Angiology: Open Access
ISSN: 2329-9495

Sharma et al., Angiol 2017, 5:1
DOI: 10.4172/2329-9495.1000190

Research Article Open Access

Carotid Intima Media Thickness in Systemic Sclerosis Patients: Results From a Single Centre, Cross Sectional, Case-Control Study

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Received date: 13 February, 2017; **Accepted date**: 09 March, 2017; **Published date**: 18 March, 2017

Abstract

Objective: To describe the parameters of subclinical vascular changes [Carotid Intima Media Thickness (cIMT), Flow Mediated Dilatation (FMD), Ankle Brachial Pressure Index (ABPI)] in patients with systemic sclerosis and compare them with age and sex matched controls.

Methods: 50 patients of systemic sclerosis aged 20-50 years were selected and compared with the same no. of age and sex matched controls. Patients with diabetes, hypertension, dyslipidemia, smoking and thyroid disorders were excluded. cIMT, FMD and ABPI were calculated for all participants.

Results: The cases and controls were well matched in terms of age, blood pressure, Body Mass Index, renal and liver functions, and lipid profiles. 34 patients had limited cutaneous SSc while 16 had diffuse cutaneous SSc. cIMT was significantly more in SSc patients as compared to controls (0.585 mm vs. 0.571 mm; p=0.001). FMD measurements in SSc patients were lower when compared to controls, but they did not achieve statistical significance (7.61% vs. 8.03%; p=0.608). ABPI values were similar in SSc patients and controls (1.056 vs. 1.036; p=0.398). cIMT did not show any correlation with age or duration of illness. ABPI showed significant inverse correlation with duration of illness (Rho=-0.385; p=0.006). However, none of these parameters varied as per the pattern of skin involvement (diffuse vs. limited), presence or absence of digital infarcts or pulmonary fibrosis

Conclusion: cIMT is increased in patients with systemic sclerosis as compared to matched controls. cIMT and ABPI may prove useful for assessing the burden of subclinical atherosclerosis and peripheral vascular disease.

Introduction

Atherosclerosis leads to cardiovascular disease. It is a leading cause of mortality worldwide. The Global Burden of Disease 2015 estimated a 12.5% rise in the number of deaths due to cardiovascular diseases, increasing from 15.9 million deaths in 2005 to 17.9 million deaths in 2015 even though the age standardized mortality rate (per 100,000) fell by 15.6% [1]. Owing to its impact on mortality and morbidity, the onus lies on the detection of subclinical atherosclerosis.

It is an established fact that accelerated atherosclerosis occurs in connective tissue diseases like systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) [2]. Subclinical atherosclerosis has been reported in both SLE as well as RA in various studies [3]. There is increasing evidence that atherosclerosis occurs prematurely in systemic sclerosis [4-6]. Although micro vascular disease is characteristic of SSc, but there is growing evidence of macro vascular disease in SSc patients. The mechanisms implicated in promoting atherosclerosis in SSc include endothelial cell dysfunction, vasculopathy and inflammation, along with traditional cardiovascular risk factors. A systematic review and meta-analysis by Au et al concluded that there is increased atherosclerosis in SSC patients in comparison to age and sex matched controls [7]. Aim of the study was to assess subclinical atherosclerosis in Indian SSc patients.

Patients and Methods

Patients of systemic sclerosis attending the Rheumatology clinic were selected and compared with age and sex matched healthy controls in 1:1 proportion. All patients fulfilled the 2013 ACR/EULAR classification criteria for systemic sclerosis [8], and gave informed consent. Patients who had Diabetes Mellitus, dyslipidemia, hypertension, history of smoking, hypothyroidism or lymphoproliferative disorders were excluded from the study. Clinical and laboratory parameters at the time of recruitment were collected.

