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Type II diabetes in systemic sclerosis patients: insights from an observational, multicenter study of GIRRCS (Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale)

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Abstract

Objective To assess the contribution of Systemic sclerosis (SSc)-specific features on type II diabetes mellitus (T2D) in a large cohort of Italian SSc patients.

Methods A total of 613 SSc patients from 11 tertiary Rheumatology Units across Italy were included. All patients underwent full history taking, clinical examination, and relevant laboratory and radiological evaluations. Demographic, socioeconomic, and disease-specific factors were compared between SSc patients with and without T2D.

Results The prevalence of T2D in the study cohort was 7.6%. SSc patients with T2D were significantly older ($P < 0.007$) and exhibited: higher prevalence of late-stage capillaroscopic pattern ($P < 0.001$), severe reduction in forced vital capacity (FVC < 50%; $P < 0.000$), moderate reduction in total lung capacity (TLC 50–69%; $P < 0.011$), electrocardiographic signs of right ventricular hypertrophy ($P < 0.018$), higher prevalence of pulmonary arterial hypertension (PAH) confirmed by right heart catheterization (RHC) ($P < 0.037$) and higher prevalence scleroderma renal crisis (SRC) ($P < 0.001$); elevated erythrocyte sedimentation rate (ESR) ($P < 0.022$), and ANA positivity. These patients more frequently assumed angiotensin-converting enzyme inhibitors (ACEi) ($P < 0.005$) when compared to their non-T2D counterparts, while the use of immunosuppressive therapies was similar between groups. Multivariate analysis identified older age, SRC, and reductions in both TLC and FVC as independent SSc-specific associated factors of T2D.

Conclusion Although the prevalence of T2D in SSc patients is lower than the global estimates reported by the International Federation of Diabetes (IFD), a distinct subgroup of SSc patients with T2D is characterized by unique

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disease manifestations and complications, including SRC and impaired lung function. These findings underscore the importance of tailored screening and management approaches to address the intersecting metabolic and vascular risks in this population.

Keywords Systemic sclerosis, Diabetes mellitus type II, Impaired fasting glucose, Traditional cardiovascular risk factors

Introduction

Systemic sclerosis (SSc) is a rare autoimmune disease characterized by widespread microangiopathy, abnormal skin and internal organs fibrosis, and autoimmunity [1, 2]. SSc patients have an increased risk of cardiovascular (CV) events attributed to the synergistic role between chronic systemic inflammation and the increased prevalence of traditional CV risk factors [3]. Type II diabetes mellitus (T2D) is a strong and independent CV risk factor in the general population [4]. Inflammatory diseases are associated with a higher prevalence of T2D [5], mainly due to chronic systemic inflammation and drug-induced insulin resistance and hyperglycemia. However, a large Australian study showed a low prevalence of T2D in SSc patients [6]. Similarly, the results of a retrospective large Taiwan study [7] confirmed a lower incidence of T2D in SSc than in controls. In a retrospective Italian study of 250 SSc patients, a low prevalence of T2D was observed, along with an increased prevalence of impaired fasting glucose (IFG) as compared to controls [8, 9]. Recently, our analysis of the GIRRCS (Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale) cohort, consisting of a large group of Italian SSc patients, showed a T2D prevalence of 7.6% [3], which is lower than that reported by the International Federation of Diabetes (IFD), further confirming previous observations.

Diabetes is also a vascular disease affecting both large and small vessels causing both microvascular and macrovascular damage leading to internal organ insufficiency [10]. Endothelial injury and increased production of endothelin-1 (ET-1), a strong vasoconstrictor, with pro-inflammatory and profibrotic properties, may play a role in the vascular damage seen in both SSc [11] and diabetes [12]. A one-month treatment with a dual endothelin receptor antagonist has been shown to improve peripheral endothelial function in patients with T2D and microalbuminuria [13], further supporting the involvement of the endothelin system in the pathophysiology of vascular complications in diabetes.

On these bases, we conducted a large cross-sectional study to investigate the prevalence of T2D in patients affected by SSc.

Patients and methods

Study design, patients, and assessment of T2D

The study population included 613 SSc patients from 11 tertiary Rheumatologic Units, throughout the whole Italy with a high experience in the management of this disease. All patients fulfilled the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2013 classification criteria [14] and were consecutively enrolled from January 1, 2021, to February 15, 2023. The Ethics committee of the coordinator of the study approved the protocol following the Good Clinical Practice Guidelines and the Declaration of Helsinki. Written informed consent was obtained from all the patients.

