Arthritis Care & Research
Vol. 68, No. 10, October 2016, pp 1538–1546
DOI 10.1002/acr.22852

ORIGINAL ARTICLE

Subclinical Atherosclerosis in Systemic Sclerosis: Not Less Frequent Than Rheumatoid Arthritis and Not Detected With Cardiovascular Risk Indices

GULSEN OZEN,[1] NEVSUN INANC,[1] ALI U. UNAL,[1] FATMANUR KORKMAZ,[1] MURAT SUNBUL,[1] MUSTAFA OZMEN,[2] SERVET AKAR,[2] RABIA DENIZ,[1] SALIM DONMEZ,[3] OMER N. PAMUK,[3] PAMIR ATAGUNDUZ,[1] KURSAT TIGEN,[1] AND HANER DIRESKENELI[1]

Objective. **To determine the frequency of subclinical atherosclerosis in patients with systemic sclerosis (SSc; scleroderma) compared to healthy subjects (HS) and rheumatoid arthritis (RA) patients and to determine the ability of cardiovascular (CV) risk indices in detecting SSc patients with subclinical atherosclerosis.**

Methods. **A total of 110 SSc patients (102 females and 8 males, mean ± SD age 50.5 ± 11.9 years), 110 age- and sex-matched RA patients, and 51 HS without CV disease were examined with ultrasonography (US). Carotid intima-media thickness (cIMT) >0.90 mm and/or carotid plaques were used as the gold standard for subclinical atherosclerosis (US+). Systematic Coronary Risk Evaluation (SCORE), QRisk II, and 2013 American College of Cardiology (ACC)/American Heart Association (AHA) CV risk indices were calculated.**

Results. **Twenty-one (19.1%) SSc patients, 24 (21.8%) RA patients, and 3 (5.9%) HS had subclinical atherosclerosis (SSc versus RA: $P = 0.62$, SSc versus HS: $P = 0.029$). cIMT in SSc was higher compared to HS (0.68 ± 0.15 mm versus 0.61 ± 0.10 mm; $P = 0.008$) but similar to RA patients (0.66 ± 0.14 mm; $P = 0.82$). Subclinical atherosclerosis in SSc was associated with age (odds ratio [OR] 1.07, $P = 0.013$), elevated erythrocyte sedimentation rate (OR 3.4, $P = 0.045$), and pulmonary arterial hypertension (OR 4.27, $P = 0.012$). Concerning CV risk indices, of the 21 US+ SSc patients only 0, 3 (14.2%), and 6 (28.6%) were classified as high CV risk according to SCORE, QRisk II, and ACC/AHA risk indices, respectively.**

Conclusion. **Subclinical atherosclerosis in SSc patients is more frequent than in HS, but is as frequent as in RA patients in which accelerated atherosclerosis is clearly defined. CV risk indices for the general population are considerably insufficient to detect SSc patients with atherosclerosis.**

INTRODUCTION

Systemic sclerosis (SSc; scleroderma) is a chronic autoimmune disease characterized by endothelial dysfunction, microvascular damage, and increased tissue fibrosis. Although microvascular disease is the hallmark of SSc, during the last decade it has been shown that macrovascular disease, regarded as cardiovascular disease (CVD), is also increased in SSc compared to healthy subjects (HS) (1–4). The increase in CVD is well-described in other autoimmune diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) (5–7). In RA and SLE, this increased CVD is related to accelerated atherosclerosis and is mostly attributed to the interaction between disease-related chronic inflammation and traditional CV risk factors (8). However, in the disease process of SSc, compared to RA and SLE, there is less prominent inflammation with more significant vascular dysfunction and fibrosis. Currently, although some conflicting data exist about atherosclerosis in SSc (9–18), it is still not clear whether increased CVD in SSc is due to accelerated atherosclerosis or disease-related processes.

Being associated with the highest mortality among the connective tissue disorders, the prognosis of SSc worsens in the presence of CVD (19). In 2010, the European League Against Rheumatism (EULAR) Scleroderma Trials and Research database survey reported that CVD accounted for 29% of the SSc mortality (20). Recently, analysis of a large

[1]Gulsen Ozen, MD, Nevsun Inanc, MD, Ali U. Unal, MD, Fatmanur Korkmaz, MD, Murat Sunbul, MD, Rabia Deniz, MD, Pamir Atagunduz, MD, Kursat Tigen, MD, Haner Direskeneli, MD: Marmara University Faculty of Medicine, Istanbul, Turkey; [2]Mustafa Ozmen, MD, Servet Akar, MD: Katip Celebi University Faculty of Medicine, Izmir, Turkey; [3]Salim Donmez, MD, Omer N. Pamuk, MD: Trakya University Faculty of Medicine, Edirne, Turkey.

