Macrovascular involvement in systemic sclerosis: evidence of correlation with disease activity

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ABSTRACT

Objective. *Systemic sclerosis (SSc) is considered as a systemic disease which mainly affects small vessels. However, macrovascular involvement in SSc is still elusive in literature. Our study is to evaluate the macrovascular involvement in SSc patient and its association with atherosclerosis, disease activity and other factors.*

Methods. *Forty-eight SSc patients were studied; 46 healthy people were enrolled as control subjects. Data on traditional cardiovascular risk factors, disease duration, inflammation indices, antibodies and other vascular involvement were collected. Systolic/diastolic interarm difference (sIAD/dIAD), pulse wave velocity (PWV) and ankle brachial index (ABI) were determined using a pulse pressure analyser. Peripheral arterial disease (PAD) was defined as ABI <0.90.*

Results. *A lower ABI (0.91±0.19 versus 1.09±0.08; p<0.001) and a higher sIAD (5.0 [range 0~35] mmHg versus 2.0[0~15] mmHg, p<0.001) were found in patients with SSc. ABI is negatively correlated with sIAD. Multiple regression analysis revealed that SSc itself (B=0.171, 95% confidence interval 0.090~ 0.252, p<0.001) is an independent risk factor of reduced ABI. Correlation analysis showed MRSS was negatively correlated with ABI (r=-0.419, p=0.003).*

Conclusion. *SSc patients are more likely to develop PAD, which may be a kind of macrovascular disease in SSc. MRSS, a maker of disease activity, is associated with this peripheral artery involvement.*

Introduction

Systemic sclerosis (SSc) is characterised by thickening and fibrosis of skin and internal organs associated with vascular damage. The vascular involvement of SSc has been considered to be mainly microvascular (1). Macrovascular involvement is considered rare. However, increased prevalence of macrovascular disease has been reported in recent literature (2). Coronary artery disease is not uncommon in SSc patients (3), but its prevalence is similar and not greater to that expected in individuals without SSc (4). An increased prevalence of distal peripheral artery disease in the digits has been found in several studies (5-6). Recently, a systematic review and meta-analysis conducted by Au *et al*. demonstrated that SSc patients had increased carotid intima-media thickness and lower flow-mediated vasodilation when compared to controls (7).

Ankle brachial index (ABI) has been validated as a diagnostic tool for lower extremity peripheral arterial disease (8). In American College of Cardiologist/ American Heart Association Practice Guidelines for the Management of Patients with Peripheral Arterial Disease, abnormal ABI value is defined as a continuous variable less than 0.90. ABI values are often considered to be mildly to moderately diminished when they are between 0.41 and 0.90, and severely decreased when ABI ≤0.40 (9). Ho M. *et al*. has proved the increasing prevalence of lower extremity peripheral arterial disease in SSc using ABI (10).

Upper extremity distal arterial disease is also not uncommon in SSc, especially ulnar artery involvement (11), which may lead to Raynaud's phenomenon and refractory digital ulcerations (12-13). Nevertheless, evidence of upper extremity proximal arterial involvement is still unclear. A blood pressure (BP) difference between arms was first reported over 100 years ago. Pooled prevalences of the interarm difference of blood pressure (IAD) from recent systemic review were 19.6% systolic ≥10mmHg, 4.2% systolic ≥20mmHg and 8.1% diastolic ≥10mmHg (14). The presence of IAD is prospectively associated with reduced event-free survival

and is predictor of cardiovascular event in hypertensive patients (15). IAD is now considered as a useful marker for the presence of upper extremity peripheral artery disease.

Pulse wave velocity (PWV) is a non-invasive parameter directly proportional to arterial wall stiffness. It has been proven to be a useful indicator of atherosclerotic vascular damage and correlates with the presence of coronary arterial disease (16-17).

Several factors have been proved to be associated with macrovascular involvement in SSc, including anti-beta (2)-glycoprotein I antibodies, homocysteine level and D-dimer concentration (18-20). A recent study on angiotensin-converting enzyme I/D polymorphism and SSc shows that presence of ACE D allele may predispose to an involvement of macrovascular system (21). However, the underlying mechanisms of these macrovascular abnormalities are still elusive, especially their association with atherosclerosis and disease activity.