All patients were subjected to full history taking, clinical examination, and relevant laboratory and radiological investigations related to their SSc, and traditional CV risk factors were reported. T2D was defined as the medical history of a past or current diagnosis of diabetes; past or current treatment with glucose-lowering drugs (insulin or oral agents); fasting plasma glucose repeatedly ≥ 126 mg/dL in the absence of a definite diagnosis of T2D made by a physician, according to American Diabetes Association (ADA) 2009 recommendations [15]. Patients who were taking anti-diabetic medications (e.g., metformin, SGLT2 inhibitors, GLP-1 analogs) for reasons other than diabetes management were not included. Furthermore, patients who were using insulin at the time of data collection were not included in the study. Patients were defined as having IFG if fasting glucose was between 100 and 125 mg/dl [15]. Traditional CV risk factors assessed in our study included a family history of clinical atherosclerosis, smoking, serum levels of total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, diagnosis of high blood pressure, metabolic syndrome (MS), body mass index (BMI). Hypercholesterolaemia was defined when cholesterol levels were higher/equal than 200 mg/dl, and/or when patients were under treatment with medications lowering the blood cholesterol levels [3, 16]. Hypertriglyceridaemia was defined by value of triglycerides higher than 130 mg/dl, and/or when patients were under treatment with medications lowering the blood triglyceride levels [3]. Metabolic syndrome was defined according to standard criteria [17]. The BMI was used to categorize patients as underweight (BMI < 18.5 kg/m2), normal weight (BMI 18.5–25 kg/m2), overweight (BMI 25–30 kg/m2), or obese (BMI > 30 kg/m2). Clinical, serological, and radiological disease-related features included disease duration from the onset of the first non-Raynaud's phenomenon (RP), disease subset according to LeRoy criteria [18], anti-nuclear antibodies (ANA) and SSc-specific autoantibodies, puffy hands, ischemic

digital ulcers, pitting scars, telangiectasias, subcutaneous calcinosis, tendon friction rubs, scleroderma renal crisis (SRC) defined as the abrupt onset of severe hypertension accompanied by rapidly progressive renal failure, hypertensive encephalopathy, congestive heart failure, and/or microangiopathic hemolytic anemia, pulmonary function tests (PFTs) with carbon monoxide diffusion capacity (DLCO), electrocardiogram (ECG), echocardiographic features, modified Rodnan skin score (mRSS), interstitial lung disease (ILD) assessed by high resolution computed tomography (HRCT), pulmonary arterial hypertension (PAH) measured by right heart catheterization (RHC), the "gold standard" technique to diagnose a PAH, although the cross-sectional design precluded RHC in all cases. The European Scleroderma Study Group (EScSG) activity index was used to assess disease activity [19, 20]. Disease severity was assessed by the core set of variables proposed by Medsger et al. [21] with percentage cut-offs determined according to the Medsger severity scale, which classifies disease severity into five categories: 0 (normal), 1 (mild), 2 (moderate), 3 (severe), and 4 (end-stage). TLC was categorized into four groups based on clinically meaningful thresholds: ≥80% (normal), 70–79% (mild restriction), 50–69% (moderate to moderately severe restriction), and < 50% (severe restriction), adapted from the ATS/ERS guidelines for restrictive lung patterns [22]. In our study, moderate and moderately severe restrictions were combined into a single group to ensure an adequate sample size for statistical analysis. The current therapy was also recorded.

Statistical analysis

Data were collected and analyzed using the statistical package SPSS version 20 SPSS (Inc., Chicago, IL, USA). We modeled 2 statistical analyses, adjusted for gender and age, by performing logistic regression, to evaluate the possible association of each identified covariate on T2D occurrence. Covariates were selected from 2 main areas: SSc-specific features and complications. The purposeful selection process of covariates started by a univariate analysis of each variable; any variable having a significant univariate test and/or a clinical relevance was considered a possible candidate for the multivariate analysis. At the end of this multistep process of deleting and refitting, the multivariate models were built, and OR estimations of significant associations with T2D were provided. A significant threshold was set at $P < 0.05$.

Results

Baseline characteristics of the evaluated SSc patients

The GIRRCS cohort study population comprised 613 SSc patients. The demographic and disease features of all SSc patients are shown in Table 1. Furthermore, the demographic and disease-specific features of T2D SSc patients were compared to non-diabetic ones evaluating the associated factors. Overall, 45 (7.6%) of the SSc patients had T2D and 40 (12%) of the patients had IFG (glycemia 100-125 mg/dl). SSc patients with T2D were significantly older (65.29 ± 11.19 vs. 59.52%±14.06; $P < 0.007$), and more likely to exhibit a late pattern on capillaroscopy [4 patients (8.9%) vs. 5 (0.9%); $P < 0.001$], reduced FVC < 50% [1 patient (3%) vs. none (0%); $P < 0.001$], reduced TLC 50–69% [6 patients (23.1%) vs. 28 (8.1%); $P < 0.011$], ECG signs of right ventricular (RV) hypertrophy [2 patients (5.3%) vs. 4 (0.9%]; $P < 0.018$), a PAH (RHC) [10 patients (25.6%) vs. 63 (13.5%); $P < 0.037$], obesity (BMI > 30 kg/m^2) [32 patients (6%) vs. 9 (20.9%); $P > 0.001$]; elevated ESR [14 patients (42.4%) vs. 117 (24.5%); $P < 0.022$], a family history of cardiovascular disease (CVD) [18 patients (45%) vs. 144 (28.8%); $P < 0.018$], hypertriglyceridemia [16 patients (53.3%) vs. 94 (27.2%); $P < 0.003$], high blood pressure [29 patients (65.9%) vs. 157 (28.6%); $P < 0.001$], metabolic syndrome (MS) [21 patients (48.8%) vs. 27 (5.1%); $P < 0.001$]. T2D SSc patients were more frequently on ACEi [12 patients (27.3%) vs. 65 (12.2%); $P < 0.005$], beta-blockers [16 patients (36.4%) vs. 35 (6.6%); $P < 0.001$], diuretics [13 patients (29.5%) vs. 53 (9.9%); $P < 0.001$] and statins [13 patients (29.5%) vs. 89 (16.7%); $P < 0.032$] compared to SSc patients without T2D. Bivariate correlation analysis showed a positive correlation between ESR and each of BMI 25–30 kg/m2 ($P < 0.039$), BMI > 30 kg/m2 ($P < 0.007$), kidney involvement ($P < 0.030$), and age ($P < 0.0001$). Immunosuppressive treatments were similar in both groups of SSc patients.

