The Egyptian Rheumatologist (2014) xxx, xxx–xxx

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The Egyptian Rheumatologist

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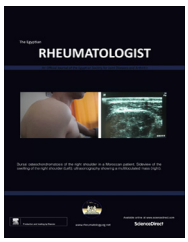

ORIGINAL ARTICLE

Subclinical atherosclerosis and peripheral vascular disease in systemic sclerosis patients: Relation to potential risk factors

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Received 19 February 2014; accepted 16 June 2014

KEYWORDS

Ankle brachial pressure index;
Cardiovascular risk;
Carotid duplex;
Systemic sclerosis

Abstract *Aim of the work:* To measure the extent of subclinical atherosclerosis in patients with systemic sclerosis, and to evaluate any potential vascular risk factors in these patients.

Patients and methods: This study included 30 patients with systemic sclerosis diagnosed according to the American college of rheumatology criteria and 20 healthy individuals were also included as a control group. Non-invasive vascular tests including; carotid duplex scanning measuring common carotid arteries (CCA) intima-media thickness (IMT), and ankle brachial pressure index (ABPI) were performed. Traditional vascular risk factors such as blood pressure, blood sugar, lipid profiles, steroid usage and other immunosuppressive medications were assessed.

Results: The mean IMT of CCA was higher in systemic sclerosis patients (right 0.67 ± 0.11 mm, left 0.67 ± 0.12 mm) when compared with the control group (right 0.48 ± 0.2 mm, left 0.54 ± 0.13 mm) ($p < 0.001$). Carotid plaques were found in 4 SSc patients. Mean IMT was correlated with patients' age ($p < 0.001$), disease duration ($p < 0.001$), systolic blood pressure ($p < 0.05$), and dyslipidemia ($p < 0.01$). Ankle brachial pressure index (ABPI) was significantly lower in SSc patients (0.94 ± 0.13) when compared with controls (1.16 ± 0.12) ($p < 0.001$). No difference was found between limited ($n = 25$) and diffuse ($n = 5$) disease subtypes in mean IMT, nor in mean ABPI. There was no significant correlation between mean IMT and steroid dose or other immunosuppressive intake.

Conclusion: There is an increased risk of subclinical atherosclerosis and peripheral arterial disease in SSc patients. Increased systolic blood pressure, dyslipidemia, long disease duration and older age were possible risk factors.

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Peer review under responsibility of Egyptian Society for Joint Diseases and Arthritis.

http://dx.doi.org/10.1016/j.ejr.2014.06.003

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1. Introduction

Systemic sclerosis (SSc) is considered as a systemic disease that mainly affects small vessels. However SSc patients are more likely to develop peripheral arterial disease (PAD) which is considered as a kind of macrovascular disease [1]. It is a rheumatic disease of unknown etiology characterized by widespread vasculopathy and extracellular matrix deposition leading to fibrosis and autoimmune processes [2]. Vascular abnormalities are one of the primary pathologic components of SSc and recent evidence suggests the presence of anti-angiogenic factors [3]. Pathological involvement of coronary arteries in asymptomatic SSc Egyptian patients is not uncommon but not paralleled by clinical symptomatology [4].

The development of accelerated atherosclerosis in SSc is less clear, however, an increase in carotid IMT in SSc patients has been reported [5,6], clinically there is also little evidence for increased macrovascular complications such as stroke and myocardial infarction in SSc patients [7].

Carotid intima-media thickness (IMT) as measured by high-resolution ultrasound is a well-validated marker of subclinical atherosclerosis [8]. The role of duplex scanning in the investigation of carotid artery disease is well established, and there is evidence to suggest that it has a predictive role in identifying those patients with a greater than normal risk of stroke [5]. The study of the IMT in other rheumatic diseases on Egyptian patients showed subclinical atherosclerosis in rheumatoid arthritis [9], systemic lupus erythematosus [10], Behçets disease [11] and primary osteoarthritis [12].

The role of ankle brachial pressure index (ABPI) in predicting cardiovascular mortality is well established [8]. It is used in the investigation of atherosclerotic peripheral obstructive disease, with the severity of arterial disease being inversely proportional to the ABPI [6].

The aim of this work is to measure the extent of subclinical atherosclerosis in patients with systemic sclerosis as well as peripheral artery disease, and to evaluate any potential vascular risk factors in these patients.

2. Patients and methods

This study was done on 30 patients with systemic sclerosis recruited from the Rheumatology and Rehabilitation departments, Cairo University. The patients fulfilled the American College of Rheumatology (ACR) classification criteria for scleroderma [13] and were further subclassified to have diffuse (dcSSc) or limited (lcSSc) cutaneous subset of SSc according to Le Roy et al. [14]. The exclusion criteria were the presence of mixed connective tissue disease and other autoimmune connective tissue pathologies overlapping with SSc.