Address correspondence to Gulsen Ozen, MD, Marmara University, Faculty of Medicine, Department of Rheumatology, Fevzi Cakmak Mah, Muhsin Yazicioglu Str. No:10, Pendik, 34899, Istanbul, Turkey. E-mail: ozengs@yahoo.com.

Submitted for publication September 2, 2015; accepted in revised form January 26, 2016.

Significance & Innovations

- The prevalence of subclinical atherosclerosis in systemic sclerosis (SSc; scleroderma) patients is higher than healthy subjects but similar to rheumatoid arthritis patients.
- Older age, elevated erythrocyte sedimentation rate, and presence of pulmonary arterial hypertension are independently associated with subclinical atherosclerosis in SSc.
- Neither the Systematic Coronary Risk Evaluation, nor the QRisk II, nor the 2013 American College of Cardiology/American Heart Association 10-year atherosclerotic cardiovascular disease risk indices could adequately identify SSc patients with subclinical atherosclerosis.

hospitalization database revealed that 5.4% of 308,452 SSc hospitalizations were related to atherosclerotic CVD (AS-CVD) as the primary discharge diagnosis. Furthermore, this study demonstrated that in-hospital mortality of SSc patients with CVD was significantly higher than SSc patients without CVD, and SLE and RA patients with CVD (21). Although interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are the leading causes of death in SSc, it is anticipated that as SSc survival improves with advances in treatment, CVD will further contribute to the mortality burden of SSc. Therefore, accurate understanding of mechanisms underlying SSc-associated CVD and appropriate CVD risk assessment in SSc patients are very important in improving overall outcomes in SSc. However, in SSc there are very few comparative studies with other inflammatory diseases in regard to atherosclerosis and CVD. Particularly, the extent of subclinical atherosclerosis in SSc compared to RA, a disease with well-established association with accelerated atherosclerosis, has never been evaluated. Furthermore, unlike RA in which certain risk models are recommended for CV risk assessment by EULAR (22), there is no data about how to assess CV risk in an SSc patient. Therefore, in this study we aimed to 1) determine the frequency of subclinical atherosclerosis in patients with SSc compared to RA patients and HS, and 2) determine the performance of CV risk models for the general population in detecting high CV risk SSc patients.

PATIENTS AND METHODS

Study design and patients. For this cross-sectional study, SSc patients age ≥18 years and fulfilling the 1980 American College of Rheumatology (ACR) criteria for SSc (23) were enrolled from 3 tertiary rheumatology clinics over a 1-year period. Control groups were comprised of age- and sex-matched RA patients fulfilling 1987 ACR criteria (24) and HS from the same rheumatology clinics. Participants with a history of CVD (ischemic heart disease, cerebrovascular events, peripheral arterial disease or heart failure), type 1 or 2 diabetes mellitus (DM), chronic kidney disease, current pregnancy, or malignancy were excluded. Among 211 SSc and 268 RA patients consecutively evaluated, 110 patients for each group were found to be eligible for the study. Fifty-one age- and sex-matched HS were also included as the control group. Demographics and disease characteristics, including autoantibodies, internal organ involvements and other comorbidities, all previous and current medications and disease activities (SSc: European Scleroderma Study Group activity index score; RA: Disease Activity Score in 28 joints [DAS28] using the erythrocyte sedimentation rate [ESR, mm/hour]), and ESR and C-reactive protein (CRP, mg/liter) level values at the recruitment period were recorded (25). Disease duration for SSc is 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 distribution of skin thickness. The extent of skin involvement was evaluated by using the modified Rodnan skin score (MRSS) (26). ILD was defined as signs of fibrosis on radiograph, high-resolution computed tomography, or by abnormal pulmonary function tests (PFTs). All SSc patients with clinical, echocardiographic, or PFT suspicion of PAH underwent right-sided heart catheterization. Patients with a mean pulmonary artery pressure ≥25 mm Hg at rest and an end-expiratory pulmonary artery wedge pressure ≤15 mm Hg, and a pulmonary vascular resistance >3 Wood units were defined as having PAH (27). Esophageal involvement was defined as any sign of dysmotility evident on endoscopy, esophagography, or manometry. Articular involvement was determined by clinical evidence of joint swelling, deformity, contractures, and tendon friction rubs or radiographic evidence of joint space narrowing or erosion.

