ADAMTS13 and insulin resistance in systemic sclerosis patients

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Abstract

Objective

To investigate the complex interplay between autoimmune disorders, metabolic dysfunction, and vascular health, we assessed the relationship between ADAMTS13, systemic sclerosis-scleroderma (SSc), and insulin resistance.

Methods

A cross-sectional study was conducted involving 81 individuals diagnosed with SSc and 76 healthy age- and sex-matched controls. Comprehensive clinical and laboratory characterisations were performed for both groups. Serum levels of ADAMTS13, standard lipid profiles, and indices of insulin resistance were assessed in all participants. To determine whether ADAMTS13 serum levels differed significantly between SSc patients and healthy controls, as well as to examine the relationship between ADAMTS13 values, disease characteristics, and cardiometabolic features, multivariable linear regression analyses were performed.

Results

Serum ADAMTS13 levels were significantly decreased in patients with SSc compared to healthy controls after multivariable analysis. A significant negative correlation was observed between C-reactive protein levels and circulating ADAMTS13 levels. However, disease characteristics, including pulmonary, articular, and cutaneous manifestations, did not show significant associations with ADAMTS13 values. Regarding cardiometabolic features, ADAMTS13 levels demonstrated a significant positive association with indices of insulin resistance, a relationship not observed in the control group.

Conclusion

ADAMTS13 serum levels are decreased in patients with SSc. Additionally, a positive correlation exists between ADAMTS13 levels and insulin resistance in SSc.

Key words
systemic sclerosis, scleroderma, ADAMTS13, insulin resistance

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Introduction

Systemic sclerosis, also known as scleroderma (SSc), is a chronic multisystem disease characterised by widespread vascular dysfunction and progressive fibrosis of the skin and internal organs (1). It is considered a heterogeneous condition, evident in the diverse range of organ manifestations, disease progression, severity, and outcomes (2). SSc is traditionally classified based on the extent of skin involvement and the accompanying patterns of internal organ involvement, as well as the presence of overlapping features with other systemic rheumatic diseases. In this regard, the major subsets of SSc include limited cutaneous, diffuse cutaneous, SSc sine scleroderma, and SSc overlap syndrome (3).

Cutaneous manifestations, such as thickening and induration, along with Raynaud's phenomenon, are nearly universal clinical features of SSc. Other characteristics of the disease include the presence of digital ulcers, tissue loss, musculoskeletal symptoms, and involvement of the gastrointestinal, pulmonary, and cardiac systems (4, 5). Cardiovascular disease is common yet often unrecognised in SSc patients. Factors contributing to vascular issues in SSc, which are also seen in atherosclerosis, include endothelial dysfunction, fewer circulating endothelial progenitor cells, and more microparticles. Indicators of higher cardiovascular risk in SSc include increased arterial stiffness, carotid intima thickening, and reduced flow-mediated dilatation (6). Consequently, SSc patients are at an increased risk of atherosclerosis compared to healthy individuals. A systematic review and meta-analysis screened over 3.000 studies, ultimately including 31 in the review and 14 in the meta-analysis, to compare SSc patients with healthy individuals using various assessments such as carotid intima-media thickness (cIMT), flow-mediated vasodilation (FMD%), and other vascular imaging techniques. Results showed that SSc patients had significantly increased cIMT and reduced FMD%, indicating a higher prevalence of coronary atherosclerosis, peripheral vascular disease, and cerebrovascular calcification. These differences were influenced by factors such as disease duration and patient age. The study concluded that SSc patients face a greater risk of atherosclerosis and calls for further research to clarify the underlying mechanisms (7).

Metabolic syndrome is relatively common in patients with SSc, potentially exacerbating the risk of cardiovascular disease (8). The presence of metabolic syndrome features, including abnormal lipid profiles and insulin resistance, may worsen their overall health outcomes and could lead to increased rates of morbidity and mortality. In this regard, Atzeni *et al*. highlight the need for routine screening for metabolic syndrome as an essential part of clinical care for SSc patients, with an emphasis on managing individual metabolic syndrome components to improve overall prognosis and reduce cardiovascular risk (8). With respect to this, SSc patients exhibit an abnormal lipid profile compared to controls, including a reduced cholesterol efflux capacity (9). Additionally, insulin resistance has been independently associated with the presence of digital ulcers in SSc patients and has been proposed as a potential biomarker of microvasculopathy in this population (10).