In addition, 20 healthy individuals with matched age, sex and BMI to the SSc patients served as the control group. All patients were assessed clinically and subjected to routine laboratory investigations. Demographic data, smoking status, disease history (duration, articular, extra-articular and organ involvements and treatment regimens) and signs of skin, articular and organ involvement were recorded. Laboratory investigations included the lipid profile; total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides (TG), and random blood sugar. A non-invasive vascular test 'carotid duplex scanning' was performed to measure the intima media thickness (IMT) of the common carotid arteries (CCA). The patients' consents were obtained and the study was approved by the local ethics committee in accordance to the 1964 Helsinki declaration.

The severity of SSc was assessed by Medsger SSc severity scale [15]. Clinical examination included a record of the blood pressure and was followed by measurement of the ankle-brachial pressure index (ABPI); using suitably sized sphygmomanometer to measure the ankle and brachial systolic pressure on each side and the lower value taken to calculate the ratio of ankle to brachial systolic pressure.

All patients underwent carotid Doppler ultrasound examination using Philips HDI 5000 duplex with a 7.5–12 megahertz linear array, the IMT of CCA was measured 1 cm distal to the carotid bifurcation in the posterior wall, performed by a skilled operator. For each patient the highest IMT among the measured segments studied on each side was recorded. According to current sonographic criteria IMT was considered "normal" when less than 0.9 mm, "thickened" when IMT was equal to or more than 0.9 mm and when the thickness was more than 1.3 mm was indicative of atherosclerotic plaque [16].

Statistical analysis: Data were collected and analyzed by SPSS version 11.0 statistical package, qualitative data were presented in the form of number and percent and analyzed by Fisher exact test. Quantitative data were expressed as mean and standard deviation (±SD) for normally distributed data and as median and range for non-normally distributed data. Student's *t*-test was used for comparison of the means of two groups which were normally distributed and Mann–Whitney U test for non-normally distributed quantitative variable. Pearson correlation coefficient (*r*) was used to test the association between two quantitative variables. A *p*-value less than 0.05 was considered statistically significant.

3. Results

Out of the 30 studied patients, 3 (10%) were males and 27 (90%) were females. Their ages ranged from 19 to 60 years with a mean age of 42.5 ± 12.38 years. Their disease duration ranged from 1 to 36 years with a mean duration of 18.5 ± 17.5 years. Their age at disease onset ranged from 17 to 46 years with a mean of 31.5 ± 14.5. Five patients out of 30 (16.7%) had dcSSc and 25/30 (83.3%) had lcSSc. The clinical characteristics, severity score index and laboratory features of the studied SSc patients are presented in Table 1.

We found that the measurements of carotid duplex IMT of SSc patients were significantly greater than those of the control group. However on comparing IMT measurements of carotid arteries regarding disease subtypes we did not find significant difference between diffuse and limited subtypes of the disease (Tables 2 and 3).

We found that 11 of SSc patients had thickened carotid artery and the other 19 had not. The mean age and disease duration and mean systolic blood pressure were found to be significantly higher in SSc patients who had thickened carotid IMT than those who had not. Also regarding the lipid profile, the mean total cholesterol, HDL, LDL, and TG levels were found to be significantly higher in SSc patients who had thickened carotid IMT than those who had not. In regard to steroid intake, use of methotrexate, hydroxychloroquine or vasodilators we did not find any significant difference between SSc

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patients who had thickened carotid artery intima and those who had not (Table 4).

The ankle brachial pressure index (ABPI) measurements in SSc patients were found to be significantly lower than that in the control group. However no significant difference was found regarding both disease subtypes (Table 5).

Table 1 Clinical characteristics, severity score index and laboratory features of the SSc patients.

Systemic sclerosis (SSc) patients (n = 30)		
Clinical manifestation	Number	(%)
Raynaud's	30	(100)
Fatigue	28	(93.3)
Weight loss	21	(70)
Cutaneous	19	(63.3)
Arthritis	9	(30)
Arthralgia	26	(86.7)
Tenosynovitis	3	(10)
Myositis	6	(20)
Pulmonary	16	(53.3)
Cardiovascular	7	(23.3)
Hypertension	14	(46.6)
Gastrointestinal	28	(93.3)
Renal	1	(3.3)
Sjögrens syndrome	3	(10)
FMS	5	(16.7)
Severity score index	Mean ± SD (range)	
General	0.70 ± 0.8	(0–2)
Peripheral vascular	1.47 ± 1.4	(0–3)
Skin	1.97 ± 0.8	(1–4)
Joints and tendons	0.87 ± 0.9	(0–3)
Muscles	0.93 ± 0.6	(0–2)
GIT	0.90 ± 1.1	(0–3)
Pulmonary	0.38 ± 0.6	(0–2)
Cardiac	0.23 ± 0.5	(0–2)
Renal	0.07 ± 0.3	(0–1)
Laboratory feature		Mean ± SD
Hb (g/dl)		12.3 ± 1.2
WBC ($\times 10^3/mm^3$)		8.3 ± 2.2
Platelets ($\times 10^3/mm^3$)		303.8 ± 80.7
ESR (mm/1st h)		45.5 ± 26.7
Creatinine (mg/dl)		0.75 ± 0.12
ALT (U/L)		21.1 ± 5.8
RBS (mg/dl)		98.8 ± 12.4
Cholesterol (mg/dl)		187.1 ± 145.9
HDL (mg/dl)		46.4 ± 45.1
LDL (mg/dl)		105.4 ± 19.6
TG (mg/dl)		98.4 ± 43.8

