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ORIGINAL ARTICLE

Established coronary artery disease in systemic sclerosis compared to type 2 diabetic female patients: a cross-sectional study

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Abstract

Introduction Systemic sclerosis (SSc) is an autoimmune disease characterized by endothelial dysfunction, which is also associated with other disorders, such as atherosclerosis. The direct role of SSc in facilitating cardiovascular events should be clarified. We compared the prevalence of established coronary artery disease (CAD) between SSc and type 2 diabetes, a well-known phenotype associated with high cardiovascular risk.

Methods In this cross-sectional study, we evaluated a cohort of 290 unselected female SSc patients, in comparison with 265 aged-matched female type 2 diabetics. "Established CAD" was defined as previous myocardial infarction, unstable angina or ischemia documented by ECG and troponin elevation, necessity/previous treatment with coronary angioplasty or stenting. Age subgroups < 45 (Q1), 45–54 (Q2), 55–64 (Q3), 65–74 (Q4), and ≥ 75 (Q5) years were considered for SSc and diabetes.

Results CAD prevalence resulted lower in SSc patients than in diabetics (10% (95%CI 6.9–14.1) versus 19.2% (95%CI 14.9–24.4); $p = 0.0023$). In Q2 patients, CAD never occurred in SSc (95%CI 0–8.4), but in 9.4% of diabetics (95%CI 3.7–20.7, $p = 0.0567$); in Q3 subjects, CAD was reported in 5.6% (95%CI 1.8–13.8) of SSc, but in 20% (95%CI 12.4–30.5) of diabetics ($p = 0.0127$). Instead, for Q4 and particularly Q5 patients, CAD prevalence was comparable in SSc and diabetes.

Conclusions The prevalence of established CAD in SSc was lower compared with diabetics. However, in older SSc patients the prevalence of CAD was similar to that observed in diabetics.

Keywords Coronary artery disease · Diabetes · Scleroderma · Systemic sclerosis

Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterized by an overproduction of collagen by altered fibroblasts and endothelial dysfunction leading to diffuse microangiopathy [1]. Clinically, Raynaud's phenomenon, digital ulcers, renal crisis, and pulmonary arterial hypertension are typical microvascular manifestations of SSc. In addition, a number of recent studies showed a macrovascular involvement in these patients, as revealed by the detection of aortic wall stiffness, vascular intima-media thickening, or impaired flow-mediated dilatation [2–4]. On the other hand, the endothelial dysfunction and diffuse vasculopathy are also known features associated with atherosclerosis, even though plaque formation is prerogative of the latter [5]. In addition, SSc patients with long-lasting disease may develop atherosclerotic alterations more frequently compared to the general population, probably because of the SSc-associated chronic inflammation, a

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predisposing condition to atherosclerosis [2]. Indeed, previous studies found higher common carotid intima-media thickness, increased aortic pulse wave velocity, and lower flow-mediated dilatation measured by Doppler ultrasonography in SSc patients compared to controls, suggesting a direct role of SSc in atherosclerosis development [6–11]. In these lights, a clear-cut differentiation between sclerodermic and atherosclerotic vascular changes is often very difficult in the clinical practice.

In type 2 diabetes mellitus (T2DM), a chronic metabolic disorder secondary to insulin resistance, atherosclerosis represents a very frequent long-term complication responsible for both diffuse microangiopathy (i.e., diabetic retinopathy and nephropathy) and macrovascular disorders including cardiovascular manifestations [12, 13]. So, T2DM may represent an interesting condition for comparison with SSc regarding both micro- and macrovascular angiopathy and related target-organ damages such as coronary artery disease (CAD). The latter was found to occur more frequently in SSc patients than in the general population [14]. Therefore, in this cross-sectional study, we aimed to compare the prevalence of established CAD in two large SSc and T2DM Italian patient series.

Patients and methods

Patients

A cohort of 290 consecutive unselected SSc female patients (age 62.8 ± 13.2 years; Table 1), who fulfilled the 2013 ACR/EULAR Classification Criteria for SSc [15], referred to the university-based rheumatology unit from January 2003 to June 2017 was evaluated.

As control group, we used a cohort of 265 consecutive aged-matched type 2 diabetic female subjects (age 63.8 ± 11.2 years), recruited in the CATAMERI (CATAnzaro MEtabolic RIsk Factors) Study at the Geriatrics Unit, University Magna Graecia of Catanzaro, Italy [16].

The present study was approved by the Ethical Committee of Modena (protocol no. 282/15); moreover, all patients gave their written consents. All clinical and laboratory data considered for the study came from the patients' clinical records.