Prevalence of T2D and related risk factors in SSc patients

Forty-five patients (7.6%) had a history of past or current diagnosis of T2D. In our study, the prevalence of T2D in SSc patients is lower. This is in contrast to the 9.9% prevalence reported for the Italian population by the International Federation of Diabetes (IFD) [15].

Univariate analysis showed an association of T2D with both SSc-related variables and complications. A significant association was observed with: ANA positivity (OR: 3.808; 95% CI: 1.164–12.456; $P < 0.027$), SRC (OR: 10.654; 95% CI: 2.755–41.201; $P < 0.001$); TLC > 80% (OR: 0.397; 95% CI: 0.175–0.899; $P < 0.027$); TLC < 69->50% (OR: 3.407; 95% CI: 1.265–9.176; $P < 0.015$), RV hypertrophy on ECG (OR: 6.236; 1.104–35.211; $P < 0.038$); PAH on RHC (OR: 2.217; 95% CI: 1.030–4.770; $P < 0.042$); late capillaroscopic pattern (OR: 3.024; 95% CI: 1.493–6.123; $P < 0.002$), muscles severity scale (OR: 2.15; 1.180–3.943; $P < 0.013$), lung severity scale (OR: 1.621; 95% CI: 1.198–2.194; $P < 0.002$), heart severity scale (OR: 1.810; 95% CI: 1.186–2.763; $P < 0.006$), ACE inhibitors treatment (OR: 2.700; 95% CI: 1.324–5.505; $P < 0.006$). On the other hand, the presence of an early capillaroscopic pattern and

Table 1 Sociodemographic, immunological, and clinical features of the study population

	SSc	SSc/without T2D	SSc/T2D	*P*
Patients n, (%)	613	551 (92.4)	45 (7.6)	0.0001
Gender (Female)	560 (91.4)	504 (91.5)	39 (86.7)	0.276
Mean age ± SD (years)	59.53%±13.93	59.52%±14.062	65.29 ± 11.196	**0.007**
Mean disease duration from non-RP ± SD (years)	12.51%±11.67	12.53 ± 11.137	13.41 ± 11.980	0.661
DcSSc	171 (28)	153 (27.8)	14 (31.1)	0.636
ANA (positive)	503 (83.4)	451 (83.1)	36 (81.8)	0.833
ACA (positive)	277 (47.1)	254 (47.9)	18 (40.9)	0.370
ATA (positive)	190 (31)	166 (30.2)	16 (35.6)	0.452
ARA (positive)	16 (2.6)	14 (2.5)	2 (4.4)	0.447
Puffy fingers	292 (47.9)	262 (47.5)	22 (48.9)	0.863
Ischemic digital ulcers	236 (38.7)	214 (38.8)	15 (33.3)	0.465
Pitting scars	179 (30.3)	166 (30.9)	12 (26.7)	0.553
Telangiectasias	288 (49.3)	268 (50.8)	14 (31.8)	**0.016**
Calcinosis	767 (12.9)	69 (12.9)	5 /11.4)	0.763
Tendon friction rubs	68 (11.2)	61 (11.1)	3 (6.7)	0.357
EScSG (active)	86 (19.5)	78 (19.2)	8 (25)	0.423
NVC				
Early pattern	131 (24.3)	123 (24.9)	1 (2.9)	**0.003**
Active pattern	206 (38.2)	192 (38.9)	12 (35.3)	0.672
Late pattern	129 (23.9)	112 (22.7)	16 (47.1)	**0.001**
SRC	9 (1.5)	5 (0.9)	4 (8.9)	**0.001**
FVC%				
> 80%	429 (84.6)	400 (85.5)	24 (72.7)	0.050
70–79%	41 (8.1)	36 (7.7)	5 (15.2)	0.131
50–69	36 (7.1)	32 ((6.8)	3 (9.1)	0.624
< 50%	1 (0.2)	0 (0)	1 (3)	**0.001**
FEV/FVC < 80%	112 (25.7)	104 (25.4)	8 (29.6)	0.628
DLCO%				
> 80%	209 (44.6)	195 (45.2)	12 (37.5)	0.395
70–79%	81 (17.3)	76 (17.6)	5 (15.6)	0.773
50–69%	128 (27.3)	114 (26.5)	11 (34.4)	0.330
< 50%	51 (10.9)	46 (10.7)	4 (12.5)	0.748
TLC%				
≥ 80%	287 (76.1)	268 (77.5)	15 (57.7)	**0.023**
70–79%	45 (11.9)	40 (11.6)	4 (15.4)	0.560
50–69%	34 (9)	28 (8.1)	6 (23.1)	**0.011**
< 50%	11 (2.9)	10 (2.7)	1 (3.8)	0.781
ECG conduction abnormalities	76 (15.2)	70 (15.5)	5 (13.2)	0.706
Arrhythmias	35 (7)	36 (1.8	4 (10.5)	0.397
RV hypertrophy	6 (1.2)	4 (0.9)	2 (5.3)	**0.018**
EF < 55%	14 (2.5)	27 (6)	2 (5.3)	0.861
Diastolic dysfunction	164 (29)	143 (27.7)	17 (40.5)	0.079
Pericardial effusion	81 (13.9)	74 (14)	5 (11.9)	0.703
PAH (RHC)	75 (14.7)	63 (13.5)	10 (25.6)	**0.037**
mRSS > 14	87 (17.5)	83 (18.3)	3 (8.6)	0.146
ILD	272 (46.9)	240 (45.4)	25 (59.5)	0.077
ESR > 30mmhg	134 (25.8)	117 (24.5)	14 (42.4)	**0.022**
CRP > 0.5 mg/dl	172 (32.8)	154 (31.6)	14 (46.7)	0.088
Family history of CVD	144 (28.8)	6 (27.4)	18 (45)	**0.018**
Smoking habitus (current or past)	207 (35)	185 (34.5)	16 (36.4)	0.804
Cholesterol > 200 mg/dl	156 (39.6)	144 (39.9	11 (36.7)	0.729
Triglycerides > 130 mg/dl	379 (29.6)	94 (27.2)	16 (53.3)	**0.003**
High blood pressure	190 (31.7)	157 (28.6)	29 (65.9)	**0.001**

