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TITLE PAGE

Title: Systemic sclerosis is associated with lower-limb vascular stiffness and microvascular impairment: results from a prospective study

Running title: Lower-limb arterial impairment in systemic sclerosis

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ABSTRACT

Objective: systemic sclerosis (SSc) is a connective tissue disease characterized by microangiopathy. Peripheral arterial disease, increasingly studied during SSc, is responsible for digital ulcers in the upper limbs, associated with a high risk of amputation. The aim of our study was to assess the frequency of lower-limb arterial impairment in SSc patients by measuring ankle-brachial index (ABI), toe pressure (TP) and toe-brachial index (TBI).

Methods: systemic sclerosis patients were included prospectively during one year in Tenon and Saint-Antoine Hospitals, Paris. Clinical and biological data were recorded. For each patient, ABI, TP and TBI were measured and an arterial duplex ultrasonography was prescribed if case of abnormal results.

Results: 86 patients were included (94% women, median age 62 years). Only 24% of them had no lower-limb hemodynamic vascular abnormalities; 44% had an isolated microvascular abnormality (normal ABI and $TBI < 0.75$); 31% had at least a macrovascular injury associated or not with microvascular impairment (abnormal ABI) and 12.6% had a $TP < 50$ mmHg.

Conclusion: by measuring ABI and TP, we showed that 76% of SSc patients had hemodynamic arterial lower-limb abnormalities related to macro- and/or microvascular impairment and that 28% had vascular stiffness. In SSc patients, ABI is not an accurate tool to detect lower limb arterial disease, likely due to underlying micro- and macrovascular changes.

Key words: systemic sclerosis, ankle-brachial index, toe-brachial index, peripheral arterial disease, microangiopathy, vascular stiffness

Key-points:

- The presence of lower-limb macro-and/or microvascular involvement was detected in 76% of SSc patients.
- In SSC patients, ABI is not an accurate tool to detect lower limb arterial disease, likely due to underlying microvascular changes and frequent arterial stiffness

DECLARATIONS

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MANUSCRIPT

Systemic sclerosis (SSc) is an autoimmune disease characterized by microvascular damage, obliteration and innate and adaptive immunity dysregulation leading to tissue fibrosis. Vascular dysfunction and endothelial damage play a central role in the pathogenesis of SSc [1] and digital ischemia is the most characteristic clinical manifestation. Whereas microvascular involvement is considered to be the hallmark of SSc, several studies have shown the increased prevalence of macrovascular arterial disease and the presence of early and accelerated atherosclerosis, particularly in the lower limbs [2, 3]. Macrovascular arterial impairment in SSc may worsen the digital ischemia related to microvascular disease, leading to an increased risk of ischemic ulcers in the lower and upper limbs [3].

Routine tests to detect and diagnose peripheral arterial disease (PAD) include physical examination, hemodynamic measures, such as ankle brachial pressure index (ABI) and toe-brachial pressure index (TBI), and imaging assessment by lower-limb duplex ultrasonography (US) or angiography [2, 4]. The palpation of foot pulses, recommended in daily practice, is not reliable in SSc patients due to skin sclerosis or leg edema.

ABI is calculated by dividing the ankle systolic pressure by the brachial systolic pressure. Measuring ABI is internationally recommended to assess peripheral vascular status in patients at risk of PAD [5]. Normal values are between 0.9 and 1.3. An ABI below 0.9 indicates the presence of PAD with high sensitivity and specificity [6]. Decreased sensitivity and specificity of ABI measurement for PAD has been demonstrated in the elderly and in patients presenting diabetes mellitus or chronic renal failure. In these cases, ABI may be falsely normal or above 1.3 because of the loss of ankle artery compressibility [7]. In such situations, measuring toe pressure and toe-brachial index (TBI) has been shown to be an

indicator of proximal or distal peripheral arterial impairment as the measure of toe pressure is never affected by arterial stiffness [8]. TBI is the ratio between the systolic toe pressure and the systolic brachial pressure, with normal values greater than 0.70 or 0.75, depending on recommendations [9]. TBI has been shown to have greater clinical efficacy in the diagnosis of PAD than ABI but is less accessible in routine practice.