Methods

The assessment of SSc visceral organ involvement included spirometry and diffusion lung for carbon monoxide (DLCO) test, high-resolution computed tomography that evidenced the occurrence of interstitial lung disease (ILD), echo-Doppler cardiography, barium esophagus X-ray, and thyroid ultrasound examination. The latter along with the eventual positivity of anti-thyroglobulin or anti-thyroperoxidase defined Hashimoto's thyroiditis. Chronic renal failure was defined as creatinine-based approximation of the glomerular filtration rate at least < 50 ml/min/1.73 m^2. SSc-related gastrointestinal involvement stands for motility dysfunctions of the digestive tract (particularly the esophagus). The treatments taken by the SSc patients at the time of the study were also reported.

Table 1 Summary of 290 SSc patients' features

Age at end of follow-up (years)	62.8 ± 13.2
Disease duration (years)	11.4 ± 7.4
Deceased	39 (13.4)
For cardiac cause	6 (2.1)
SSc features	
Limited/diffuse skin subsets	254/36 (88/12)
Digital ulcers	161 (55.5)
Gastrointestinal inv.	148 (51)
Scl70/ACA/ANoA	94/138/42 (32/47/14)
ILD	165 (56.9)
PAPs ≥ 45	39 (13.4)
ESR > 30 mm/h	84 (28.9)
Treatments	
Ca-channel-blockers	254 (87.6)
Low-dose aspirin	211 (72.7)
Prostanoids	211 (72.7)
Bosentan	75 (25.9)
Sildenafil	15 (5.2)
Steroids	161 (55.5)
Immunosuppressors	65 (22.4)
ACE inhibitors	30 (10.3)
Statins	27 (9.3)
Beta-blockers	17 (5.9)
Diuretics	34 (11.7)

The table illustrated the main features of SSc patients at the end of follow-up. No significant differences between subgroups as regards treatments were found. Data are expressed as mean ± standard deviation, or number of cases (%). *Scl70*, anti-topoisomerase I antibodies; *ACA*, anticentromere antibodies; *ANoA*, antinucleolar antibodies; *ILD*, interstitial lung disease; *PAPs*, systolic pulmonary arterioal pressure (estimated by means of echocardiography); *ESR*, erythrocyte sedimentation rate

The presence of cardiac disease was evaluated by anamnestic records, electrocardiograms (ECG), and 2D echocardiography. Left ventricular measures were obtained by M-mode with 2D guidance at conventional levels, according to the American Society of Echocardiography recommendations [17]. Right ventricle end-diastolic diameter was measured in apical four-chamber view at middle level. PAPs was estimated using Doppler recordings of tricuspid regurgitation, measuring the peak velocity of the tricuspid regurgitation jet.

In both SSc and T2DM patients, the presence of established CAD (fatal and non-fatal myocardial infarction, unstable angina, coronary revascularization procedures (percutaneous interventions and bypass graft surgery)) was reported. In order to consider age-dependent variability, age subgroups < 45

(Q1), 45–54 (Q2), 55–64 (Q3), 65–74 (Q4), and ≥ 75 (Q5) years were considered separately.

Finally, the presence of obesity (body mass index > 29.9 kg/m^2), hypertension (blood pressure > 140/90 mmHg or specifically treated with anti-hypertensive therapy), hypercholesterolemia (total cholesterol > 200 mg/dl or ongoing treatment with statins or ezetimibe), and tabagism were recorded. Statistical descriptive analysis was made using mean ± standard deviation for continuous variables which were normally distributed. Proportions for categorical data were represented as percentages. For the inferential analysis, we used Fisher's exact test or the chi-square test, as appropriate. Moreover, the 95% intervals of confidence were obtained with the modified Wald method. For the comparison between SSc patients and diabetics, we did not consider SSc women who were also affected by diabetes.

Finally, a multinomial logistic regression was made in order to evaluate the impact of both SSc features and cardiovascular risk factors for CAD development; the variables were as follows: age, presence of hypertension, smoking, hypercholesterolemia, obesity, and SSc features (skin subset, serology, digital ulcers, interstitial lung disease, pulmonary hypertension, gastrointestinal involvement, VES > 30 mm/h, and drug exposure). Data were considered significant for a $p = 0.05$.

Results

Clinical characteristics of SSc patients are reported in Table 1. Both in SSc and T2DM series the frequencies of the major cardiovascular risk factors are reported in Table 2. The prevalence of CAD in SSc and diabetes series is indicated in Table 3.

Age variability was taken into account comparing the respective age SSc and diabetes subgroups (< 45, 45–54, 55–64, 65–74, and ≥ 75 years).

Of note, in SSc patients, the CAD prevalence appears associated with age and increases abruptly up to more than 25% in women ≥ 75 years old.