Table 1 (continued)

	SSc	SSc/without T2D	SSc/T2D	*P*
MS	48 (8.4)	27 (5.1)	21 (48.8)	**0.001**
BMI				
Normal (BMI = 18.5–25 kg/m^2)	433 (74)	411 (76.7)	22 (51.2)	**0.001**
Overweight (BMI = 25–30 kg/m^2)	105 (18.1)	93 (17.4)	12 (27.9)	0.084
Obese (BMI > 30 kg/m^2)		32 (6)	9 (20.9)	**0.001**
MMF	90 (15.6)	83 (15.6)	7 (15.9)	0.953
AZA	37 (6.4)	34 (6.4)	3 (6.8)	0.912
MTX	54 (9.2)	48 (9)	5 (11.4)	0.603
HCQ	84 (14.2)	74 (13.9)	6 (13.6)	0.964
GC	179 (30.3)	160 (30)	14 (31.89	0.803
COLCHICINE	9 (1.5)	7 (1.3)	2 (4.5)	0.097
RTX	15 (2.5)	14 (2.6)	0 (0)	0.276
TCZ	9 (1.55)	8 (1.5)	1 (2.3)	0.694
Antifibrotics	3 (0.5)	2 (0.4)	0 (0)	0.684
CCB	345 (58.5)	316 (59.3)	23 (52.3)	0.364
Iloprost	224 (38)	206 (38.6)	12 (27.3)	0.135
Tadalafil	4 (0.7)	15 (2.8)	3 (6.8)	0.142
Riociguat	3 (0.5)	4 (0.8)	0 (0)	0.569
Bosentan	139 (23.6)	3 (0.6)	0 (0)	0.618
Macitentan	12 (2)	139 (26.1)	11 (25)	0.875
Ambrisentan	2 (0.3)	127 (23.8)	10 (22.7)	0.869
Antiplatelet	324 (54.9)	298 (55.9)	23 (52.3)	0.641
Anticoagulant	19 (3.2)	16 (3)	3 (6.8)	0.174
ACEi	77 (13.1)	65 (12.2)	12 (27.3)	**0.005**
ARB	46 (7.8)	40 (7.5)	5 (11.1)	0.359
B-blockers	51 (8.6)	35 (6.6)	16 (36.4)	**0.001**
Diuretics	67 (11.4)	53 (9.9)	13 (29.5)	**0.001**
Statins	103 (17.5)	89 (16.7)	13 (29.5)	**0.032**