The primary aim of this prospective study was to assess the frequency of lower-limb arterial impairment in SSc patients by measuring ABI and TBI, complemented if necessary, by lower-limb duplex US imaging. In addition, we determined clinical characteristics that are associated with abnormal TBI at inclusion and during follow-up.

PATIENTS AND METHODS

This prospective, observational, cohort study, using routinely collected data, was conducted in compliance with the Declaration of Helsinki, between 2015 and 2019. According to French law, formal Ethics Committee approval was not required for this type of study. Consecutive SSc patients were recruited between 2015 and 2016 from the Tenon Hospital Dermatology Department and the Internal Medicine Department of Saint Antoine Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France, then followed-up until 2019. All patients included fulfilled the 2013 ACR/EULAR criteria for SSc [1] and attended the hospital for a routine follow-up visit. Oral consent was collected from all patients included.

Clinical assessment

Patients' medical histories and treatments were assessed, and they underwent a complete physical examination. Patients were systematically evaluated for the presence of arterial hypertension and pulmonary, cardiac, esophageal and renal involvement.

During follow-up, major adverse events (MAE) were defined as all-cause mortality, non-fatal stroke, non-fatal myocardial infarction and lower-limb ischemic manifestations.

Measurement of arterial pressure and duplex US imaging

Examinations were performed, once at inclusion, in a room with a temperature over 24°C and patients' feet were warmed to obtain a cutaneous temperature of 28°C, verified by infrared cutaneous thermometer, to avoid any impact of a possible phenomenon of Raynaud on the measurement[10]. Measurements were performed after 10 minutes' rest in supine position.

Ankle systolic pressure in the dorsalis pedis and posterior tibial arteries at the ankle were measured using an 8-MHz Doppler probe and a cuff (12 cm) around the lower leg just above the ankle.

For toe blood pressure, a cuff with a width depending on the diameter of the hallux (1.5, 2.5, or 3.3 cm disposable cuffs, Hokanson, Bellevue, Washington) was wrapped around the base of the toe. Two standard laser Doppler (LD) probes (PF 408, Perimed, Järfälla, Sweden) connected to the LD instrument (Periflux 4001, Perimed, Järfälla, Sweden) were attached to the apex of the big toe with double-sided adhesion tape with a notch for the probe (Double-Stick Discs, 3M Health Care, Borken, Germany) and a probe holder (PF 104, Perimed Järfälla, Sweden). The cuff was rapidly inflated to a pressure at least 30 mmHg higher than that at which the pulsations in the LD 0.03 signal disappeared. Initially, the LD showed an increase in flux, after which the signal declined to the baseline. After the LD signal had reached a stable baseline (after approximately 3 seconds), the cuff was slowly deflated with a speed of approximately 3 mmHg/s. The systolic pressure was defined as the pressure at which the (pulsatile) signal reappeared or rose gradually from the baseline.

ABI and TBI were calculated as the highest ankle (dorsalis pedis or posterior tibial artery) and toe systolic pressures divided by the highest brachial systolic pressure, respectively. We performed measurement on both legs and considered the worst result.

For patients with abnormal TBI and/or ABI, a color duplex US was conducted on the lower limbs. Peripheral arterial disease was defined as the presence of parietal thickening, and stenosis was defined as the presence of one > 50% stenosis, in any studied artery.

Classification of lower-limb hemodynamic vascular involvement

Consistent with current guidelines [11], an ABI value <0.9 indicated the presence of a PAD with hemodynamic stenosis, an ABI ≥ 0.9 and ≤ 1.3 was considered as normal and an ABI >1.3 as evidence of loss of arterial compressibility. Although there is no consensus on the pathological limit, TBI values <0.75 were considered to reflect the presence of peripheral lower-limb arterial involvement as validated in a case-control study on diabetes patients [12]. A low ABI value always implies a decreased TBI value as the latter is measured on more distal arteries. For normal ABI values, TBI may be either normal in absence of peripheral arterial involvement or decreased in cases of falsely normal ABI related to a partial loss of artery compressibility or in cases of isolated distal arterial involvement (below the ankle).