Glucocorticoid exposure of all patients was also determined as "exposure duration." Data regarding total glucocorticoid and separately low-dose (<10 mg/day prednisolone or equivalent) and high-dose (≥10 mg/day prednisolone or equivalent) glucocorticoid treatment durations were collected by examining all previous records (median [minimum–maximum] visit count: 15 [2–80]). During the review of previous records, all DAS28 scores of RA patients in each visit were also collected and an average DAS28 score was calculated for each RA patient. CV risk factors including hypertension (HT), smoking status, and family history of CVD were determined. At the time of recruitment, blood pressure (BP), waist circumference (cm), weight (kg), and height (m) were measured, and body mass index (BMI) was calculated. HT was defined by use of antihypertensive medication or systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg on at least 2 occasions. The fasting lipid and glucose concentrations of all patients and HS that were measured enzymatically with commercially available assay kits (AU5800, Beckman Coulter, and E170 Modular, Roche, respectively) in each hospital laboratory within the previous 6 months were recorded. Atherogenic index (total cholesterol/high-density lipoprotein [HDL] cholesterol) was calculated. Impaired fasting glucose (defined as fasting plasma glucose 100–125 mg/dl) was regarded as

prediabetes (28). All participants were also evaluated for the presence of metabolic syndrome, which was defined according to the National Cholesterol Education Programme's Adult Treatment Panel III definition (29). The study was approved by the local Institutional Research Ethics Board for multicenter studies, and informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

Carotid ultrasonography (US) examination. All participants were evaluated with carotid US. Carotid US examination was performed by using a commercially available Vivid 7 (GE Healthcare) ultrasound system with a 10-MHz linear transducer. Images were obtained for the detection of focal plaques in the extracranial carotid tree and measurement of carotid intima-media thickness (cIMT) in the common carotid artery, 2 cm distal from carotid bifurcation. All the obtained images were examined and read by a single, blinded, experienced sonographer-cardiologist (MS). cIMT >0.90 mm and/or carotid plaques were used as the gold-standard test for subclinical atherosclerosis and high CV risk (30,31). Patients with any of the mentioned US findings were regarded as having subclinical atherosclerosis and being true high CV–risk patients (US+).

Cardiovascular risk assessment. Three CV risk assessment algorithms, including Systematic Coronary Risk Evaluation (SCORE) (32), QRisk II (33), and 2013 American College of Cardiology (ACC)/American Heart Association (AHA) 10-year AS-CVD (34) were used to calculate the 10-year risk of a CV event in SSc patients. All risk algorithms include sex, smoking, atherogenic index, and systolic BP. The 2013 ACC/AHA 10-year AS-CVD and QRisk II additionally consist of treatment for high BP (yes/no) and presence of DM (yes/no). QRisk II also involves the presence of family history of early CVD, chronic kidney disease, atrial fibrillation, BMI, and Townsend deprivation score (33). As the latter was not available in our cohort, the adjusted QRisk II algorithm was calculated excluding this variable (35). In QRisk II, RA is included as an independent risk factor as well; in RA cases the calculated risk score is multiplied by 1.4 (33). For SSc patients, QRisk II was also calculated a second time as if SSc were RA equivalent, and this score was recorded as modified QRisk II (mQRisk II). Patients with SCORE ≥5% or QRisk II or modified version ≥20%, or AS-CVD ≥7.5% were categorized as high CV–risk patients.