FMS, fibromyalgia syndrome; Hb, hemoglobin; WBC, white blood cells; ESR, erythrocyte sedimentation rate; ALT, alanine transaminase; FBS, fasting blood sugar; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglycerides.

On correlation between carotid artery measurements and various parameters among SSc patients we found a significant correlation between carotid IMT and age of the patients, disease duration, systolic blood pressure, LDL, HDL, TG and total cholesterol levels. However, no significant correlation was found between it and ESR nor with blood sugar level (Table 6).

4. Discussion

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. 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 [17].

With this background, we have studied two controversial issues, the first was measuring the extent of subclinical atherosclerosis as well as peripheral artery disease in patients with SSc compared with controls; and the second was to evaluate any potential vascular risk factors including blood pressure, blood sugar, lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), and steroid usage.

The present study showed that the mean IMT of the common carotid arteries was significantly greater in SSc patients than in the controls. This finding goes in line with many studies which reported a significant increase in the IMT of common carotid arteries than in the controls [5,6,17–24].

In contrast to the previous findings, other studies [25–31] found that the mean common carotid arteries IMT were not significantly increased compared with healthy controls. The differences between the results of the present study and the results of these studies may be due to the larger percentage of diffuse cutaneous SSc subtype in these studies compared with ours. Also the mean disease duration in these studies was less than that of the present study and this may explain the differences in the findings.

Regarding disease subtypes, we did not find any significant difference in the mean values of common carotid IMT between limited and diffuse disease subtypes. Our results matched those of Cheng and colleagues [25], Szucs and coworkers [27], Kaloudi and others [28] and Hettema and others [29].

In this study, we correlated IMT of carotid arteries with some clinical and laboratory parameters in SSc patients including age, disease duration, systolic blood pressure, ESR, lipid profile levels, random blood sugar and ankle brachial pressure index (ABPI). We found that macrovascular affection in the form of thickened common carotid IMT in SSc patients correlates positively with the mean age of SSc patients, disease duration, systolic blood pressure, total cholesterol level and HDL cholesterol level levels. But there was no significant correlation

Table 2 Comparison between SSc patients and controls regarding the CCA IMT.

IMT mean ± SD	SSc patients (n = 30)	Controls (n = 20)	p	Sig.
Rt CCA	0.67 ± 0.11	0.48 ± 0.20	<0.001	S
Lt CCA	0.67 ± 0.12	0.54 ± 0.13	<0.001	S

IMT, intima media thickness; CCA, common carotid artery; S, significant.

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Table 3 Comparison between lcSS and dcSS subtypes as regards the CCA IMT.

IMT mean ± SD	lcSSc (n = 25)	dcSSc (n = 5)	p	Sig.
Rt CCA	0.65 ± 0.11	0.74 ± 0.05	> 0.05	NS
Lt CCA	0.67 ± 0.12	0.69 ± 0.12	> 0.05	NS

IMT, intima media thickness; CCA, common carotid artery; NS, non significant.

Table 4 Comparison between SSc patients with thickened CCA IMT and those without regarding demographic and other risk factors.

Demographic and other risk factors mean ± SD or n (%)	Common carotid artery IMT		p	Sig.
	Thickened (n = 11)	Normal (n = 19)		
Age (years)	53.6 ± 3.6	36.2 ± 11.1	< 0.001	S
Duration of disease (years)				
Mean ± SD	18.0 ± 10.5	6.1 ± 5.4	< 0.001	S
Median (range)	15 (5–36)	5 (1–24)		
Gender				
Male	1 (9.1)	2 (10.5)	> 0.05	NS
Female	10 (90.9)	17 (89.5)		
Total	11 (100)	19 (100)		
Smoking				
Positive	1(9.1)	1 (5.3)	> 0.05	NS
Negative	10 (90.9)	18 (94.7)		
Total	11 (100)	19 (100)		
Diabetes				
Positive	1 (9.1)	1 (5.3)	> 0.05	NS
Negative	10 (90.9)	18 (94.7)		
Total	11 (100)	19 (100)		
Blood pressure				
Systolic (mmHg)	134.6 ± 10.4	123.7 ± 12.5	< 0.05	S
Diastolic (mmHg)	84.1 ± 7	77.9 ± 9.3	> 0.05	NS
Cholesterol (mg/dl)	247.4 ± 46.1	152.2 ± 18.9	< 0.001	S
HDL (mg/dl)	50.04 ± 8.4	44.30 ± 2.5	< 0.01	S
LDL (mg/dl)	123.6 ± 14.1	94.79 ± 13.6	< 0.001	S
TG (mg/dl)	134.5 ± 36.7	77.54 ± 33.02	< 0.001	S
Steroid	5 (45.5)	19 (100)	> 0.05	NS
Methotrexate	7 (63.3)	9 (47.3)	> 0.05	NS
Hydroxychloroquine	2 (18.2)	11 (57.9)	> 0.05	NS
Vasodilators	9 (81.8)	5 (26.3)	> 0.05	NS