ACA: anticentromere antibodies; ACEi: angiotensin converting enzyme inhibitors; ANA: antinuclear antibodies; ARA: Anti-RNA polymerase III; ARBS: angiotensin 2 receptor blockers; ATA: anti-topoisomerase I antibodies; AZA: azathioprine; CCB: calcium channel blockers; CRP: C reactive protein; CVD: cardiovascular disease; DcSSc: diffuse cutaneous systemic sclerosis; DLCO: Diffusing capacity for carbon monoxide; ECG: elettrocardiogram; EF: ejection fraction; ESR: erythrocyte sedimentation rate; EScSG: European Scleroderma Study Group activity index; FVC: Forced vital capacity; FEV1/FVC: Forced Expiratory Volume in the first second to forced vital capacity; GC: glucocorticoid; HCQ; hydroxychloroquine; IFG: impaired fasting glucose; ILD: interstitial lung disease; LcSSc: limited cutaneous Systemic sclerosis; MMF: mycophenolate; mRSS: modified skin score; MS: metabolic syndrone; MTX: methotrexate; NVC: nailfold videocapillaroscopy; PAH: pulmonary arterial hypertension; PAPs: estimated pulmonary arterial pressure by echocardiography; RHC: right heart catheterization; RP: Raynaud's phenomenon; RTX: rituximab; SRC: scleroderma renal crisis; TCZ: tocilizumab; TLC: total lung capacity;

telangiectasias have emerged as protective factors to T2D occurrence in SSc individuals (Table 2).

After multivariate analysis (Tables 3 and 4), based on the selection of covariates of SSc-related complications, SRC (OR: 10.777; 95% CI: 1.996–58.116; $P < 0.006$), and severely reduced TLC 50–69% (OR: 6.085; 95% CI: 2.052–18.048; $P < 0.001$) were confirmed to be independent associated factors with T2D. Furthermore, after multivariate analysis, based on the selection of covariates of SSc-related features, the presence of NVC late pattern was confirmed to be an independent factor associated with T2D (OR: 2.863; 95% CI: 1.222–6.712; $P < 0.015$) while telangiectasias (OR: 0.308; 95%CI: 0.115–0.828; $P < 0.020$) showed again a protective role on T2D occurrence. Furthermore, our analysis confirmed older age as an independent risk factor for T2D (OR: 1.040; CI: 1.040–1.005; $P < 0.017$ and OR: 1.036; CI: 1.000-1.073; $P < 0.048$ for both multivariate models, respectively). Furthermore, after multivariate analysis, based on disease duration from RP and non-RP onset, age (OR: 1.032; CI: 1.006–1.058; $P < 0.014$ and OR: 1.031; CI: 1.003–1.059; $P < 0.027$, respectively) was confirmed to be an independent associated factor with T2D but not disease duration. Lastly, disease duration and subset, SSc-specific autoantibodies, puffy fingers, ischemic digital ulcers, pitting scars, calcinosis, tendon friction rubs, FVC, DLCO, diastolic dysfunction, pericardial effusion, mRSS > 14, ILD, EScSG (active disease), and CRP > 0.5 mg/dl, were not statistically associated with the history of T2D.

Table 2 T2D univariate analyses in SSc patients

Univariate analyses	OR	SE	*P*	CI 95%
Gender	0.606	0.464	0.281	0.244–1.506
Age	1.033	0.012	**0.008**	1.009–1.059
RP onset	1.001	0.012	0.927	0.978–1.025
Non-RP onset	1.006	0.014	0.661	0.979.1.034
DcSSc	1.172	0.336	0.637	0.607–2.263
ANA (positive)	3.808	0.605	**0.027**	1.164–12.456
SSc Abs (positive)	1.008	0.407	0.984	0.454–2.237
ACA (positive)	0.752	0.319	0.372	0.403–1.405
ATA (positive)	1.276	0.325	0.453	0.675–2.413
RNA Pol III (positive)	1.784	0.772	0.454	0.393–8.107
Puffy fingers	1.055	0.310	0.863	0.574–1.938
Ischemic digital ulcers	0.787	0.328	0.466	0.414–1.498
Pitting scars	0.813	0.352	0.553	0.409–1.613
Telangiectasias	0.453	0.335	**0.018**	0.235–0.873
Calcinosis	0.862	0.492	0.763	0.329–2.262
Tendon friction rubs	0.573	0.613	0.363	0.172–1.903
SRC	10.654	0.690	**0.001**	2.755–41.201
FVC%				
> 80%	0.453	0.412	0.055	0.453–1.017
70–79%	2.143	0.516	0.139	0.780–5.886
50–69%	1.362	0.633	0.625	1.362–4.708
< 50%	-	-	-	-
DLCO%				
> 80%	0.726	0.378	0.397	0.346–1.523
70–79%	0.865	0.503	0.773	0.323–2.318
50–69%	1.4573.1	0.388	0.332	0.681–3.115
< 50%	1.196	0.557	0.748	0.401–3.561
TLC%				
≥ 80%	0.397	0.417	**0.027**	0.175–0.899
70–79%	1.391	0.569	0.562	0.456–4.242
50–69%	3.407	0.505	**0.015**	1.265–9.176
< 50%	1.344	1.069	0.782	0.165–10.925
FEV1/FVC%	1.235	0.436	0.629	0.525–2.905
ECG Conduction abnormalities	0.829	0.497	0.706	0.313–2.197
Arrhythmias	1.602	0.560	0.401	0.534–4.803
RV hypertrophy	6.236	1.830	**0.038**	1.104–35.211
Diastolic dysfunction	1.774	0.329	0.082	0.930–3.383
Pericardial effusion	0.829	0.493	0.704	0.316–2.178
PAH (RHC)	2.217	0.391	**0.042**	1.030–4.770
ILD	1.771	0.326	0.080	0.934–3.357
EScSG (active)	1.406	0.427	0.425	0.609–3.248
NVC				
Early pattern	0.091	1.020	**0.019**	0.012–0.673
Active pattern	0.855	0.371	0.673	0.414–1.768
Late pattern	3.024	0.360	**0.002**	1.493–6.123
Severity scale				
General	1.501	0.331	0.220	0.785–2.870
Peripheral vascular	0.790	0.205	0.249	0.529–1.180
Skin	0.849	0.230	0.475	0.541–1.332
Joint/tendon	0.636	0.451	0.316	0.263–1.540
Muscles	2.157	0.308	**0.013**	1.180–3.943
GI	1.006	0.283	0.983	0.578–1.751
Lung	1.621	0.154	**0.002**	1.198–2.194