Carotid Intima Media Thickness (CIMT) was calculated using a linear probe (L 12-5 MHz) on a Philips iU 22 ultrasound machine. The common carotid artery was imaged at a distance of 2 cm from the carotid bulb and measurements were made at the far wall. A mean of the left and right CIMT was calculated [9].

All ultrasound measurements were taken in a quiet temperature controlled room at the same time of the day (between 8 AM and 11 AM, to avoid diurnal variation in FMD) by a single observer with the patient fasting for at least 8 hours. The sonographer was blinded to the patient's disease status. Endothelium-dependent flow mediated dilatation (FMD) of brachial artery was expressed as the percentage change in brachial artery diameter from baseline. The brachial artery was imaged by a longitudinal section approximately 5 cm above the antecubital fossa. After obtaining the baseline image blood pressure

cuff was placed around the arm above the scanned part of the artery and cuff inflated to 200 mmHg for 5 min. The blood pressure cuff was gradually deflated. The next ultrasound image was taken 1 min after cuff deflation. Measurement of the artery diameter was done between m-lines (media-adventitia interface) of the near and far walls. The average of the right and left brachial artery FMD was studied [10].

Ankle Brachial Pressure Index (ABPI) of both right and left lower limb was measured (using Doppler) and the average value of ABPI was considered. The pressure in the dorsalis pedis and posterior tibial arteries was measured and the ABPI was calculated by dividing the highest ankle systolic pressure by the highest brachial artery systolic pressure to two decimal places [11].

Statistical Analysis

All the data was maintained on Microsoft excel sheet and descriptive statistics was used. The measures of central tendency and dispersion of data was calculated using mean and standard deviation. ANOVA (analysis of variance), Tukey's post-hoc test and independent sample t-test was used as per the requirement. Pearson's coefficient of correlation was calculated to look at the possible association. All the statistical analysis was performed using the SPSS. v20 software. P value <0.05 was considered statistically significant.

Results

A total of 50 patients diagnosed with progressive systemic sclerosis and 50 age and sex matched were enrolled in the study. Patients were grouped into limited cutaneous and diffuse cutaneous based on LeRoy classification [12]. 34 patients had limited disease while 16 had diffuse cutaneous systemic sclerosis. The more common manifestations were Raynaud's phenomenon and sclerodactyly, all patients exhibited these findings (Figure 1).

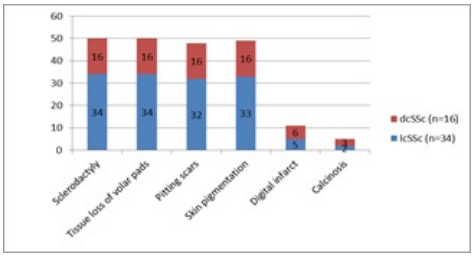

Figure 1: Skin manifestations in present study (n=50).

	Cases	Controls	p-value
Total no. of subjects	50	50	
Mean age(years)	35.26 ± 9.551	35.52 ± 7.686	0.881
Female: Male	7.3:1	2.9:1	0.074
Body Mass Index (kg/m^2)	21.314 ± 2.774	22.293 ± 2.353	0.06
Blood Pressure(systolic mm Hg)	123.96 ± 8.345	121.56 ± 11.287	0.23
Blood Pressure(diastolic mm Hg)	80.26 ± 8.873	77.44 ± 7.217	0.084
Hemoglobin (g/dL)	11.70 ± 1.524	11.276 ± 1.435	0.156
Urea(mg/dL)	23.168 ± 7.292	22.681 ± 8.401	0.758
Creatinine(mg/dL)	0.713 ± 0.26	0.741 ± 0.223	0.573
Protein(g/dL)	7.692 ± 0.909	7.911 ± 0.795	0.203
Albumin(g/dL)	4.079 ± 0.486	4.386 ± 0.417	0.001
AST (Median,IQR U/l)	28.50 (22.46-40.37)	27.00 (23.00-39.75)	0.823
ALT(Median,IQR U/l)	33.12 (21.00-45.00)	36.92 (26.00-49.00)	0.028
Total Cholesterol (mg/dl)	168.782 ± 17.235	168.138 ± 21.522	0.869
HDL-C (mg/dl)	44.347 ± 5.989	46.674 ± 8.442	0.115
LDL-C (mg/dl)	95.405 ± 13.789	92.771 ± 18.473	0.421
VLDL-C (mg/dl)	29.030 ± 16.00	28.691 ± 9.849	0.899
Triglycerides (mg/dl)	130.672 ± 16.50	122.830 ± 47.4	0.272
AST=aspartate aminotransferase, ALT=alanine aminotransferase, HDL=High-density lipoproteins, LDL=Low-density lipoproteins, VLDL=Very low-density lipoproteins			