ADAMTS13 (A Disintegrin and Metalloprotease with Thrombospondin Motifs (13) is an enzyme essential for maintaining blood flow by cleaving von Willebrand factor (vWF), a protein that plays a key role in clot formation (11). Recessive mutations in *ADAMTS13*, the gene that encodes ADAMTS13, lead to a condition called thrombotic thrombocytopenic purpura (TTP), which arises from the failure to cleave prothrombogenic ultra-large vWF multimers in the circulation. This results in platelet aggregation and vessel occlusion (12). Lower levels of ADAMTS13 have been associated with cardiovascular disease (13) and polymorphisms in the *ADAMTS13* gene are associated with an increased risk of death in patients with coronary artery disease (14). Patients with SSc have decreased serum levels of ADAMTS13, leading to excessive accumulation of vWF, which may contribute to microangiopathy, thrombotic events, and interstitial lung disease associated with the condition

(15, 16). However, the association between ADAMTS13 and disease manifestations, as well as cardiovascular risk factors such as lipid profile, insulin resistance, and subclinical atherosclerosis, has not been thoroughly investigated in SSc. In this study, we aim to determine whether ADAMTS13 levels differ between patients and controls and to assess its relationship with specific disease characteristics, including a comprehensive cardiovascular profile encompassing metabolic syndrome, insulin resistance, lipid profile, and subclinical carotid atheromatosis.

Methods

Study participants

This was a cross-sectional study that included 81 patients with SSc and 76 sex- and age-matched controls. All participants were 18 years or older, and SSc patients met the American College of Rheumatology/European League Against Rheumatism 2013 classification criteria for SSc (17). They had been diagnosed by rheumatologists and were periodically followed up at the rheumatology outpatient clinics of our institution. For inclusion in the present study, the duration of SSc had to be ≥1 year. Patients and controls who had experienced a cardiovascular event were excluded. Subjects were also excluded if they had a history of cancer or any other chronic disease, evidence of active infection, or a glomerular filtration rate of <60 ml/min/1.73 m^2. We believe those disorders could have influenced our results, as these patients might have had high insulin resistance disturbance, or this could have also affected serum ADAMTS13 levels. The study protocol was approved by the Institutional Review Committee at Hospital Universitario de Canarias, and all subjects provided informed written consent (Approval code: EscleZ).

Assessments and data collection

Surveys in SSc patients and controls were performed to assess cardiovascular risk factors and medication use. Subjects completed a questionnaire and underwent a physical examination to determine anthropometric measurements and blood pressure. Medical records were reviewed to ascertain specific diagnoses, medications, and comorbidities. Hypertension was defined as a systolic or a diastolic blood pressure higher than, respectively, 140 and 90 mmHg. Obesity, defined as a body mass index (BMI) equal to or greater than 30 kg/m^2. Disease duration for SSc was defined as the time since the onset of the first SSc-related symptom other than Raynaud's phenomenon. SSc subtypes, limited and diffuse, were determined according to the distribution of skin thickness. The modified Rodnan Skin Score (mRSS) skin score was used to assess skin thickening (18). This score has been commonly used as an outcome measure in clinical trials. It rates the severity of these features from 0 (normal) to 3 (most severe) in 17 distinct areas of the body and shows an acceptable degree of intra-rater variability. Oesophageal involvement was defined as any sign of dysmotility evident on manometry. Articular involvement was determined by clinical evidence of joint swelling, deformity, contractures, and tendon friction rubs. Interstitial lung disease was defined instrumentally by forced vital capacity (FVC) ≤ 80%, forced expiratory volume in one second-FEV1/FVC ≥ 70%) and/or diffusing capacity of the lung for carbon monoxide (DLCO) < 80% and interstitial changes on chest high-resolution computed tomography. Nailfold capillaroscopy was performed as previously described (19) and scleroderma patterns were sub-graded as 'early', 'active' and 'late' (19).

Cardiovascular risk score (SCORE2) was calculated according to the 2021 European Society of Cardiology guidelines on cardiovascular disease prevention in clinical practice (20). SCORE2 categorises risk as low to moderate, high, or very high based on different age groups (<50, 50–69, and ≥70 years). The SCORE2 scoring system is designed to estimate the 10-year risk of both fatal and non-fatal cardiovascular events in individuals between the ages of 40 and 69 years. However, for healthy individuals who are 70 years or older, the SCORE2-OP (older persons) algorithm provides estimates for both 5-year and 10-year risk of fatal and non-fatal cardiovascular events.

In patients with SSc, a carotid ultrasound examination was performed to evaluate the cIMT within the common carotid artery. The objective was to identify any localised plaques in the carotid arteries situated outside the skull (extracranial carotid tree). The measurements were carried out using the EsaoteMylab 70 ultrasound system from Genova, Italy. This system is equipped with a 7-12 MHz linear transducer and employs the Quality Intima Media Thickness in real-time (QIMT) automated software-guided radiofrequency technique developed by Esaote in Maastricht, Holland. The assessment process adhered to the guidelines established in the Mannheim consensus (21), which establishes criteria for identifying plaques within the accessible extracranial carotid arteries. These arteries include the common carotid artery, the bulb, and the internal carotid artery. Plaque criteria were established as the presence of a localised bulge within the arterial lumen, with a measurement of cIMT exceeding >1.5 mm. In addition, the bulge needed to be at least 50% larger than the adjacent cIMT or result in an arterial lumen reduction of >0.5 mm (21).