Table 2 (continued)

Univariate analyses	OR	SE	*P*	CI 95%
Heart	1.810	0.216	**0.006**	1.186–2.763
Kidney	1.574	0.440	0.302	0.665–3.730
ESR > 30mmHg	2.274	0.368	**0.026**	1.105–4.676
CRP > 0.5 mg/dl	1.892	0.379	0.092	0.901–3.975

ACA: anticentromere antibodies; ACEi: angiotensin converting enzyme inhibitors; ANA: antinuclear antibodies; ARA: Anti-RNA polymerase III; ARBS: angiotensin 2 receptor blockers; ATA: anti-topoisomerase I antibodies; AZA: azathioprine; CCB: calcium channel blockers; CRP: C reactive protein; CVD: cardiovascular disease; CYC: cyclophosphsmide; DcSSc: diffuse cutaneous systemic sclerosis; DLCO: Diffusing capacity for carbon monoxide; ECG: elettrocardiogram; EF: ejection fraction; ESR: erythrocyte sedimentation rate; EScSG: European Scleroderma Study Group activity index; FVC: Forced vital capacity; FEV1/FVC: Forced Expiratory Volume in the first second to forced vital capacity; GC: glucocorticoid; HCQ; hydroxychloroquine; IFG: impaired fasting glucose; ILD: interstitial lung disease; IVIG: intravenous normal immunoglobulins; LcSSc: limited cutaneous Systemic sclerosis; MMF: mycophenolate; mRSS: modified skin score; MS: metabolic syndrone; MTX: methotrexate; NVC: nailfold videocapillaroscopy; PAH: pulmonary arterial hypertension; PAPs: estimated pulmonary arterial pressure by echocardiography; RHC: right heart catheterization; RP: Raynaud's phenomenon; RTX: rituximab; SRC: scleroderma renal crisis; TCZ: tocilizumab; TLC: total lung capacity;

Table 3 Multivariate regression analyses exploring the potential association between disease-related variables, and the development of T2D in patients with SSc

Multivariate analyses (1)	OR	SE	*P*	CI 95%
Gender	0.342	0.708	0.129	0.085–1.367
Age	1.040	0.017	**0.023**	1.040–1.005
SRC	10.777	0.860	**0.006**	1.996–58.116
TLC 50–69%	6.085	0.555	**0.001**	2.052–18.048
Teleangiectasies	0.308	0.505	**0.020**	0.115–0.828

SRC: scleroderma renal crisis; TLC: total lung capacity

Table 4 Multivariate regression analyses exploring the potential association between disease related variables and the development of T2D in patients with SSc

Multivariate analyses (2)	OR	SE	*P*	CI 95%
Gender	0.859	0.785	0.847	0.184–4.004
Age	1.036	0.018	**0.048**	1.000-1.073
ANA positive	1.197	0.652	0.782	0.334–4.297
ESR > 30mmHg	2.114	0.443	0.091	0.887–5.035
NVC late pattern	2.863	0.435	**0.015**	1.222–6.712

ANA: antinuclear antibodies; ESR: erythrocyte sedimentation rate; NVC: nailfold videocapillaroscopy

Discussion

To our knowledge, this is the largest cohort analyzed in an observational multicentric study to specifically define the prevalence of T2D in SSc patients, identifying a distinct subset of those patients characterized by a clinical phenotype including a late capillaroscopic pattern, reduced TLC, and an increased frequency of SRC. On the other hand, the presence of an early capillaroscopic pattern and telangiectasia emerged as protective factors against the occurrence of T2D.

Our study aligns with other national and retrospective cohort studies, confirming a lower prevalence and incidence of T2D in SSc patients. It has been suggested that severe gastrointestinal involvement (assessed using the Medsger severity score, which is a widely used tool to assessing gastrointestinal severity in SSc), particularly malabsorption, and malnutrition, may lead to weight loss, thus decreasing the obesity-dependent insulin resistance, which is considered one of the main factors associated with the occurrence of T2D. Due to their gastrointestinal involvement, these patients generally have a dietary regimen or small meals which may also have a protective role [9]. It has been also reported that whole-body insulin sensitivity is higher in SSc patients, further supporting that gastrointestinal involvement and subsequent weight loss may improve glucose metabolism in these individuals [9]. Indeed, we found that IFG, was similar or slightly lower in our patients compared to available controls matched for age and sex [5, 8]. Furthermore, previous research on immune-metabolic alterations in T2D of SSc patients found increased serum levels of molecules such as interleukin (IL)-13, IL-10, and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), which have a protective effect against T2D [7].