For the comparison between SSc patients and diabetics, we did not consider SSc women who were also affected by diabetes (9 cases). The comparison of SSc and diabetes series showed that the overall CAD prevalence is significantly higher in diabetic patients, as expected (SSc: 28/281 patients, 10%, 95%CI 6.9–14.1 versus 51/265 patients, 19.2%, 95%CI 14.9–24.4; $p = 0.0023$). However, looking at age subgroups, the statistical difference resulted significantly for Q3 subjects (4/72 SSc patients, 5.6%, 95%CI 1.8–13.8 versus 15/75 T2DM patients, 20%, 95%CI 12.4–30.5; $p = 0.0127$). The significance did not reach the conventional level for Q2 patients (SSc: 0/51 patients, 95%CI 0–8.4 versus 5/53 patients, 9.4%, 95%CI 3.7–20.7; $p = 0.0567$). Otherwise, for Q4 and Q5 patients, the difference between SSc and diabetic CAD frequencies was completely lost.

As compared with SSc (Table 2), diabetic women showed a significantly higher prevalence of hypertension, hypercholesterolemia, and obesity, as expected, so explaining the higher rate of CAD. Notably, tabagism was more frequent in SSc patients than in diabetics (30.7% vs 16.6%, $p < 0.0001$), probably reflecting socio-cultural differences between the women living in the area of Modena (Emilia-Romagna, Northern Italy) and the women living in the area of Catanzaro (Calabria, Southern Italy).

Among a total of 30 SSc patients with CAD, 2 were affected also by diabetes (excluded in the comparison study with the diabetic series, Tables 2 and 3). Concerning the other 28 SSc patients, 11 have mild hypercholesterolemia (9/11 treated with statins), 7 presented former smoking habit, and 21 have hypertension (all treated with calcium channel blockers). Indeed, in the majority of SSc patients who developed CAD, the estimated cardiovascular risk considering the classical risk factors [18] was low.

Finally, considering the whole SSc series, CAD was significantly and independently associated with age ($p < 0.0001$),

Table 2 Comparison of cardiovascular risk factors between SSc and diabetes women

	SSc patients (281)		Diabetes patients (265)		SSc vs Diab.
CV risk factors	*n*	%	*n*	%	*p* values
Mean age (± SD), years	62.8 ± 13.2		63.8 ± 11.2		ns
Hypertension	104	37	241	90.9	< 0.0001
Tabagism	84	29.9	44	16.6	< 0.0001
Hypercholesterolemia	64	22.8	109	41.1	< 0.0001
Obesity	0	0	154	58.1	< 0.0001
CAD	28	10	51	19.2	0.0031

The table shows the frequencies of the major cardiovascular (CV) risk factors in 265 diabetic women and 281 SSc female patients (290 cases less 9 patients affected also by diabetes). CAD cases were summarized at the bottom of the table. In the last right column, the statistical comparison between diabetics and SSc patients is illustrated. Notably, tabagism is significantly more frequent in SSc than in diabetics

Table 3 Prevalence of CAD in SSc and diabetes series and in the general population

Age	SSc (281)			Type 2 diabetes (265)			*p* values
	n	%	95%CI	*n*	%	95%CI	SSc vs. diabetes
< 45	0/27	0	0–14.8	0/9	0.0	0–34.5	ns
45–54	0/51	0	0–8.4	5/53	9.4	3.7–20.7	ns
55–64	4/72	5.6	1.8–13.8	15/75	20.0	12.4–30.5	0.0127
65–74	9/74	12.2	6.3–21.7	17/75	22.7	14.6–33.4	ns
≥ 75	15/57	26.3	16.5–39.1	14/49	26.4	16.3–39.7	ns
Total	28/281	10	6.9–14.1	51/265	19.2	14.9–24.4	0.0023

The table illustrates the frequencies (numbers and percentages) plus 95% confidence intervals of CAD in each age subgroup, in 281 SSc (290 cases less 9 patients affected also by diabetes) and 265 diabetes case series. The findings of statistical analysis between SSc and diabetic patients are listed in the right column

Overall, diabetic women present more CAD cases than SSc. Notably, CAD prevalence in diabetes is higher in the age group 45–54 years, even if the statistical significance was not reached because of the small number of cases ($p = 0.057$). This difference becomes evident in the age group 55–64 years, while in the over 65 women, the prevalence of CAD in SSc tends to reach the values of diabetics

systemic hypertension ($p < 0.0001$), and pulmonary arterial hypertension ($p < 0.009$) as the unique SSc-related feature. Moreover, considering the significantly lower blood levels of total cholesterol and the lower prevalence of obesity in SSc series, we might assume that the gastro-esophageal SSc involvement stimulated a more balanced diet without lipid or sugar excesses.

Discussion

In the present study, we compared two cohorts of SSc female patients and diabetic women, regarding CAD prevalence. On the whole, a higher prevalence of cardiovascular events among diabetics patients was found, as expected; however, the prevalence gap between the two cohorts in each age subgroup was variable. Namely, CAD prevalence in SSc cases increased with age, up to reach the same level observed in diabetic women in older individuals. Therefore, the significant difference of CAD prevalence showed in patients < 65 years old was gradually reducing in older women. Furthermore, the high CAD prevalence reported in older SSc patients (and not in younger ones) could be explained by the fact that the weight of the variable "age" was more relevant in SSc than in diabetes.