Statistical analysis. Statistical analysis was performed using the SPSS software, version 16.0. Continuous variables were presented as mean ± SD or median with interquartile range, depending on the distribution of the data. The differences in demographics, clinical features, and carotid US findings among study and control groups were evaluated using either chi-square and Student's *t*-test or nonparametric tests (Wilcoxon's signed rank test, Mann-Whitney U test), as applicable. Correlations between carotid US findings and clinical parameters were analyzed by Pearson's correlation coefficient. Multivariable logistic regression analysis was used to adjust the baseline differences between study groups. The potential confounders were age, disease duration, BP, total and HDL cholesterol, waist circumference, prediabetes, acute-phase reactants, average DAS28 score, vasodilator, antiaggregant and glucocorticoid treatments, and synthetic and biologic disease-modifying antirrheumatic drugs (DMARDs). As the strongest evidence for CVD protection exists for methotrexate and tumor necrosis factor inhibitors (TNFi) in RA, these 2 DMARDs were included in the multivariable regression analysis as "ever-used." Ever-used was defined as active or previous methotrexate or TNFi treatment of at least 1 year's duration. Additionally, a stepwise multivariable logistic regression model was used to analyze for determination of SSc-related independent risk factors for subclinical atherosclerosis. The following variables with a P value of less than 0.05 in univariate analysis were included in the analysis: age, PAH, elevated ESR at recruitment, HT, metabolic syndrome, and disease duration. Hosmer-Lemeshow goodness-of-fit statistics were used to assess model fit. The level of significance was chosen to be P less than 0.05.

To evaluate the capacity of the CV risk indices to discriminate between patients with and without subclinical atherosclerosis, receiver operating characteristic curves with corresponding areas under the curve (AUCs) were calculated. The sensitivity and specificity of the CV risk indices were also evaluated by 2 × 2 classification tables.

RESULTS

Patient characteristics and carotid US results. The study cohort consisted of 110 SSc patients (47 diffuse and 63 limited, 98.2% antinuclear antibody positive), 110 RA patients (80% seropositive for rheumatoid factor and/or anti–cyclic citrullinated peptide, mean ± SD DAS28 3.42 ± 1.35), and 51 HS (Table 1). Anti–Scl-70 antibody was positive in 17 (15.5%), and anticentromere antibody was positive in 23 (20.9%) patients. ILD, PAH (both SSc pulmonary vasculopathy–related PAH and ILD-related PAH), esophageal and articular involvement, and active/previous digital ulcers were present in 58 (52.7%), 22 (20%), 64 (58.2%), 48 (43.6%), and 47 (42.7%) SSc patients, respectively.

Twenty-one SSc patients (19.1%), 24 RA patients (21.8%), and 3 HS (5.9%) had subclinical atherosclerosis (SSc versus RA: $P = 0.62$; SSc versus HS: $P = 0.029$). Both left (0.68 ± 0.15 mm versus 0.61 ± 0.10 mm; $P = 0.008$) and right (0.66 ± 0.15 mm versus 0.61 ± 0.09 mm; $P = 0.033$) cIMT in SSc patients were significantly higher compared to HS. Prevalence of carotid plaques was also significantly higher in SSc patients compared to HS (Table 1). On the other hand, the prevalence of subclinical atherosclerosis (both cIMT and carotid plaques) was similar in SSc and RA patients (for RA: left cIMT 0.68 ± 0.14 mm; right cIMT 0.66 ± 0.14 mm).

Comparison of demographics and traditional CV risk factors of SSc and RA patients and HS are shown in Table 1. After adjustment of baseline differences between disease groups and HS, the risk of subclinical atherosclerosis was found to be significantly higher both in SSc patients

Table 1. Demographics, CV risk factors, and carotid US findings of SSc, RA, and healthy subjects*