Laboratory assessments

Fasting serum samples were collected and frozen at -80°C until analysis. Cholesterol, triglycerides, and HDL-cholesterol were measured using the enzymatic colorimetric assay (Roche). LDL-cholesterol was calculated using the Friedewald formula. Dyslipidaemia was defined if one of the following was present: total cholesterol >200 mg/dl, triglycerides >150 mg/dl, HDL-cholesterol <40 in men or <50 mg/dl in women, or LDL-cholesterol >130 mg/dl. A standard technique was used to measure high-sensitivity C-reactive protein (CRP). ADAMTS13 and D-dimer were measured by electrochemiluminescence immunoassay method (MERCK® MILLIPLEX map Multiplex Detection). Both the intra- and inter-coefficients of variability were <10% for these assays. The homeostatic model assessment (HOMA) method was performed to determine IR. Briefly, the HOMA model enabled an estimate of insulin sensitiv-

ity (%S) and β-cell function (%B) from fasting plasma insulin, C peptide, and glucose concentrations. In this study we used HOMA2, the updated-computer HOMA model (22). This model can be used to assess insulin sensitivity and β-cell function from paired fasting plasma glucose and specific insulin, or C peptide, concentrations across a range of 1–2.200 pmol/l for insulin and 1–25 mmol/l for glucose. C peptide better estimates β-cell function since it is a marker of secretion; and insulin data is preferable when calculating %S since HOMA-%S is derived from glucose disposal as a function of insulin concentration. In our study, IR and %S were calculated using insulin serum levels. Otherwise, %B was calculated using C-peptide serum levels. The computer model provided a value for insulin sensitivity expressed as HOMA2-%S (in which 100% is normal). HOMA2-IR (insulin resistance index) is simply the reciprocal of %S. Higher HOMA2-IR values indicate greater insulin resistance and, therefore, worse metabolic control. Besides, HOMA2-%B values represent beta-cell function, where higher values generally indicate better pancreatic beta-cell activity. However, in the early stages of insulin resistance, HOMA2-%B might be elevated as beta cells compensate by secreting more insulin to maintain normal glucose levels. For the normal population, a HOMA2-IR value of approximately 1.0 is considered typical, while values exceeding 1.7–1.8 are commonly used to identify insulin resistance (23, 24). Insulin (Architect Abbott, 2000I) and C peptide (Immulite 2000, Siemens) were determined by chemiluminescent immunometric assays.

Statistical analysis

Demographic and clinical characteristics of patients SSc and controls were presented as mean (standard deviation) or percentages for categorical variables. For continuous variables that did not follow a normal distribution, data were reported as median and interquartile range (IQR). The association between disease-related data and ADAMTS13 was examined using multivariable linear regression analysis, with adjustments made for confounding variables. Confounders were selected from demographics if their *p*-values were below 0.20 in the univariable analysis to ADAMTS13. All analyses were conducted using Stata software, version 17/SE (StataCorp, College Station, TX, USA), with a two-sided

Table I. Demographics of systemic sclerosis patients and controls.

	Controls (n=76)	Scleroderma (n=81)	*p*
Demographics			
Female, n (%)	71 (93)	76 (94)	0.92
Age, years	61 ± 12	60 ± 11	0.44
BMI, kg/m^2	**31 ± 3**	**29 ± 6**	**0.022**
Cardiovascular comorbidity			
Hypertension, n (%)	37 (49)	32 (40)	0.25
Current smoking, n (%)	11 (14)	7 (9)	0.25
Diabetes, n (%)	**19 (26)**	**7 (9)**	**0.006**
Dyslipidaemia, n (%)	63 (83)	72 (89)	0.28
BMI >30 kg/m^2, n (%)	20 (26)	26 (32)	0.43
Statins, n (%)	29 (38)	20 (25)	0.069
Aspirin, n (%)	6 (20)	22 (27)	**<0.001**
Metabolic syndrome, n (%)	26 (63)	47 (61)	0.80
Carotid atherosclerosis			
Intima media thickness, microns		663 ± 146	
Plaque		28 (34)	
SCORE2 calculator, %	5 (2-9)	4 (2-7)	0.15
SCORE2 categories, n (%)			
Low to moderate	38 (50)	45 (56)	
High	30 (39)	27 (33)	0.72
Very high	8 (11)	9 (11)	
Systemic sclerosis related data			
SSc type, n (%)			
Limited, n (%)		66 (81)	
Diffuse, n (%)		15 (19)	
Disease duration, years		8 (4-11)	
Modified Rodnan Skin Score, units		4 (1-8)	
Raynaud phenomenon, n (%)		72 (90)	
Digital ulcers, n (%)		12 (15)	
Calcinosis, n (%)		13 (16)	
Arthritis, n (%)		8 (10)	
Gastric reflux, n (%)		41 (51)	
Pathological oesophageal manometry, n (%)		18 (55)	
Nailfold capillaroscopy pattern			
Normal		16 (22)	
Early		24 (33)	
Active		11 (15)	
Late		2 (3)	
Unclassified or not valuable		19 (26)	
Interstitial lung disease, n (%)		13 (17)	
FVC, %		93 ± 18	
FEV1, %		100 ± 18	
DLCO, %		75 ± 20	
Pulmonary hypertension, n (%)		12 (18)	
Anti-centromere antibody positivity, n (%)		55 (72)	
Anti-Scl70 antibody, n (%)		11 (14)	
Therapies			
Current NSAIDs, n (%)		8 (11)	
Current prednisone, n (%)		13 (16)	
Prednisone, mg/day		5 (5-7.5)	
Methotrexate, n (%)		4 (5)	
Chloroquine, n (%)		4 (5)	
Bosentan, n (%)		3 (4)	