Table 1: Baseline characteristics of cases and controls.

CIMT, FMD and ABPI were measured in all patients and controls as depicted in Table 2.

Paramter	SSc patients	Controls	p value
CIMT (mm)	0.586 ± 0.089	0.571 ± 0.105	0.001
FMD (%)	7.610 ± 4.462	8.033 ± 3.742	0.608
ABPI	1.056 ± 0.117	1.036 ± 0.121	0.398
CIMT=Carotid Intima Media Thickness, FMD=Flow mediated dilatation, ABI =Ankle Brachial Pressure Index			

Table 2: Measurements of CIMT, FMD and ABPI among SSc patients and controls.

CIMT thickness was significantly higher in SSc patients as compared to controls (0.585 mm vs. 0.571 mm; P=0.001). FMD measurements in SSc patients were lower as compared to controls but the difference did not achieve statistical significance (7.61% vs. 8.03%; p=0.608. We did not find a difference in measurement of ABPI in SSc patients compared to controls (1.056 vs. 1.036; p=0.398).

We further correlated these measurements with various clinical and laboratory factors in the SSc patients (Table 3). CIMT did not correlate with age or duration of illness. FMD showed a weak positive correlation with age (Rho=0.294; P=0.039) and an inverse correlation with serum triglycerides (Rho=-0.316; p=0.025). ABPI showed significant inverse correlation with both age (Rho=-0.580; p=0.001) and duration of illness (Rho=-0.385; p=0.006).

Variables	CIMT	FMD	ABPI
Age (yrs)	P=0.514	P=0.039	p=0.001
Duration of illness (yrs)	P=0.674	P=0.964	p=0.006
BMI (kg/m^2)	P=0.531	P=0.239	P=0.930
RODNAN score	P=0.093	P=0.284	P=0.364
Systolic BP (mmHg)	P=0.562	P=0.994	P=0.223
Diastolic BP (mmHg)	P=0.699	P=0.370	P=0.862
Hb (g/dl)	P=0.049	p=0.60	P=0.325
ESR (mm/hr)	P =0.356	P=0.225	P=0.514
Urea (mg/dl)	P=0.232	p=0.248	P=0.221
Creatinine (mg/dl)	P=0.081	p=0.596	P=0.357
Protein (g/dl)	P=0.313	p=0.535	P=0.706
Albumin (g/dl)	P=0.887	p=0.693	P=0.023
SGOT (U/l)	P=0.989	p=0.337	P=0.289
SGPT (U/l)	P=0.831	p=0.519	P=0.209
Total Cholesterol (mg/dl)	P=0.80	p=0.570	P=0.866
HDL-C (mg/dl)	P=0.427	p=0.195	P=0.513
LDL-C (mg/dl)	P=0.109	p=0.999	P=0.905
VLDL-C (mg/dl)	P=0.425	p=0.898	P=0.968
Triglycerides (mg/dl_)	P=0.469	p=0.025	P=0.146
AST=aspartate aminotransferase, ALT=alanine aminotransferase, HDL=High-density lipoproteins, LDL=Low-density lipoproteins, VLDL=Very low-density lipoproteins			

Table 3: Correlates of CIMT, FMD and ABPI in SSc patients.

