the table represent the significance of Mann-Whitney tests; while in the left part they represent the significance of Spearman or Pearson correlation coefficients.
Abbreviations: S/DBP – systolic/diastolic blood pressure; ABI – ankle-brachial index; r/l CIMT – right/left carotid intima-media thickness; ATS – atherosclerotic; ESR – erythrocyte sedimentation rate; FPG – fasting plasma glucose; DD – disease duration; TC – total cholesterol; H/LDL – high/low density lipoproteins; TG – triglycerides; SSc – systemic sclerosis

for cardiovascular morbidity and mortality. Moreover, the severity scores of the disease showed significant and positive correlations with CIMT, while disease duration exhibited the strongest correlations with CIMT and carotid plaques. Regression analysis for these indices was considered inappropriate because of the low study sample and the use of surrogate cardiovascular markers. Still, these results clearly show that the longer the patients had active disease the more adverse the cardiovascular profile is, especially LSSc patients. The fact that Egyptian patients had a significantly higher incidence of LSSc phenotype indicates either a sampling bias or a true higher incidence of LSSc among the Egyptian population, a question best answered by further studies with representative samples of this population.

Comparing with other studies

It is well known that SSc patients have an increased risk of atherosclerosis compared to healthy subjects, (1) which translates into a higher risk of myocardial infarction, stroke and peripheral vascular disease (10). But the information regarding the impact of disease phenotype on cardiovascular markers is scarce and conflicting. Although our study did not measure arterial stiffness, it is interesting to note that in 2003, Cheng et al. showed that DSSc patients had a significantly higher carotid artery stiffness compared to LSSc, with no differences in CIMT (11). In 2007, Bezante et al. observed that DSSc patients had significantly lower ventricular ejection fractions on MRI than LSSc (12). Unfortunately, cardiac ultrasound data were available only for some our patients. The same year, Szucs et al. found no differences between flow-mediated dilatation, nitroglycerin-mediated dilatation and CIMT between the SSc subtypes, (13) a later difference which we found to be significant. Concordant with these later findings are the results of Belloli et al. who observed in 2008 that DSSc and LSSc were not different regarding myocardial perfusion defects (14). A small cohort followed by Poormoghim et al. showed that there were no significant difference in the severity of cardiovascular involvement between the two subtypes of SSc in the late stage of the disease (15). Consistent with our findings is the report of Colaci et al. who showed in 2012 that arterial stiffness was more frequently associated with the limited cutaneous pattern and with longer disease duration (16). Despite of the fact that some of this evidence points out that the limited phenotype is more prone to atherosclerosis, a Brazilian cohort study reported by Sampaio-Barros et al. in 2012 showed that the patients presented worse 5 year and 10 year prognosis if they had diffuse disease phenotype, using true cardiovascular endpoints (17).

Possible mechanisms

The results show two observations that might argue for a more adverse cardiovascular profile in LSSc patients: on one hand, LSSc patients had a significantly higher median ESR and glucocorticoids treatment frequency than DSSc. Inflammation and glucocorticoids treatment are established cardiovascular risk factors which can account for the excess atherosclerosis seen in LSSc patients. If in deed inflammation and use of glucocorticoids are responsible for the observed differences, the therapeutic implications follow: a tighter disease control with immunosuppressive agents and a more thorough application of guidelines for glucocorticoids use (lower doses, shorter disease duration etc.) would lower the cardiovascular risk of LSSc patients.

Study limitations

There are several limitations which can bias the study results. First of all the cross-sectional design did not allow follow-up of patients and the use of true cardiovascular markers instead of surrogate markers. Secondly, the small sample size could affect the significance of the statistical tests we used. Lastly, the effect of genetic differences between Egyptian and Romanian patients is unknown and therefore it could not be accounted for.

CONCLUSIONS

Our observations lead to the conclusion that the limited phenotype of systemic sclerosis is associated with a more adverse cardiovascular risk profile compared to the diffuse phenotype. Higher tolls of inflammation and disease severity seem to be the explanation of this observation, although prospective studies are needed to confirm this hypothesis. The translational potential of these findings can be applied to therapeutic strategies which would require on one hand a tighter disease control in order to reduce systemic inflammation and disease severity and on the other hand a more aggressive cardiovascular preventive strategy for patients with limited systemic sclerosis.

Conflicts of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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