The aim of the study was to evaluate the macrovascular involvement in patients with SSc, using ABI (for lower extremities arterial disease), IAD (for upper extremities proximal arterial disease) and PWV. We also try to determine the association between the macrovascular disease and traditional cardiovascular risk factors, disease related factors (anti Scl-70 antibody, modified Rodnan skin thickness score and disease duration) and organ involvements (renal function, pulmonary hypertension and Raynaud's phenomenon) in SSc.

Table I. Comparison of Traditional risk factors between SSc patients and control subjects.

	SSc† group (n=48)	Control group (n=46)	*p*-value
Age, years	46.79 ± 10.22	46.52 ± 9.87	0.897
Male, n. (%)	5/48 (10.4%)	10/46 (21.7%)	0.165
Body mass index, kg/m^2	22.12 ± 3.16	24.66 ± 3.44	<0.001
Overweight (>25.0 kg/m^2), n. (%)	10/48 (31.2%)	19/46 (41.3%)	0.032
Normal weight (18.5~25.0 kg/m^2), n. (%)	29/48 (50%)	23/46 (50%)	0.100
Underweight (<18.5 kg/m^2), n. (%)	9/48 (18.8%)	4/46 (8.7%)	0.158
Blood pressure			
Systolic pressure, mmHg	129.27 ± 18.74	117.60 ± 15.14	<0.001
Diastolic pressure, mmHg	74.69 ± 12.16	71.25 ± 11.20	0.018
Hypertension, n (%)	11/48 (23.9%)	4/46 (8.7%)	0.060
Glucose metabolism			
Fast plasma glucose, mmol/L*	5.28 (4.13~14.39)	4.75 (4.10~12.10)	0.007
Impaired fasting glucose (≥5.6mmol/L), n. (%)	16/48 (33.3%)	5/46 (10.9%)	0.008
Lipid profile			
Total cholesterol, mmol/L	5.48 ± 1.47	5.17 ± 1.49	0.314
Triglyceride, mmol/L*	1.65 (0.58~9.86)	1.37 (0.37~19.13)	0.208
Low density lipoprotein cholesterol, mmol/L	3.17 ± 0.94	2.81 ± 0.89	0.063
High density lipoprotein cholesterol, mmol/L	1.51 ± 0.51	1.41 ± 0.39	0.332
Smoking, n. (%)	5 /48 (10.4%)	5 /46 (10.9%)	1.000
Family history, n. (%)	3 /48 (6.3%)	5 /46 (10.9%)	0.481
Hs-CRP, mg/L*	1.98 (0.15~59.60)	1.05 (0~4.30)	<0.001
Hs-CRP (>3mg/L), n. (%)	17/48 (35.4%)	4/46 (8.7%)	<0.001
Ankle brachial index	0.91 ± 0.19	1.09 ± 0.08	<0.001
Pulse wave velocity, cm/s	1387.32 ± 338.55	1313.45 ± 220.24	0.215
Systemic interarm difference, mmHg*	5.0 (0~35)	2.0 (0~15)	<0.001
Diastolic interarm difference, mmHg*	3.0 (0~17)	2.0 (0~18)	0.012

*Non-normal distribution variable, present as median (range). †SSc: systemic sclerosis.