We classified patients as follows, according to clinical examination, using ABI and TBI:

- **normal hemodynamic status** (normal ABI and TBI);
- **lower-limb arterial impairment** (low TBI):
 - isolated microvascular impairment (low TBI associated with both normal or high ABI and absence of arterial stenosis on lower-limb duplex US);
 - macrovascular impairment (TBI and ABI both low; or low TBI with arterial stenosis on lower-limb duplex US, regardless of ABI);

- **isolated arterial vascular stiffness** (isolated ABI >1.3 with normal TBI).

Statistical analysis

Quantitative variables were reported as median and interquartile range (IQR), qualitative ones by number and percentage. Univariate comparisons between cases and controls used Mann–Whitney tests, for quantitative variables, and Pearson’s χ^2 tests or Fisher’s exact tests, for qualitative variables. Time to event analysis was done using Kaplan-Meier method and groups were compared by the log-rank test. The multivariate logistic regression model was used to identify parameters independently associated with low TBI with a stepwise procedure based on *Akaike Information Criterion* (AIC). Variables with $p < 0.1$ in the univariate analysis were included in the multivariate logistic regression model. Age, gender and digital ulcers were forced into the model for adjustments.

Two-tailed “p” less than 0.05 was considered statistically significant. Statistical procedures were performed using R version 3.1.3 statistical software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Characteristics of patients

Eighty-six patients were included between September 2015 and September 2016, 74.4% of them presenting limited cutaneous systemic sclerosis (Table 1). The median follow-up was 29.3 months, IQR: [24.70-31.8] and 6 patients out of 86 were lost to follow-up.

Clinical manifestations of lower-limb peripheral arterial involvement

All patients presented Raynaud phenomenon, 66 (76.7%) had no other clinical vascular manifestations (i.e. abnormal pulse, vascular claudication, rest pain), 11 (12%) had isolated abnormal pulses at the ankle, without functional signs, and 7 (8%) had both abnormal pulses at the ankle and functional signs. Vascular claudication was present in 6 patients and rest pain in 2 patients.

Normal hemodynamic status is rare during SSc

Only 21 (24.4%) SSc patients had no lower-limb hemodynamic arterial involvement characterized by both normal ABI comprised between 0.9 and 1.3 and normal TBI>0.75 (Figure 1).

Most SSc patients exhibit decreased distal arterial perfusion in the lower limbs

Considering all cases with a TBI<0.75, impairment of distal arterial perfusion was present in 53 (61.6 %) patients (Figure 1).

Isolated microvascular impairment

Thirty-eight (44%) had isolated distal perfusion impairment defined as a TBI<0.75, associated with a normal or high ABI and a normal duplex US. Among them, 9 had a high ABI reflecting microvascular impairment associated with arterial stiffness.

Peripheral arterial disease

PAD was present in 8 (9.3%) patients. Among them, an ABI<0.9 and a TBI<0.75 reflecting an arterial stenosis above the ankle were found in 3 patients. A normal or high ABI associated

with a low TBI and a significant arterial stenosis above the ankle on duplex US was found in 5 other patients.

Among patients with a low TBI, a duplex US could not be obtained in 7 patients who therefore could not be classified as patients presenting PAD or isolated microvascular impairment.

High prevalence of isolated arterial vascular stiffness

Elevated ABI with normal TBI was found in 12 (14%) patients, reflecting isolated arterial vascular stiffness. For these patients, all duplex USs we obtained were normal (Figure 1).

Abnormal TBI is associated with clinical manifestations

We considered a $TBI < 0.75$ for univariate and multivariate analysis. In univariate analysis, the low TBI group had lower-limb sclerosis (OR=7.44, $p=0.02$) and were treated more commonly with statins (OR=3.59, $p=0.04$), calcium channel blockers (OR=4.17, $p=0.01$) and iloprost (OR=3.22, $p=0.04$). Multivariate analysis did not reveal any significant association between the presence of an abnormal TBI and clinical or biological SSc characteristics.