Overall, CAD prevalence in SSc appeared to be higher than that in the general population, even though a direct comparison between SSc and the general population was not done. In fact, looking at the data obtained by the Italian Cardiovascular Epidemiologic Observatory, recruiting a casual sample of the Italian general population, overall CAD prevalence was 5.4%, from 2.5% in Q1 subjects to 8.2% in Q4 persons [19].

The finding of an increased prevalence of CAD in SSc was already reported in the literature. In particular, a systematic review [14] found that 7/8 controlled studies showed an increased CAD prevalence, even though traditional cardiovascular risk factors reported in 5/6 studies were not augmented in SSc. Thus, the authors stated that SSc is an independent risk factor for CAD [14].

In this direction, it should be interesting to consider the impact of SSc, as cardiovascular risk factor, in the general population. This could be indirectly estimated by the comparison of SSc with diabetics, which is a well-known major cardiovascular risk factor. To the best of our knowledge, data concerning direct comparisons between SSc patients and patients with metabolic disorders are very scarce in the literature. In this respect, a cross-sectional study by Ngian GS et al. [20] evaluated the CAD prevalence in the participants of the Australian Scleroderma Cohort Study (850 patients) and of the Australian Diabetes, Obesity and Lifestyle Study - AusDiab (8802 subjects, of whom 588 diabetics). Both genders were considered. Moreover, 6% of SSc patients were also diabetics. The authors concluded that age- and gender-adjusted odds ratio of CAD in SSc was almost 2 times higher than the AusDiab controls, and more than 3 times higher if further adjusted for the major cardiovascular risk factors.

In the present study, CAD was found associated with pulmonary hypertension only, if we consider SSc features. In the 2015 systematic review by Ali H et al. [14], renal involvement, disease duration, and pulmonary arterial hypertension were reported associated with CAD. The first one was never observed in our SSc series; thus, we cannot evaluate this point. Instead, the disease duration was not found associated with CAD in our study, probably because of the late SSc diagnosis in our few elderly patients.

Other inflammatory rheumatic diseases are known to increase the risk for CAD. The case of rheumatoid arthritis is paradigmatic, with a risk ranging 1.5–2 times higher than the general population or diabetics [21–23]. On these bases, the European League Against Rheumatism recommended annual cardiovascular risk assessment and management for all

patients affected by chronic inflammatory arthropathies. Of note, the suppression of inflammation was remarked as primary outcome to lower the risk [24]. These recommendations cannot be directly applied to SSc, because this disease, unlike other rheumatologic disorders, cannot be adequately identified as an inflammatory disease, given the multifaceted pathophysiological aspects and the high heterogeneity of the clinical picture. Despite that, the cardiovascular assessment of SSc patients is mandatory, particularly in older decades, not just using the risk charts validated for the general population [25]. Indeed, the presence of micro- and macrovascular alterations in SSc patients reported in several studies [2–4, 6–11, 14] seems to be the pathophysiological background of the increased incidence of cardiovascular events in SSc patients compared with the general population. Consistently, during the last decades, death rate due to cardio- and cerebrovascular diseases has gradually increased [3, 26].

Overall, the present study first directly compared SSc and diabetic patients in regard to CAD prevalence, using two cohorts of patients referred in two centers highly specialized in the management of SSc and diabetes, respectively. Moreover, in order to minimize the risk of bias, we evaluated the entire SSc and diabetes cohorts, choosing female patients only, also considering the age groups; nonetheless, the possibility of over/underestimation of CAD was virtually excluded by considering the established CAD. However, some limitations should be also considered: (1) the two cohorts are representative of two universitary centers, whereas larger series may be studied considering registry-based or multicenter surveys; this could be a purpose for further studies in order to confirm our findings; (2) SSc and diabetes cohorts are recruited in different areas of Italy; hence, potential biases related to local confounders cannot be excluded. However, all patients were Caucasians, and based on the findings of the Italian Cardiovascular Epidemiologic Observatory, no relevant differences of cardiovascular risk between the north and the south of Italy [18] have been documented so far.

In conclusion, our study of established CAD prevalence in a SSc series showed a generally lower prevalence compared with a diabetes cohort, but presumably higher than the general population (no direct comparison made). Moreover, considering the age decades, CAD prevalence of SSc grows up to values of diabetics in elderly patients. Overall, although SSc can be considered an independent risk factor for CAD, this finding deserves further validation by longitudinal studies.

Compliance with ethical standards

The present study was approved by the Ethical Committee of Modena (protocol no. 282/15); moreover, all patients gave their written consents.

Disclosures None.

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