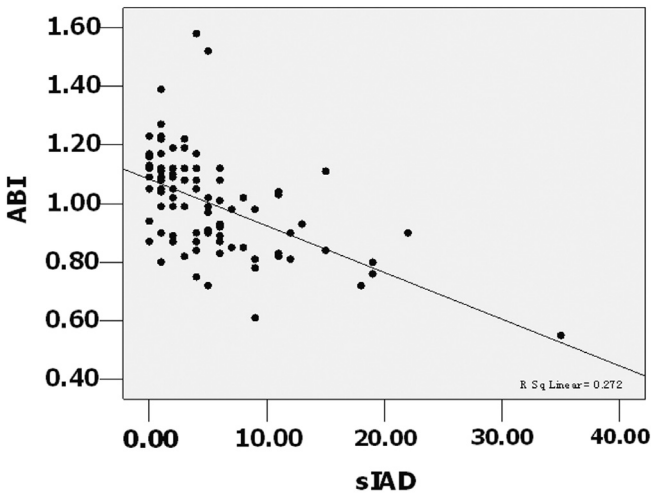

Fig. 1. Relationship between ankle brachial index (ABI) and systolic interarm difference (sIAD).

Materials and methods

Patients

The study was approved by Peking Union Medical College Hospital Institutional Review Board. Forty-eight consecutive patients with an established SSc diagnosis, defined according to the American Rheumatism Association criteria (22), were recruited from the Department of Rheumatology of Peking Union Medical College Hospital. Forty-six healthy subjects were involved in the study from a community-based prospective cohort study of healthy population in Beijing (on-going). All participants enrolled had provided informed consent and none of them refused to participate or withdrew from the study.

Methods

– Laboratory test

Blood pressure was measured at rest in a sitting position for three times. Body mass index was defined as the individual's body weight (kilogram) divided by the square of its height (metre). Fasting plasma glucose, total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), creatinine, high sensitive C-reactive protein

(hs-CRP) were determined by standard methods using Olympus AU5400 chemistry auto-analyser (Olympus, Tokyo, Japan). Anti-Scl-70 antibodies were determined by immunodiffusion against calf thymus extract using commercial kits (INOVA Diagnostics, San Diego, USA).

Modified Rodnan skin thickness score (MRSS) was calculated for each SSc patient. The MRSS is an assessment of the extent of skin thickness in 17 body areas, on a scale of 0~3 (*i.e.* 0=normal, 1=mild skin thickness, 2=moderate skin thickness, and 3=severe skin thickness; maximum score 51). A pre-study training session was held with all examiners to standardise the techniques used to measure the MRSS.

– Echocardiography

Systolic pulmonary arterial pressure (PAPs) was estimated when a tricuspid regurgitation was detected by continuous wave Doppler echocardiogram using conventional transthoracic Doppler echocardiographic examination (Vivid 7, GE, USA). PAPs was measured by adding the estimated right atrial pressure (10 mmHg) to the peak systolic pressure gradient across the tricuspid valve (peak regurgitant velocity).

– Systolic/diastolic interarm difference, ankle brachial index and pulse wave velocity

Systolic/diastolic interarm difference (sIAD/dIAD), ankle brachial index (ABI) and pulse wave velocity (PWV) were determined using a pulse pressure analyser (model BP-203RPE II; Nihon Colin, Japan). The three pairs of BP measurements were averaged to obtain a mean systolic and diastolic BP for each arm, which allowed calculation of the mean sIAD and mean dIAD for further analysis. The ABI was performed by measuring the systolic blood pressure from both brachial arteries and from both posterior tibial arteries after the patient had been at rest in the supine position for 10 minutes, then was automatically calculated by the device as the ratio of systolic blood pressure in the leg to that in the arm on each side and the average value was used for analysis. Pulse waves were recorded using sensors placed on both posterior tibial arteries. Electrocardiograms were obtained with electrodes placed at two points on the left arm and one point on the right arm. The time intervals required for the pulse waves to travel from the heart to both posterior tibial arteries were measured, and the distances between the heart and both posterior tibial arteries were estimated from the patient's height. The best 10 consecutive pulses were analysed, and the average PWV from the heart to the posterior tibial artery was calculated by dividing the distance by the time interval. Two measurements were performed in each leg, and the average value was used for analysis. PWV was expressed in centimeters per second (cm/m).