We further divided these patients on the basis of age (<35 years; >35 years), disease duration (<2.5 years; >2.5 years), type of SSc (limited or diffuse), presence or absence of digital infarcts and pulmonary fibrosis as shown in Table 4.

We noted a statistically significant decrease in ABPI in the age group >35 years compared to <35 years (0.986 ± 0.095 vs. 1.126 ± 0.094; P=0.001). However, CIMT, FMD and ABPI did not differ significantly between the pattern of skin involvement, presence or absence of digital infarcts or pulmonary fibrosis.

Variables	CIMT(mm)		FMD(%)		ABPI	
	Mean ± SD	P value	Mean ± SD	P value	Mean ± SD	P value
Age						
<35 years(n=25)	0.579 ± 0.092	0.602	6.865 ± 4.204	0.242	1.126 ± 0.094	0.001
>35 years(n=25)	0.592 ± 0.088		8.354 ± 4.761		0.986 ± 0.095	
Disease duration						
<2.5 years(n=25)	0.579 ± 0.090	0.633	6.882 ± 4.037	0.253	1.078 ± 0.122	0.187
>2.5 years(n=25)	0.592 ± 0.089		8.337 ± 4.822		1.034 ± 0.109	
Limited SSc(n=34)	0.587 ± 0.092	0.887	7.185 ± 3.643	0.331	1.061 ± 0.109	0.653
Diffuse SSc(n=16)	0.583 ± 0.084		8.512 ± 5.879		1.045 ± 0.136	
With digital infarcts (n=11)	0.584 ± 0.084	0.965	8.630 ± 6.618	0.396	1.025 ± 0.127	0.318
Without infarcts (n=39)	0.586 ± 0.092		7.322 ± 3.710		1.065 ± 0.114	
With pulmonary fibrosis (n=31)	0.586 ± 0.081	0.964	8.228 ± 4.667	0.214	1.050 ± 0.117	0.666
Without pulmonary fibrosis (n=19)	0.585 ± 0.104		6.601 ± 4.021		1.065 ± 0.119	

Table 4: Comparison of CIMT, FMD and ABPI in SSc patients according to age, duration of disease, type of SSc, digital infarcts and pulmonary fibrosis.

Discussion

Patients with systemic autoimmune diseases are at higher risk of developing cardiovascular diseases than the general population. Significant cardiovascular involvement in SSc indicates a poor prognosis [13]. While there is well established data regarding atherosclerosis and cardiovascular risk factors in RA and SLE [2,14], there is growing evidence that accelerated atherosclerosis occurs in SSc. In particular, the 2010 survey from the European League against Rheumatism Scleroderma Trials and Research (EUSTAR) database estimated that 26% of SSc-related causes of death were due to cardiac causes (mainly heart failure and arrhythmias) and 29% of non-SSc-related causes of death were due to CV causes [15]. Interestingly, a recent cross-sectional analysis of a large United States hospitalization database [1993-2007] estimated that approximately 5.4% of 308,452 SSc hospitalizations were associated with atherosclerotic CV disease as a primary discharge diagnosis. The same study also reported that SSc hospitalizations were more likely to result in death than similar hospitalizations of SLE and control patients [16].

In our study mean age of the patients was 35.26 ± 9.55 years with a female: male ratio of 7.3:1. Our patients were younger than the patients in other published series where it has been shown that the disease mostly affects women in their 4th or 5th decade of life [4-5,17-19]. Limited cutaneous involvement was predominant, which was expected [4-5,20]. Though the mean duration of Raynaud's was more in dcSSc than lcSSc, this difference was not statistically significant (Table 5).