Notably, the SSc patients with comorbid T2D were significantly older, and exhibited a higher prevalence of advanced disease-related variables and complications, including a late capillaroscopic pattern, severely reduced FVC, moderately impaired TLC and SRC. They were more likely to exhibit ECG signs of RV hypertrophy, PAH on RHC, and elevated ESR. Additionally, these patients were more frequently treated with ACEi than their non-T2D counterparts. In contrast, the use of immunosuppressive therapies did not significantly differ between the 2 groups.

In our study, multivariate analysis identified SRC, defined as the abrupt onset of severe hypertension, rapidly progressive renal failure, hypertensive encephalopathy, congestive heart failure, and/or microangiopathic hemolytic anemia, which distinguishes it from diabetic nephropathy, as independently associated with T2D in SSc patients. While kidney involvement may be influenced by diabetic nephropathy, the definition of SRC in our study specifically pertains to SSc-related renal pathology. It has been suggested that T2D, a metabolic disease with vascular complications associated with an inflammatory mechanism, shares certain mediators of inflammation and endothelial damage, such as ESR and endothelin-1 (ET-1), with the pathogenesis of SSc, thus suggesting a potential link between the two diseases at

least in a subset of patients [23]. Both in T2D and SSc, we may observe an endothelial injury leading to vascular permeability associated with overexpression of vascular endothelial growth factor (VEGF) and ET-1. Increased levels of ET-1 and overexpression of its receptors (ETA and ETB) are found in serum and vascular lesions in SRC biopsies, underscoring their role in SRC pathophysiology [24]. On the other hand, a significant correlation has been observed between increased plasma ET-1 levels and T2D complications (microalbuminuria, elevated glycosylated hemoglobin concentrations, retinopathy) [12]. On these bases, some Authors suggested the use of non-selective endothelin receptor antagonists, such as bosentan, to manage these conditions. In fact, bosentan has shown efficacy in improving endothelial-dependent vasodilation in T2D patients with microalbuminuria and may enhance endothelial function in individuals with refractory diabetes-related ulcers, potentially reducing amputation risk [25–27].

In our study, a significant association between PAH, confirmed by RHC, and T2D in SSc patients was observed. PAH, a fibroproliferative vasculopathy characterized by endothelial dysfunction and disrupted balance between vasodilation and vasoconstriction, remains a leading cause of mortality in SSc patients [1, 2]. Emerging evidence suggests common molecular mechanisms between PAH and insulin resistance, including endothelial dysfunction, chronic inflammation, oxidative stress, and PI3K/Akt signaling dysregulation, supporting a potential bidirectional relationship [28, 29].

Notably, in SSc patients with PAH, capillaroscopic abnormalities—characterized by a late pattern with severe capillary loss, avascular areas, and neoangiogenesis—appear significantly more pronounced and severe [30]. In our study, the late capillaroscopic pattern was independently associated with T2D in SSc patients. It must be pointed out that increasing evidence also shows diabetic patients exhibit similar capillary abnormalities, such as capillary dilatation and avascular zones, linked to complications like diabetic retinopathy [31].

Our study also found that a decreased TLC was associated with T2D in SSc patients. Studies have also shown that diabetic patients also experience impaired lung function, as a chronic complication, independently of factors such as smoking, sex, and BMI [32]. Due to their extensive vascularization and connective tissue content, the lungs are particularly vulnerable to hyperglycemia, similar to other organs affected by microvascular complications [33]. Prolonged hyperglycemia activates several pathogenic pathways, including oxidative stress, protein glycation, and NF-κB signaling, driving tissue damage and fibrosis progression [34, 35]. These findings highlight the complex mechanisms linking chronic hyperglycemia to pulmonary dysfunction. Autopsy studies of diabetic patients revealed thickened capillary and epithelial basement membranes, which disrupt pulmonary microcirculation and impair pulmonary perfusion, potentially contributing to reduced DLCO in T2D patients [36]. Additionally, T2D patients exhibit significantly altered pulmonary function, including reduced FEV_1, FVC, FEV_1/FVC ratio, and TLC. Linear regression analysis has found a negative association between fasting plasma glucose and lung function parameters, with T2D inversely correlated with TLC, possibly resulting from loss of lung elasticity, insufficient pulmonary surfactant, reduced muscle function, and impaired DNA repair [37–41]. A meta-analysis also identified reduced lung function as a predictor of future T2D onset [42].

As expected, our analysis showed that age is an independent associated factor for T2D. Regarding the impact of disease duration on T2D, we did not find any statistical association in our patients, further confirming our hypothesis on the early role of inflammation or low-grade inflammation on endothelial damage.