Statistical analysis

SPSS statistical package was used for analysis. All the data were described as mean ± standard deviation or median (range) in the case of non-normal distribution. Between-group differences were compared by two-sample *t*-tests or Mann-Whitney tests (non-normal distribution) for continuous variables and by chi-square analysis for categorical variables. Multiple linear regression analysis was used to test for independent associations between ABI and various factors. Correlation was tested with Spearman's rank-order or Pearson's correlation coefficient to determine the possible relationship between macrovascular involvement and disease related factors and organ involvements in SSc patients. A significance level was set at $p<0.05$.

Table II. Linear regression analysis of ankle brachial index (ABI).

	B†	95% CI	*p*-value
Age	0.004	0.001~0.007	0.019
Gender	-0.046	-0.155~0.064	0.410
Body mass index	-0.001	-0.013~0.011	0.829
Systolic pressure	-0.002	-0.006~0.001	0.182
Diastolic pressure	0.005	-0.155~0.064	0.092
Fast plasma glucose	-0.006	-0.032~0.020	0.644
Total cholesterol	-0.003	-0.035~0.030	0.871
Triglyceride	0.002	-0.015~0.019	0.845
Low density lipoprotein cholesterol	-0.006	-0.048~0.036	0.785
High density lipoprotein cholesterol	-0.032	-0.177~0.054	0.463
Smoking	0.071	-0.057~0.200	0.273
Family history of CHD*	-0.007	-0.121~-0.001	0.902
High sensitive C-reactive protein	0.002	0.003~0.006	0.487
Systemic sclerosis	0.171	0.090~0.252	<0.001

Multiple coefficient of determination of this model (R2) = 0.437, $p<0.001$.
*CHD: Coronary heart disease. †Unstandardised regression coefficient.

Results

Forty-eight consecutive SSc patients (24 with diffuse and 24 with limited disease) with median disease duration of 69.9 months were recruited. There were no differences in gender ratio, age and lipid profile (including total cholesterol, triglyceride, LDL-C and HDL-C) between two groups (Table I). The SSc patients were more likely to be hypertensive and had higher level of Hs-CRP and FPG than control subjects ($p<0.01$). A lower BMI was also noted in our SSc patients ($p<0.01$), Further categorisation of BMI using WHO/National Heart, Lung, and Blood Institute criteria (23) found that the proportion of overweight was significantly lower while the proportion of underweight was slightly but not statistically higher in our SSc patients. Other traditional cardiovascular risk factors, such as family history of coronary heart disease, current smoking, did not differ between the two groups.

SSc patients had a lower ABI level but a higher sIAD and dIAD level when compared with the control subjects (Table I). ABI correlated negatively with sIAD ($r=-0.521$, $p<0.001$) (Fig. 1). However, PWV did not differ between two groups (Table I).

Then, we included these 48 SSc patients and 46 control subjects in a single group for linear regression analysis. We found factors associated with

reduced ABI were age (B=0.004; 95% confidence interval [CI] 0.001~0.007; p=0.019) and SSc (B= 0.171, 95% CI 0.090~0.252, <0.001) (Table II).

Correlation analysis showed MRSS was negatively correlated with ABI (r=-0.419, p=0.003) (Fig. 2), While disease duration, PAPs and creatinine did not correlated with ABI (all p>0.05). ABI in SSc patients with positive anti Scl-70 antibody did not differ from those without positive anti Scl-70 antibody (0.88±0.20 *vs*. 0.92±0.14, p=0.44).

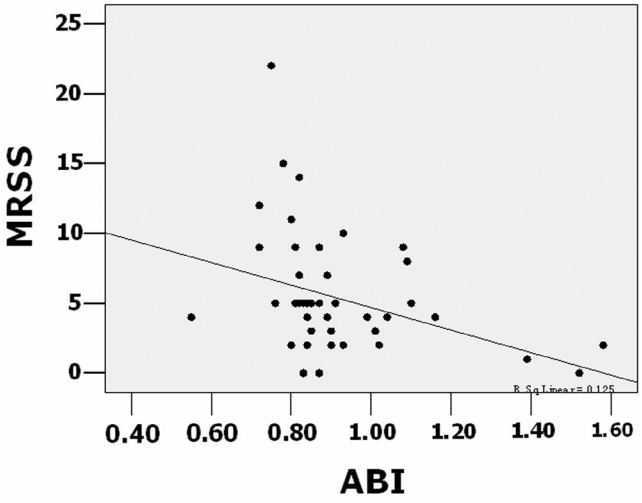

Fig. 2. Relationship between Modified Rodnan skin thickness score (MRSS) and ankle brachial index (ABI).