Among 46 patients who had both low TBI and an available duplex US, parietal vascular infiltration was observed in 26 patients and significant stenosis only in 6 patients. The mean follow-up duration was similar in both groups (29 [22.75-31] months in the low-TBI group and 28 [23-31] months in the normal-TBI group, $p=0.13$) and mean time to MAE from diagnosis, defined by the beginning of Raynaud phenomenon was 18.2 [8.6-35.9] years. During follow-up, there was a trend towards association of low TBI with more MAE (all-cause mortality, non-fatal stroke, non-fatal myocardial infarction and lower-limb ischemic

manifestations) than normal TBI, though this trend was not statistically significant ($p=0.08$) (Table 2)(Figure 2).

DISCUSSION

In this study, 76% of SSc patients presented a lower-limb peripheral hypoperfusion and 28% an elevated ABI in line with arterial stiffness. Moreover, among the 68% of SSc patient who had a normal ABI, more than half also had a low TBI, reflecting either isolated microvascular disease or falsely normal ABI due to the frequent presence of vascular stiffness. Low TBI at inclusion was associated with MAE during follow-up, although not significantly, probably due to lack of power.

To our knowledge, our study was the first to evaluate the frequency of arterial stiffness during SSc ($ABI>1.3$), and to assess peripheral perfusion by measuring both ABI and TBI. The high frequency of arterial stiffness seems consistent with the pathophysiology of the disease, which associates early vascular and inflammatory alterations, and progressive vessel wall thickening. The association of a low TBI with a normal ABI is higher in our study (44%) than in the general population or in populations suspected of PAD, where it was estimated to be between 9% and 27% [8]. In SSc patients, ABI measurement alone is not a valid tool to detect early peripheral hypoperfusion for two reasons. First, vascular stiffness is frequent, and ABI may be falsely normal in this case, as has already been reported in diabetic patients [7]. Studies comparing mean or median ABI between SSc and controls may therefore underestimate the prevalence of PAD in this population. Second, SSc microvascular disease may have an additive effect on proximal arterial impairment, worsening the peripheral ischemia. In view of our results, ABI alone should not be used to test for lower-limb arterial

disease in SSc patients, but in combination with TBI, or with duplex US if TBI is not available [9].

Macrovascular involvement during SSc is characterized by the formation of a neointima leading to intimal hyperplasia. The relative risk of lower-limb arterial involvement during SSc is estimated between 4.4 and 9.2. Moreover, a recent systematic review showed that SSc was an independent risk factor of coronary heart disease (OR between 1.7 and 3.3) [13].

Our study has some limitations: first, despite a reasonable population cohort we were not able to reach significance concerning the association between TBI and MAE because of a short follow-up duration, second as discussed below there is no consensual TBI value in the literature. Finally, as it was an observational non interventional study, we could not obtain US doppler from patients with normal TBI/ABI and from a control population.

There is no consensus on the pathological limit of TBI. We chose 0.75 as it had been validated in a case-control study on diabetes patients [12]. Some guidelines proposed a TBI threshold of 0.7, but did not include any references offering strong support for this limit [9].

The prevalence of low ABI<0.9 in our population was comparable to that reported in the general population: we observed it in 3.49% (95% CI 0.00% to 7.37%) of patients, compared to 4.3% (95% CI 3.1% to 5.5%) in the general population defined from the National Health and Nutrition Examination Survey, 1999–2000; this population was characterized by a mean age of 56.5yo, 48% were male and 76.9% had cardiovascular risk factor[9]. Our results are in accordance with the studies of Bartoli et al. [14] and Kaloudi et al.[15], who reported a prevalence of low ABI in SSc patient of 5.3% and 4.5%, respectively. Only Ho et al.[16] found a greater prevalence of low ABI, at 17%.

Monitoring of traditional cardiovascular risk factors is required in cases of micro- or macrovascular impairment, such as the implementation of preventive measures to avoid traumatic wounds on the feet. Although it did not reach significance, a low TBI seems to be associated with overall prognosis in SSc patients, highlighting the fact that these patients should be carefully managed regarding cardiovascular disease.

In this prospective study, we showed that 76% of SSc patients had hemodynamic arterial lower-limb abnormalities and that 28% had vascular stiffness, illustrated by an elevated ABI, which in any case appears to be a poor indicator when screening for PAD during SSc. Measuring toe pressure seems essential in diagnosing lower-limb PAD during SSc, as it is recommended in diabetes mellitus and chronic kidney failure, two factors also associated with arterial stiffness.