	SSc patients (n = 110)	RA patients (n = 110)	Healthy subjects (n = 51)	SSc vs. RA, *P*	SSc vs. HS, *P*
Female, no. (%)	102 (92.7)	101 (91.8)	43 (84.3)	0.80	0.10
Age, mean ± SD years	50.5 ± 11.9	49.6 ± 10.3	47.4 ± 10.4	0.52	0.11
Disease duration, mean ± SD years	6.8 ± 6.3	11.7 ± 7.5	–	< 0.001	–
Ever smoked, no. (%)	32 (29.1)	32 (29.1)	13 (25.5)	1.0	0.64
Hypertension, no. (%)	39 (35.5)	37 (33.6)	12 (23.5)	0.77	0.13
Systolic blood pressure, mean ± SD mm Hg	116.4 ± 19.8	123.6 ± 20.5	117.4 ± 17.7	0.008	0.73
Diastolic blood pressure, mean ± SD mm Hg	73.6 ± 13.1	76.9 ± 19.9	75.2 ± 11.8	0.043	0.45
Body mass index, mean ± SD kg/m^2	26.2 ± 4.9	27.0 ± 9.0	26.6 ± 3.5	0.40	0.58
Obesity, no. (%)†	30 (27.3)	39 (35.5)	8 (15.7)	0.19	0.11
Waist circumference, mean ± SD cm	89.8 ± 14.3	97.1 ± 15.7	96.1 ± 10.2	< 0.001	0.005
Total cholesterol, mean ± SD mg/dl	185.7 ± 43.2	197.3 ± 41.2	194.2 ± 44.9	0.042	0.25
Total cholesterol/HDL cholesterol, mean ± SD mg/dl	3.71 ± 1.19	3.68 ± 1.33	3.65 ± 1.09	0.83	0.75
LDL cholesterol, mean ± SD mg/dl	108.3 ± 35.5	113.2 ± 34.0	113.6 ± 36.0	0.29	0.38
HDL cholesterol, mean ± SD mg/dl	53.3 ± 18.2	57.6 ± 16.9	53.9 ± 14.4	0.072	0.83
Low HDL cholesterol, no. (%)‡	56 (50.9)	46 (41.8)	18 (35.3)	0.18	0.064
Triglycerides, mean ± SD mg/dl	126.0 ± 64.5	119.8 ± 58.7	121.8 ± 58.5	0.46	0.16
Triglycerides ≥150 mg/dl, no. (%)	30 (27.3)	23 (20.9)	10 (19.6)	0.27	0.29
Prediabetes mellitus, no. (%)	19 (17.3)	16 (14.5)	2 (3.9)	0.58	0.019
Metabolic syndrome, no. (%)§	35 (31.8)	36 (32.7)	8 (15.7)	0.88	0.031
ESR, mm/hour, median (IQR)	19 (12–29.5)	20 (10–31)	13 (7–22)	0.84	0.003
CRP, mg/liter, median (IQR)	3.7 (1.7–6.9)	5.2 (2.3–10.6)	3.4 (1.7–4.1)	0.037	0.064
Glucocorticoid treatment, no. (%)	48 (44)	59 (53.6)	–	0.15	–
Total glucocorticoid exposure duration, median (IQR) months	12 (0–30)	18 (12–42)	–	0.001	–
Low-dose exposure period	10.5 (0–30)	18 (11.2–37.5)	–	0.001	–
High-dose exposure period	0 (0–0)	0 (0–0.25)	–	0.41	–
Statin treatment, no. (%)	3 (2.7)	5 (4.5)	2 (3.9)	0.48	0.68
Anti-aggregant treatment, no. (%)	36 (32.7)	24 (21.8)	3 (5.9)	0.069	< 0.001
Vasodilator treatment, no. (%)	68 (61.8)	54 (49.1)	12 (23.5)	0.059	< 0.001
Left cIMT, mean ± SD mm	0.68 ± 0.15	0.68 ± 0.14	0.61 ± 0.10	0.82	0.008
Right cIMT, mean ± SD mm	0.66 ± 0.15	0.66 ± 0.14	0.61 ± 0.09	0.94	0.033
Carotid plaques, no. (%)	13 (11.8)	16 (14.5)	1 (2)	0.55	0.039
cIMT ≥0.90 mm, no. (%)	15 (13.6)	14 (12.7)	2 (3.9)	0.84	0.044
cIMT ≥0.90 mm and/or carotid plaques, no. (%)	21 (19.1)	24 (21.8)	3 (5.9)	0.62	0.029

* CV = cardiovascular; US = ultrasonography; SSc = systemic sclerosis; RA = rheumatoid arthritis; HS = healthy subjects; HDL = high-density lipoprotein; LDL = low-density lipoprotein; ESR = erythrocyte sedimentation rate; IQR = interquartile range; CRP = C-reactive protein; cIMT = carotid intima-media thickness.
† Obesity is defined as body mass index ≥30 kg/m^2.
‡ Low HDL cholesterol is defined as HDL cholesterol <40 mg/dl in males and <50 mg/dl in females.
§ Metabolic syndrome is defined according to the National Cholesterol Education Programme's Adult Treatment Panel III definition.

(odds ratio [OR] 3.65, 95% confidence interval [95% CI] 1.02–13.06, $P = 0.046$) and RA patients (OR 3.62, 95% CI 1.02–12.94, $P = 0.048$). When we adjusted baseline differences between SSc and RA patients, the risk of subclinical atherosclerosis in SSc patients (OR 0.50, 95% CI 0.12–2.04, $P = 0.33$) was not lower compared to RA patients.