Data represent mean±SD or median (IQR) when data were not normally distributed.
Oesophageal manometry assessment was available only for 33 patients.
BMI: body mass index; CRP: C reactive protein. SSc: systemic sclerosis.
NSAIDs: Non-steroidal anti-inflammatory drugs. SCORE2: Systematic Coronary Risk Assessment. FVC: forced vital capacity; FEV: forced expiratory volume; DLCO: diffusion capacity of the lung for the carbon monoxide. Significant *p*-values are reported in bold.

Table II. Differences in laboratory data between systemic sclerosis patients and controls.

	Univariable			Multivariable	
	Controls	Patients	*p*	Beta coef. (95%)	*p*
Laboratory data					
ADAMTS13, ng/ml	**2095 ± 562**	**1216 ± 359**	**<0.001**	**-706 (-920-493)**	**<0.001**
CRP, mg/dl	2.0 (1.0-4.3)	2.2 (0.8-4.6)	0.51		
D-dimer, ng/ml	61 ± 12	60 ± 11	0.44		
Lipid profile					
Cholesterol, mg/dl	205 ± 43	207 ± 37	0.71		
Triglycerides, mg/dl	**146 ± 64**	**187 ± 92**	**0.002**	**50 (0.6-100)**	**0.047**
HDL-cholesterol, mg/dl	55 ± 16	52 ± 12	0.16	**-10 (-18-(-2))**	**0.011**
LDL-cholesterol, mg/dl	120 ± 37	118 ± 33	0.66		
LDL:HDL-cholesterol ratio	2.3 ± 0.9	2.4 ± 0.9	0.74		
Non-HDL-cholesterol, mg/dl	149 ± 40	155 ± 36	0.35		
Lipoprotein A, mg/dl	49 (14-102)	36 (13-91)	0.80		
Apolipoprotein A1, mg/dl	**184 ± 40**	**165 ± 27**	**<0.001**	**-42 (-59-(-24))**	**<0.001**
Apolipoprotein B, mg/dl	105 ±30	105 ± 25	0.88		
ApoB:Apo A1 ratio	**0.6 ± 0.2**	**0.7 ± 0.2**	**0.048**	0.07 (-0.05-0.2)	0.23
Atherogenic index	3.9 ± 1.2	4.2 ± 1.2	0.21		
Insulin resistance indices					
Glucose, mg/dl	105 ± 27	98 ± 22	0.098	-8 (-20-3)	0.16
Insulin, µU/ml	8.9 (6.4-14.5)	9.4 (4.9-18.0)	0.15	3.8 (-4.5-12.0)	0.37
C-peptide, ng/ml	**2.6 ± 1.6**	**4.1 ± 3.2**	**<0.001**	1.6 (-0.1-3.3)	0.069
HOMA2-IR	1.2 (0.8-2.0)	1.3 (0.6-2.2)	0.17	0.5 (-0.61.5)	0.38
HOMA2-S%	91 ± 53	80 (45-160)	0.091	34 (-48-115)	0.42
HOMA2-B%-C-peptide	**120 ± 59**	**181 ± 122**	**<0.001**	58 (-12-127)	0.11
Insulin resistance indices in non-diabetic and glucose <110 mg/dl patients					
Glucose, mg/dl	93 ± 9	91 ± 11	0.24	1 (-7-9)	0.78
Insulin, µU/ml	10.3 ± 6.5	11.9 ± 14	0.46	-0.5 (-10-9)	0.92
C-peptide, ng/ml	**2.5 ± 1.4**	**3.7 ± 3.1**	**0.008**	1.2 (-0.9-3)	0.26
HOMA2-IR	1.3 ± 0.8	1.5 ± 1.6	0.54	-0.09 (-1-1)	0.87
HOMA2-S%	98 ± 48	142 ± 162	0.066	51 (-65-166)	0.39
HOMA2-B%-C-peptide	**134 ± 50**	**190 ± 130**	**0.004**	42 (-52-137)	0.37