Telangiectasia and the early capillaroscopic pattern seem to be protective factors to the development of T2D. Indeed, studies on T2D patients using nailfold video capillaroscopy (NVC) revealed significant microvascular abnormalities linked to poor glycemic control [43], and longer disease duration, particularly in those with diabetic retinopathy [44]. These findings suggest glycemic dysregulation drives vascular structural changes.

In our multivariate analysis, sex and age were included as confounding factors, as these variables are well-established in the literature to potentially influence the outcomes under investigation. Additionally, other potential confounders were selected based on the results of univariate analysis, which identified variables that could have an impact on the outcomes. These variables were deemed necessary for adjustment in the subsequent multivariate models to control for their potential effects and provide more accurate, unbiased results. This approach allowed us to ensure that the observed associations were not confounded by these key factors.

The treatment data in this study reflect the therapeutic regimens of patients at the time of enrollment, given the cross-sectional design of the study. It is well established that high doses of steroids, particularly prednisone doses greater than 10 mg, are associated with an increased risk of inducing SRC. However, in this cohort, steroid use was limited, with most patients receiving low doses for short periods. This likely minimized any significant metabolic effects associated with steroid therapy. Moreover, the proportion of patients receiving steroid treatment was relatively small, further reducing its potential impact on the study's findings.

In cross-sectional observational studies, the lack of preassigned therapy can confound outcome-exposure

associations, risking incorrect conclusions. Thus, to avoid the well-known "confounding by indication bias," in our study, we did not assess the impact of different treatments on T2D [45, 46].

We are aware of some limitations of this study. Firstly, the observational and cross-sectional design may preclude the establishment of causal relationships. Secondly, the lack of clear differentiation between T2D and type I diabetes, and the absence of comprehensive metabolic markers, should be considered when interpreting the results, and further studies with more precise diagnostic methods and longitudinal data are needed. Thirdly, the lack of standardized criteria for evaluating gastrointestinal manifestations other than the Medsger severity score may have impacted the accuracy of assessing gastrointestinal involvement and its contribution to T2D. Fourthly, the assessment of body fat percentage was not included, reflecting the observational nature of the study and its limited routine use in clinical practice. Lastly, while the study focused on the prevalence of T2D, the dynamic nature of metabolic disease progression and its long-term impact on patients with SSc was not assessed, as a longitudinal follow-up would be necessary to capture the evolving nature of T2D in this patient group.

In conclusion, to the best of our knowledge, this is the largest cohort analyzed in an observational multicentric study to specifically define the prevalence of T2D in SSc Italian patients. Almost 8% of patients have comorbid T2D and they are clinically characterized by a late capillaroscopic pattern, reduced TLC, and an increased frequency of SRC. On the other hand, the presence of an early capillaroscopic pattern and telangiectasias emerged as protective factors for the development of T2D. Identifying shared risk factors and overlapping pathways underscores the need for targeted screening and management strategies focused on reducing vascular and metabolic complications in this distinct population of patients. Larger prospective studies are needed to confirm these associations in SSc.

Abbreviations

ACA	Anticentromere antibodies
ACEi	Angiotensin converting enzyme inhibitors
ANA	Antinuclear antibodies
ARA	Anti-RNA polymerase III
ARBS	Angiotensin 2 receptor blockers
ATA	Anti-topoisomerase I antibodies
AZA	Azathioprine
CCB	Calcium channel blockers
CRP	C reactive protein
CVD	Cardiovascular disease
DcSSc	Diffuse cutaneous systemic sclerosis
DLCO	Diffusing capacity for carbon monoxide
ECG	Elettrocardiogram
EF	Ejection fraction
ESR	Erythrocyte sedimentation rate
EScSG	European Scleroderma Study Group activity index
FVC	Forced vital capacity
FEV1/FVC	Forced Expiratory Volume in the first second to forced vital capacity
GC	Glucocorticoid
HCQ	Hydroxychloroquine
IFG	Impaired fasting glucose
ILD	Interstitial lung disease
LcSSc	Limited cutaneous Systemic sclerosis
MMF	Mycophenolate
mRSS	Modified skin score
MS	Metabolic syndrone
MTX	Methotrexate
NVC	Nailfold videocapillaroscopy
PAH	Pulmonary arterial hypertension
PAPs	Estimated pulmonary arterial pressure by echocardiography
RHC	Right heart catheterization
RP	Raynaud's phenomenon
RTX	Rituximab
SRC	Scleroderma renal crisis
TCZ	Tocilizumab
TLC	Total lung capacity

Author contributions

VL, RG, FC: study conception and design, data interpretation, literature search, writing, paper revision and acceptance; VL, GF, PR, LN, FB, FC, GG, LLB, CR, AC, PT, ALG, GM, LC, BF, PC, FPC, MSC, EF, FP, AI, RG, FC: acquisition of data, data interpretation, literature search, writing, paper revision and acceptance; All authors gave final approval for submitting the manuscript for review and agree to be accountable for all aspects of the work.

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Declarations

Ethics approval and consent to participate

All patients gave fully informed written consent approved by the institutional ethics committee.

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Consent for publication

Not applicable.

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