Type	lcSSC	dcSSC	p-value
Age (yrs)	33.59 ± 9.384	38.81 ± 9.19	0.071
Age at onset(yrs)	30.470 ± 8.020	35.396 ± 8.393	0.052
Rodnan Score	18.85 ± 6.885	22.44 ± 9.838	0.183
Median duration of Raynaud's Phenomenon (yrs)	3.00 (1.00-4.00)	2.00 (1.25-3.00)	0.590
Median duration of skin tightening (yrs)	1.00 (1.00-2.00)	2.00 (1.00-3.00)	0.269

Table 5: Disease characteristics between limited and diffuse scleroderma.

Various non-invasive modalities have been described for the detection of subclinical atherosclerosis such as coronary calcium score and B mode Ultrasonography [21]. While some studies have reported that coronary calcium score is a better predictor of cardiovascular risk as compared to CIMT by Ultrasonography [22], the lack of radiation with the latter technique tilted the balance for us.

In our study, even though the absolute value of CIMT did not exceed 0.9 mm, the CIMT in SSc patients were significantly increased

when compared with controls. Similar results have been reported by Lekakis et al. [23], Bartoli et al. [17], Sherer et al. [24], and Kaloudi et al. [25]. However, other studies have failed to find a difference [5,26-30]. Age is an important factor responsible for atherosclerosis, the younger age of our patients implies a much reduced burden of atherosclerosis resulting in lower CIMT values. The difference between the two groups while statistically significant (p=0.001), failed to reach clinical significance (0.015 mm). As has been reported in a previous meta-analysis, a difference of one standard difference between the groups would likely yield a significant clinical risk for cardiovascular events [19].

Our study did not show any correlation of CIMT with age or duration of illness. On the contrary, a study from Hungary showed positive correlation of CIMT with age and disease duration in [27]. This may be due to the fact that their group had a higher mean age (mean 51.8 yrs) and disease duration (mean 9.43 ± 3.78 yrs) when compared with our study population. We did not find any correlation of CIMT with the presence of digital infarcts or with the extent of skin involvement, the same has been noted previously also [27].

Endothelial dysfunction is an early event in atherosclerosis [31]. FMD provides a useful non-invasive measure of endothelium-derived nitric oxide function. We estimated FMD by placing the occluding cuff proximal to the ultrasound probe. Green et al. have previously concluded in their meta-analysis that proximal cuff placement is as predictive as distal cuff placement [31]. We did not find a statistically significant difference in FMD values in SSc patients as compared to controls. Other studies also support our findings [29,32]. FMD values exhibited a weak positive correlation with age (Rho=0.294; P=0.039) and an inverse correlation with serum triglycerides (Rho=-0.316; p=0.025), the same has not been reported previously [27]. Similar to other published data, we did not find any correlation of FMD measurements with duration of disease, types of SSc or digital infarcts [27,29,33].

In our study, ABPI values in SSc patients did not differ significantly with the controls. The same has also been reported by Bartoli et al. [17], kaloudi et al. [25] and Muro et al. [34]. However studies by Ho et al. [35] and Wan et al. [20] had contradictory results. Furthermore, our study revealed a statistically significant inverse correlation with age and duration of disease. This suggests an increased progression of peripheral vascular disease with increasing age and duration of illness.

Our study provides evidence to suggest that markers of peripheral vascular disease and subclinical atherosclerosis are evident in patients with SSc. CIMT, but not FMD or ABPI were increased in patients with SSc as compared to healthy controls. This was seen despite the fact that our patients were younger, had short disease duration and other traditional cardiovascular risks were excluded. Treatment may have a protective effect against atherosclerosis. Immunosuppressants like cyclophosphamide, hydroxychloroquine, and methotrexate are associated with absence of plaques in SLE patients [36]. CIMT and ABPI may prove to be useful for assessing the burden of subclinical atherosclerosis and peripheral vascular disease, respectively, in patients with systemic sclerosis.

One major limitation of our study is the lack of serial measurement of these parameters which may help in a better understanding of the atherosclerotic process in these patients. To the end, larger studies with serial measurement of these parameters are needed.

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