Discussion

SSc used to be considered as a connective tissue disease which mainly affects small vessel. Our study show that SSc patients have lower ABI compared with control subjects, suggesting that SSc patients are more likely to develop peripheral arterial disease, which means SSc may be associated with large vessel disease. However, our patients do not have a higher PWV, which is a symbol of aortic wall stiffness. This is not consistent with the results of previous studies in non-Chinese population (24).

Several autoimmune rheumatic diseases are characterised by premature and accelerated atherosclerosis in which both classical and non-classical risk factors contribute to atherogenesis. Endothelial dysfunction has been described in patients with SSc, which may precede the atherosclerosis (25). In our study, slight increase in blood pressure and fasting glucose were found in our SSc patients. Lifestyle change is essential to control these traditional cardiovascular risk factors, and further investigation including blood pressure monitor and oral glucose tolerance is also indispensable to establish the diagnosis of hypertension and diabetes. A higher level of hs-CRP may be contributed to the systemic inflammation caused by systemic sclerosis. Besides, BMI is lower in SSc patients. A large scale epidemiological study in China showed that both underweight and overweight were associated with increased mortality in the Chinese adult population. The mortality of underweight (<18.5kg/m^2) was even higher than severe obesity (>30kg/m^2) (26). Thus, the role of low BMI in SSc should be notified and long term follow up is needed for determine the relationship between low BMI and clinical outcomes.

Since the imbalance of these traditional cardiovascular risk factors could be the reasons why SSc patients are tend to have PAD, we perform a linear regression analysis, which shows SSc itself is a risk factor of PAD, independent of other traditional risk factors. Since our study has proven the SSc is an independent risk factor of PAD, and we do not find any relation between PAD and traditional atherosclerosis risk factors, it would be more appropriate if we contribute the PAD mainly to SSc, not to the atherosclerosis.

sIAD is another marker of PAD and a useful indicator of cardiovascular events. In our study, SSc patients have significantly higher IAD (including sIAD and dIAD) when compared with general population and we also find a strongly negative correlation between ABI and sIAD. These again confirm the conclusion that SSc patients are more likely to have peripheral artery involvement, including upper and lower extremities arteries. So far as we know, it is the first time to use IAD to evaluate macrovascular disease in SSc patient in the literature.

Since our findings suggest that SSc is an independent risk factor for PAD, we looked for the underlying mechanism associated with this process. MRSS is a marker of disease activity which associated with visceral involvement and predicted mortality in SSc patients (27-28). Improvement in skin thickening is related to improved survival (29). In our study, MRSS is relative to ABI in SSc patients, which means this macrovascular disease is associated with disease activity. Other disease associated factors, including disease duration, auto-antibodies and parameter of other vascular involvement, do not seem to be associated with PAD and peripheral vascular involvement is not parallel with other vascular involvements such as pulmonary hypertension, renal dysfunction and Raynaud's phenomena. Therefore, we assume that peripheral arterial involvement is another process which is different from other vascular disease in SSc.

Our study has several limitations. First, it is cross-sectional study with a small sample size and it does not estimate the true magnitude of the contribution of variables such as disease activity and therapy. A large-scale prospective study might demonstrate a greater effect over time. Second, our study has shown the association between SSc and reduced ABI, but the mechanism by which SSc promotes PAD is still unclear. Further study is needed for the better understanding of their relationship.

Based on the results of the study, we have found that SSc itself may be a risk factor of PAD, which is independent of traditional atherosclerosis risk factors. It implies that PAD in SSc may be a kind of macrovasular disease, not atherosclerosis. This peripheral artery involvement is relative to MRSS which is maker of disease activity.

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