HOMA2-IR: insulin resistance index through homeostatic model assessment (calculated with glucose and insulin serum levels).
HOMA2-S%: insulin sensitivity index through homeostatic model assessment (calculated with glucose and insulin serum levels).
HOMA2-B%-C-peptide: β-cell function index through homeostatic model assessment (calculated with glucose and C-peptide serum levels).
Non-diabetic and glucose <110 mg/dl controls and patients are respectively 51 y 61. Multivariable analysis is adjusted for body mass index, diabetes and the use of statins and aspirin. Significant *p*-values are reported in bold.
ADAMTS13: A disintegrin-like and metalloprotease with thrombospondin type 1 motif no. 13; LDL: low density lipoprotein; HDL: high density lipoprotein.

significance level set at 5%. A *p*-value less than 0.05 was considered statistically significant.

Results

Demographic, laboratory, and disease-related data in patients and controls

In our study, we included 81 patients with SSc and 76 healthy controls matched by age and sex. The characteristics of both populations are described in Table I. The subjects with SSc had a significantly lower BMI than the controls, although the effect size of this difference was small. No differences were found in the frequency of hypertension, dyslipidaemia, or smoking; however, patients with SSc were less frequently diabetic. Additionally, although patients with SSc tended to take statins less often, they were more likely to be on aspirin treatment. The SCORE2 values did not differ between the groups.

Eighty-one percent of the patients with SSc had the limited and 19% the diffuse type. The mean age at recruitment was 60±10 years. The disease duration was 8 (IQR 4–11) years. The median mRSS score was 4 (IQR 1-8). The presence of digital ulcers and calcinosis was reported in 15% and 19% of the patients, respectively. At the time the study was conducted, 16% of patients were taking prednisone, with a median dose of 5 (IQR 5–7.5) mg/day, and 5% of the patients were taking methotrexate. Additionally, 55 patients (72%) tested positive for anti-centromere antibodies, and 11 patients (14%) were positive for anti-Scl70 antibodies. Other features related to the disease are shown in Table I.

Differences in laboratory data between patients and controls are shown in Table II. ADAMTS13 serum values differed between controls and patients (2095±562 ng/ml *vs*.1216±359 ng/ml, $p<0.001$). This difference remained statistically significant after multivariable adjustment for BMI, diabetes, and the use of statins and aspirin. In contrast, CRP and D-dimer levels showed no differences between the two groups. Regarding the lipid profile, after adjusting for covariates, SSc patients had significantly higher triglyceride levels and lower HDL-cholesterol and apolipoprotein A1 values. Additionally, SSc patients tended to have higher indices of insulin resistance, both when considering all patients and only those without diabetes and with fasting glucose below 100 mg/dL. However, after

Table III. Relationship of disease characteristics to ADAMTS13 in patients with systemic sclerosis.