IMT, intima media thickness; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglycerides; S, significant; NS, non significant.

Table 5 Comparison between SSc patients, control and subtypes as regards the measurement of ABPI.

ABPI mean ± SD	SSc patients (n = 30)	Controls (n = 20)	p	Sig.
All patients	0.94 ± 0.13	1.16 ± 0.12	< 0.001	NS
Sub types				
lcSSc (n = 25)	0.95 ± 0.18			
dcSSc (n = 5)	0.9 ± 0.11		> 0.05	NS

ABPI, ankle brachial pressure index; lcSSc, limited cutaneous systemic sclerosis; dcSSc, diffuse cutaneous systemic sclerosis; n, number; NS, non-significant.

with ESR, random blood sugar level or ABPI. Results matched those of other studies done by Szucs and colleagues [27] and Hettema and others [29].

Treatment with immunosuppressive agents, especially corticosteroids, influences the atherogenic process. Corticosteroids are considered to have atherogenic properties, like

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Table 6 Correlation between common carotid artery (CCA) IMT measurements and various parameters among SSc patients.

Parameter	Rt CCA IMT			Lt CCA IMT		
	R	*p*	Sig.	*R*	*p*	Sig.
Age (years)	0.68	< 0.001	S	0.60	< 0.001	S
Disease duration (years)	0.56	< 0.001	S	0.52	< 0.01	S
Systolic BP (mmHg)	0.54	< 0.05	S	0.43	< 0.05	S
ABPI	−0.2	> 0.05	NS	−0.17	> 0.05	NS
Cholesterol	0.78	< 0.001	S	0.62	< 0.001	S
HDL	0.52	< 0.01	S	0.53	< 0.01	S
LDL	0.58	< 0.001	S	0.51	< 0.01	S
TG	0.67	< 0.001	S	0.54	< 0.001	S
ESR	0.24	> 0.05	NS	0.39	> 0.05	NS
RBS	0.30	> 0.05	NS	0.11	> 0.05	NS

IMT, intima media thickness; BP, blood pressure; ABPI, ankle brachial pressure index; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglycerides; ESR, erythrocyte sedimentation rate; RBS, random blood sugar; S, significant; NS, non significant.

azathioprine, whereas for hydroxychloroquine and methotrexate, a protective effect against atherosclerosis has been described [29]. It is difficult to establish whether the observed association between immunosuppressive agents and atherosclerosis is due to the immunosuppressive agents themselves or to their effect on the activity of the autoimmune disease.

Regarding drug intake, we did not find significant difference between SSc patients with thickened common carotid IMT and those without regarding steroid intake, methotrexate or hydroxychloroquine intake. Our results matched those of Hettema et al. [29], who reported that, no association was found between common carotid IMT and prednisolone dose and use of other immunosuppressive agents.

The above results can be explained by that glucocorticoid treatment increases total cholesterol and HDL cholesterol more quickly, with a concomitant faster improvement of the atherogenic index (total cholesterol/HDL ratio) [30]. Corticosteroids also decrease the risk of atherosclerosis by controlling inflammation [31–34].

Among the limitations of this study is the small number of the patients and a larger scale is recommended taking into consideration a total skin thickness measure. A longitudinal study design and extended statistical tests including a regression analysis should be considered to further elucidate the impact of the risk factors on the development of subclinical atherosclerosis.

We can conclude that, there is an increased risk of subclinical atherosclerotic macrovascular disease in SSc patients which is evidenced by increased IMT of common carotid arteries compared with healthy controls. No correlations were found between IMT and disease related variables including disease subtypes and severity as assessed by Medsger severity scale, but a significant correlation was displayed with disease duration, age of the patients and systolic blood pressure. Further research is necessary to identify the mechanism of increased risk of atherosclerosis in SSc and to elucidate the nature of macrovascular abnormalities and the risk factors associated with it.

Conflict of interest

None.

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