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TABLES

Table 1. Clinical and biological characteristic of patients

	<i>n=86 (%) [IQR]^a</i>
DEMOGRAPHY	
median age (years)	62 [53-71.8]
sex	women: 81 (94) men: 5 (6)
CARDIOVASCULAR RISK FACTORS	
median BMI ^b (mg/m ²)	22.5 [20.5-26.3]
chronic kidney failure ^c	9 (10)
history of MAE ^d	4 (4.7)
diabetes mellitus	6 (7)
high blood pressure	18 (20.9)
smoking	17 (19.8)
dyslipidemia	18 (20.9)
family history of cardiovascular disease	8 (9.3)
CLINICAL PRESENTATION OF systemic sclerosis	
median disease duration since Raynaud (years)	15 [9-22]
median disease duration since other symptoms (years)	10 [5-16]
median Rodnan score at inclusion	5 [2-11.8]
lung involvement	30 (35)
pulmonary arterial hypertension	5 (5.8)
cardiac involvement	2 (2.3)
GERD ^e	64 (74.4)
renal crisis	1 (1.2)
VASCULAR CLINIC	
digital ulcers (present or history)	33 (38)
lower-limb ulcers (present or history)	6 (6.9)
history of amputation	8 (9)
history of revascularization	2 (2.3)
toe necrosis (present or history)	3 (3.5)
BIOLOGY	
anti-centromere	56 (65)
anti-topoisomerase	16 (19)
anti-ARN pol III	3 (3.5)

^a IQR: interquartile range. ^b BMI: body mass index. ^{SSc}: systemic sclerosis. ^c clearance<60 mL/min. ^d MAE: major adverse events, ^e GERD: gastroesophageal reflux disease. Qualitative data are expressed in number and %; quantitative data are expressed in median and 1st-3rd quartile.

Table 2. Characteristics of patients at inclusion and during follow up between normal and low TBI

	Low TBI ^a (n=53)	Normal TBI (n=33)	p value
ABI ^b			
normal ABI	n=38	n=21	p=0.22
low ABI	n=3	n=0	
high ABI	n=12	n=12	
DEMOGRAPHY			
Median Age (years)	64 [53-75]	66 [57-71]	p=0.9
Median disease duration (years)	15 [8-21]	16 [10-25]	p=0.53
VASCULAR CLINICAL MANIFESTATIONS			
functional signs	n=6	n=0	p=0.07
lower-limb ulcers	n=5	n=1	p=0.39
upper-limb ulcers	n=24	n=9	p=0.11
DUPLEX ULTRASONOGRAPHY (US)	n=46	n=9	
normal US	n=20	n=4	p=0.99
US vascular infiltration	n=26	n=5	
US stenosis	n=6	n=0	p=0.57
AUTO ANTIBODIES			
Centromers (n=56)	n=35	n=21	
Topo-isomerase (n=15)	n=9	n=6	P=0.98
ARN pol III (n=3)	n=2	n=1	
No antibodies (n=12)	n=8	n=4	
EVENTS DURING FOLLOW-UP			
MAE ^c	n=9	n=1	p=0.08

^a TBI: toe-brachial index. ^b ABI: ankle-brachial index. ^c MAE: major adverse events. Qualitative data are expressed in number; quantitative data are expressed in median and 1st-3rd quartile. Groups have been compared by Pearson's χ^2 tests, Fisher's exact tests or Mann-Whitney tests as appropriate.

FIGURES LEGENDS

Figure 1. Graphical representation of the lower-limb arterial vascular involvement during systemic sclerosis based on ankle-brachial index, toe-brachial index and ultrasonography Doppler

Patients are categorized as follows: green – normal hemodynamic status; orange – macrovascular lower-limb arterial impairment; yellow – microvascular lower-limb arterial impairment; blue – isolated arterial vascular stiffness; pink – uncategorized.

Height of boxes are proportionate with percentages of patients.

Figure 2. Kaplan-Meier curve of MAE (all-cause mortality, non-fatal stroke, non-fatal myocardial infarction and lower-limb ischemic manifestations) between inclusion in the study and last follow-up. Low TBI group is represented in red and normal TBI group is represented in blue. Log-rank p value, $p=0.1$.