	ADAMTS13, ng/ml Beta coef. (95% CI),		*p*
Demographics			
Female, n (%)	-96	(-428-237)	0.57
Age, years	-2	(-10-6)	0.60
BMI, kg/m^2	4	(-10-18)	0.60
Cardiovascular comorbidity			
Hypertension, n (%)	40	(-129-208)	0.64
Current smoking, n (%)	-130	(-414-154)	0.37
Diabetes, n (%)	-84	(-369-201)	0.56
Dyslipidaemia, n (%)	45	(-211-300)	0.73
BMI > 30 kg/m2, n (%)	33	(-143-209)	0.71
Statins, n (%)	-55	(-242-132)	0.56
Aspirin, n (%)	-124	(-313-65)	0.20
Metabolic syndrome, n (%)	38	(-134-211)	0.66
Carotid atherosclerosis			
Intima media thickness, microns	-1	(-1-0.05)	0.074
Plaque	-35	(-261-190)	0.75
SCORE2 calculator, %	-3	(-22-16)	0.77
SCORE2 categories, n (%)			
Low to moderate	ref.		
High	-57	(-240-127)	0.54
Very high	22	(-257-300)	0.88
D-dimer, ng/ml	0.02	(-0.04-0.08)	0.53
Laboratory data			
CRP, mg/dl	**-29**	**(-53-(-5))**	**0.017**
Cholesterol, mg/dl	-2	(-4-0.5)	0.13
Triglycerides, mg/dl	-0.5	(-1-0.4)	0.27
HDL-cholesterol, mg/dl	-4	(-11-3)	0.29
LDL-cholesterol, mg/dl	-0.9	(-3-2)	0.51
LDL:HDL-cholesterol ratio	-20	(-127-86)	0.70
Non-HDL-cholesterol, mg/dl	-1	(-3-1)	0.24
Lipoprotein A, mg/dl	-0.6	(-2-0.5)	0.29
Apolipoprotein A1, mg/dl	-1	(-4-2)	0.37
Apolipoprotein B, mg/dl	-2	(-6-1)	0.17
ApoB:Apo A1 ratio	-195	(-621-231)	0.36
Atherogenic index	-30	(104-45)	0.43
Systemic sclerosis related data			
SSc type, n (%)			
Limited, n (%)	ref.		
Diffuse, n (%)	-29	(-237-179)	0.78
Disease duration, years	2	(-13-18)	0.75
Modified Rodnan Skin Score, units	-5	(-17-6)	0.36
Raynaud phenomenon, n (%)	-141	(-408-125)	0.29
Digital ulcers, n (%)q	-205	(-436-25)	0.080
Calcinosis, n (%)	-137	(-362-87)	0.23
Arthritis, n (%)	-67	(-353-218)	0.64
Gastric reflux, n (%)	-71	(-237-94)	0.40
Pathological oesophageal manometry, n (%)	15	(-266-296)	0.91
Nailfold capillaroscopy pattern			
Normal	ref.		
Pathological	144	(-56-344)	0.16
Interstitial lung disease, n (%)	-132	(-354-89)	0.24
FVC, %	-1	(-7-4)	0.65
FEV1, %	0.5	(-8-8)	0.91
DLCO, %	6	(0.007-11)	0.050
Pulmonary hypertension, n (%)	-100	(-346-146)	0.42
Anti-centromere antibody positivity, n (%)	-11	(-202-179)	0.91
Anti-Scl70 antibody, n (%)	0.6	(-240-241)	0.99
Therapies			
Current NSAIDs, n (%)	36	(-219-292)	0.78
Current prednisone, n (%)	100	(-118-319)	0.36
Prednisone, mg/day	0.7	(-158-160)	0.99
Methotrexate, n (%)	49	(-321-419)	0.79
Chloroquine, n (%)	33	(-338-403)	0.86
Bosentan, n (%)	-331	(-749-87)	0.12

In this analysis ADAMST3 is the dependent variable. Significant *p* values are reported in bold. NSAIDs: non-steroidal anti-inflammatory drugs; oesophageal manometry assessment was available only for 33 patients; BMI: body mass index; CRP: C reactive protein; SSc: systemic sclerosis; ADAMTS13: a disintegrin-like and metalloprotease with thrombospondin type 1 motif no. 13; SCORE2: Systematic Coronary Risk Assessment; FVC: forced vital capacity; FEV: forced expiratory volume; DLCO: diffusion capacity of the lung for the carbon monoxide.

multivariable adjustment, the statistical significance of these differences was lost (Table II).

Relationship of disease characteristics to ADAMTS13 in patients with SSc

Demographic characteristics, including age, sex, and BMI, as well as various cardiovascular risk factors, showed no significant association with ADAMTS13 levels (Table III). Similarly, no classical cardiovascular risk factors, the presence of metabolic syndrome, lipid profile, subclinical carotid atheromatosis, or the cardiovascular risk index SCORE2 were significantly related to serum ADAMTS13 values.

Concerning disease related data, CRP values were significantly and negatively related to ADAMTS13 (Table III). However, disease characteristics such as SSc subtype (diffuse or limited), Rodnan skin score, nailfold capillary patterns and the presence of visceral involvement (joint, pulmonary, or other) were not associated with ADAMTS13 levels. Similarly, the autoantibody profile and the use of specific therapies showed no relationship with ADAMTS13 (Table III). It should be noted that no multivariable analysis was conducted in this assessment due to unmet criteria for its application.

Relationship of insulin resistance indices to ADAMTS13 in patients and controls

The relationship between glucose homeostasis molecules and insulin resistance indices with ADAMTS13 in patients with SSc and controls is shown in Table IV. Both the total patient population and the subgroup of non-diabetic patients with glucose levels below 110 mg/dL demonstrated a positive and significant association between insulin, C-peptide, and indices of insulin resistance (HOMA2-IR) and beta-cell dysfunction (HOMA2-B%) with ADAMTS13 levels. In contrast, this relationship was not observed in healthy controls (Table IV). Since prednisone use and other disease characteristics were not associated with ADAMTS13, multivariable adjustment was not necessary.

Table IV. Relationship of insulin resistance indices to ADAMTS13.

	ADAMTS13, ng/ml Beta coefficient (95% CI), *p*					
	SSc patients (n=76)		Nondiabetic and glucose <110 mg/dl SSc patients (n=61)		Controls (n=81)	
Insulin resistance indices						
Glucose, mg/dl	0.3 (-4-4)	0.89	-3 (-12-6)	0.49	-3 (-7-2)	0.30
Insulin, μU/ml	**10 (5-15)**	**<0.001**	**14 (9-20)**	**<0.001**	6 (-9-21)	0.45
C-peptide, ng/ml	**35 (9-60)**	**0.008**	**38 (8-68)**	**0.014**	29 (-52-110)	0.48
HOMA2-IR	**74 (36-112)**	**<0.001**	**120 (71-169)**	**<0.001**	345 (-87-157)	0.57
HOMA2-S%	-0.2 (-0.8-0.4)	0.47	-0.2 (-0.8-0.4)	0.43	0.3 (-2-3)	0.80
HOMA2-B%-C-peptide	**0.9 (0.2-2)**	**0.009**	**0.9 (0.2-2)**	**0.011**	2 (-0.5-4)	0.12

In this analysis ADAMST3 is the dependent variable. Significant *p*-values are reported in bold.
HOMA2-IR: insulin resistance index through homeostatic model assessment (calculated with glucose and insulin serum levels).
HOMA2-S%: insulin sensitivity index through homeostatic model assessment (calculated with glucose and insulin serum levels).
HOMA2-B%-C-peptide: β-cell function index through homeostatic model assessment (calculated with glucose and C-peptide serum levels).
ADAMTS13: a disintegrin-like and metalloprotease with thrombospondin type 1 motif no. 13

Discussion

The present study confirms that serum ADAMTS13 levels are decreased in patients with SSc. This reduction in ADAMTS13 levels was negatively correlated with CRP levels. Moreover, a positive correlation between ADAMTS13 levels and insulin resistance was observed in SSc patients, a correlation that was not observed in the control group.

In our study, insulin resistance levels did not differ between patients and controls, but beta-cell function levels, as measured by the HOMA2-%B index, did. It is well known that, in early insulin resistance, beta cells increase C-peptide production as a compensatory response to counteract insulin resistance (25). Accordingly, our findings are consistent with prior reports on the pathophysiology of insulin resistance.

Matsuyama *et al*. assessed plasma ADAMTS13 levels in 127 patients with connective tissue diseases and thrombotic microangiopathies, including systemic lupus erythematosus, polymyositis/dermatomyositis, rheumatoid arthritis, and SSc, along with 64 patients with acquired idiopathic TTP (26). They found that ADAMTS13 activity was significantly decreased in patients with inflammatory/connective tissue diseases and thrombotic microangiopathies, regardless of the underlying condition. The frequency of severe deficiency was higher among patients with inflammatory/connective tissue diseases compared to those with acquired idiopathic TTP (26).

Consistent with our findings, Mannucci *et al*. found that ADAMTS13 levels were significantly lower in 87 SSc patients than in normal controls (27). Similarly, Gerlicz-Kowalczuk *et al*. reported decreased ADAMTS13 levels when comparing 39 SSc patients with 11 healthy controls (15). In another study, plasma levels of ADAMTS-13 were significantly lower in SSc patients with a D-dimer level of ≥1 μg/mL (16). However, we could not find an association between D-dimer and ADAMTS13 levels in our SSc patients. We do not have a definitive explanation for this discrepancy. However, it could potentially be attributed to the low D-dimer levels observed and the absence of thrombotic events among the patients.

As reported by Gerlicz-Kowalczuk *et al*. (15), our study also found no significant correlations between serum ADAMTS13 levels and organ changes in SSc patients. With respect to this, Zeng *et al*. evaluated blood samples from 19 healthy controls, 17 patients with idiopathic pulmonary fibrosis, 16 with interstitial lung disease associated with diffuse SSc, 11 with diffuse SSc without associated interstitial lung disease, 23 with limited SSc, and 18 with limited SSc without interstitial lung disease. Regardless of the phenotype, all patients with SSc exhibited lower levels of ADAMTS13 compared to healthy controls (28).

Levels of ADAMTS13 may have prognostic value in patients with SSc. In this regard, Mismetti *et al*. conducted a prospective multicentre study in patients with SSc-pulmonary hypertension associated with interstitial lung disease (29). They performed an untargeted proteomic analysis using mass spectrometry to identify plasma protein changes associated with long-term overall survival in these patients. Thirty-two patients were included in the analysis, of whom 13 died during follow-up (median survival: 76.5 months). Notably, in the survivor group, ADAMTS13 levels were higher compared to the non-survivor group (29). These findings suggest that low ADAMTS13 levels may be markers of poor prognosis and an increased risk of mortality among SSc patients.

Additionally, studies have shown that low ADAMTS13 activity is closely linked to endothelial dysfunction and an increased thrombotic risk (30, 31). For example, in a study of with a follow-up time of 10.7 years (56.403 total person-years), after adjustment for cardiovascular risk factors, individuals with ADAMTS13 activity in the lowest quartile had a higher risk of ischemic stroke (absolute risk, 7.3%) than did those in the reference highest quartile (30). Besides, in a study of 216 patients with systemic lupus erythematosus, reduced ADAMTS13 activity was a significant thrombotic risk factor in patients with antiphospholipid antibodies (31). ADAMTS13 is essential for cleaving vWF, and if this process is unregulated, it can lead to the accumulation of large vWF multimers that encourage

platelet aggregation and thrombus formation, especially in high-shear blood flow conditions. This dysfunction is associated with an increased risk of cardiovascular events, as reduced ADAMTS13 activity contributes to a prothrombotic state. For instance, in chronic conditions like renal failure and acute cases such as severe COVID-19, low ADAMTS13 levels correlate with increased cardiovascular mortality risk and more extensive vascular complications due to the imbalance in the ADAMTS13-vWF axis (32).

Another point of potential interest from our study is the relationship between ADAMTS13 levels, inflammation, and insulin resistance in SSc patients. In a recent study, we observed that interleukin-6 serum levels are associated with disease features and cardiovascular risk in patients with SSc (33). CRP is produced in response to interleukin-6 stimulation, and in our present study, we observed a significant negative association between CRP and ADAMTS13 levels. Chronic inflammation and fibrosis in SSc may contribute to insulin resistance by altering glucose metabolism and promoting systemic inflammation, which could impact vascular function and contribute to the progression of vasculopathy.

In individuals with metabolic disorders, reduced ADAMTS13 activity is linked to endothelial dysfunction and an elevated risk of thrombosis. Since insulin resistance can create a pro-inflammatory and pro-thrombotic environment, it may further worsen ADAMTS13 function, especially in SSc, where vascular damage is already a concern. Together, low ADAMTS13 and insulin resistance may synergistically increase disease severity. Insulin resistance can enhance systemic inflammation, further reducing ADAMTS13 activity and promoting clot formation via elevated vWF levels. This cycle of impaired ADAMTS13 function and insulin resistance may exacerbate microvascular injury, increasing the risk of complications in SSc patients. Additionally, insulin resistance is associated with endothelial dysfunction, potentially due to chronic low-grade inflammation and oxidative stress, both of which may worsen with decreased ADAMTS13 levels. In SSc, lower ADAMTS13 may contribute to a pro-inflammatory state that aggravates insulin resistance, with oxidative stress directly impairing insulin signalling.

In line with these findings, our study identified ADAMTS13 serum levels as an independent marker of insulin resistance in patients with SSc. Although this finding may initially appear paradoxical, it aligns with previous observations linking ADAMTS13 to metabolic markers associated with type 2 diabetes risk. However, ADAMTS13 activity has previously been shown to influence the risk of type 2 diabetes mellitus in a population-based cohort, including 5, 176 participants from the Rotterdam Study (34). Interestingly, both ADAMTS13 activity and VWF antigen levels were positively associated with baseline fasting insulin levels, and ADAMTS13 activity was also positively associated with baseline fasting glucose levels (34). The authors concluded that ADAMTS13 activity was associated with an increased risk of incident type 2 diabetes mellitus, even after adjusting for other known risk factors, including VWF antigen, fasting glucose, and fasting insulin levels. The authors pointed out that the mechanism underlying the association between ADAMTS13 activity and diabetes remains unclear. They argued that this association is unlikely to be explained solely by ADAMTS13's established function as a cleaving protease of VWF. If that were the case, we would expect VWF levels (prothrombotic) and ADAMTS13 activity (antithrombotic) to be associated with diabetes in opposite directions. Instead, they suggested that ADAMTS13 may possess additional proteolytic functions beyond VWF cleavage. They hypothesised that the link between ADAMTS13 activity and incident type 2 diabetes could involve interactions with one or more currently unknown proteins (34). These authors proposed that the association could involve pathways affected by ADAMTS13 activity. Notably, ADAMTS13 is known to upregulate vascular endothelial growth factor (VEGF), a protein involved in angiogenesis that may contribute to the development of type 2 diabetes (35, 36). These observations may also explain the positive correlation observed between ADAMTS13 levels and insulin resistance in patients with SSc.

We acknowledge the limitation that the prevalence of diabetes was significantly higher in controls compared to patients. For this reason, and to prevent this from influencing the results, diabetes was included as a confounder in the multivariable analysis. Furthermore, when the relationship between insulin resistance indices and ADAMTS13 levels was analysed, this was done separately for scleroderma patients with and without diabetes. In both analyses, significant associations were observed. For all the reasons mentioned, we believe that the difference in diabetes prevalence between patients and controls has not influenced our results. Moreover, the cross-sectional design of our study represents a limitation, as it precludes any inference of causality. Therefore, prospective longitudinal studies are needed to better elucidate the temporal relationships and potential causal mechanisms underlying our findings.

In summary, the interplay between ADAMTS13 serum levels and insulin resistance in SSc underscores a complex relationship that may contribute to the metabolic dysregulation observed in these patients. This emphasises the potential benefit of addressing insulin resistance and monitoring ADAMTS13 levels as part of a comprehensive approach to managing SSc.

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