Factors associated with subclinical atherosclerosis in SSc patients. Comparison of disease characteristics and traditional CV risk factors of US+ and US− SSc patients is shown in Table 2. Age, elevated ESR, and presence of PAH were significantly higher in US+ SSc patients. Although cIMT showed significant positive correlation with the disease duration ($r = 0.226$, $P = 0.018$), disease durations of US+ and US− patients were not significantly different. Likewise, autoantibody profiles, glucocorticoid and other immunosupressive treatments (including cyclophosphamide), mean MRSS, diffusion capacity of the lung for carbon monoxide, and forced vital capacity were not different in US+ patients compared to US− patients.

Regarding traditional risk factors, HT and metabolic syndrome were significantly higher in US+ patients (Table 2).

We also analyzed the differences between SSc patients with and without plaques regardless of cIMT and patients with and without cIMT ≥0.90 mm regardless of plaque presence. The differences were exactly the same as the comparison of patients with and without subclinical atherosclerosis.

Baseline variables that were associated with subclinical atherosclerosis at $P < 0.05$ in univariate analysis and disease duration that was significantly correlated with cIMT

Table 2. Characteristics of US+ and US– SSc patients*

	US (+) (n = 21)	US (–) (n = 89)	*P*
Female, no. (%)	19 (90.5)	83 (93.3)	0.66
Age, mean ± SD years	58.9 ± 11.5	48.5 ± 11.1	< 0.001
Disease duration, mean ± SD years	7.2 ± 7.3	6.7 ± 6.1	0.75
Diffuse SSc, no. (%)	7 (33.3)	40 (44.9)	0.33
Anticentromere positivity, no. (%)	4 (19)	19 (21.3)	0.81
MRSS (0–51), mean ± SD	10.8 ± 7.6	12.0 ± 7.9	0.52
Interstitial lung disease, no. (%)	12 (57.1)	46 (51.7)	0.65
PAH, no. (%)	10 (47.6)	12 (13.5)	< 0.001
Digital ulcer, no. (%)	9 (42.9)	38 (42.7)	0.98
Articular involvement, no. (%)	39 (43.8)	9 (42.9)	0.94
Active disease†	6 (28.6)	18 (20.2)	0.22
Current glucocorticoid treatment, no. (%)	9 (42.9)	39 (43.8)	0.94
Total glucocorticoid exposure duration, median (IQR) months	6 (0–28.5)	12 (0–33)	0.66
Low-dose exposure period	6 (0–25)	12 (0–30)	0.79
High-dose exposure period	0 (0–0)	0 (0–0)	0.35
ESR above upper reference value, no. (%)	16 (76.2)	37 (41.6)	0.004
CRP above upper reference value, no. (%)	10 (47.6)	30 (33.7)	0.23
Hypertension, no. (%)	12 (57.1)	27 (30.3)	0.021
Ever smoked, no. (%)	6 (28.6)	26 (29.2)	0.95
Pre–diabetes mellitus, no. (%)	4 (19)	15 (16.9)	0.81
Obesity, no. (%)‡	7 (33.3)	23 (25.8)	0.49
Low HDL cholesterol, no. (%)§	12 (57.1)	44 (49.4)	0.53
Total cholesterol/HDL cholesterol, mean ± SD	3.74 ± 1.05	3.72 ± 1.22	0.92
LDL cholesterol, mean ± SD mg/dl	102.3 ± 29.7	109.7 ± 36.8	0.39
Metabolic syndrome, no. (%)¶	11 (52.4)	24 (27)	0.025
Statin treatment, no. (%)	2 (2.2)	1 (4.8)	0.53
Anti-aggregant treatment, no. (%)	29 (32.6)	7 (33.3)	0.95
Vasodilator treatment, no. (%)	52 (58.4)	16 (76.2)	0.13

* US = ultrasonography; SSc = systemic sclerosis; MRSS = modified Rodnan skin score; PAH = pulmonary arterial hypertension; IQR = interquartile range; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
† Active disease is defined as the European Scleroderma Study Group activity index score of >3.
‡ Obesity is defined as body mass index ≥30 kg/m^2.
§ Low HDL cholesterol is defined as HDL cholesterol <40 mg/dl in males and <50 mg/dl in females.
¶ Metabolic syndrome is defined according to the National Cholesterol Education Programme's Adult Treatment Panel III definition.

were used in multivariable logistic regression analysis. In regression analysis, older age, having PAH, and elevated ESR were independently associated with subclinical atherosclerosis (Table 3). Addition of glucocorticoid exposure (ever [≥1 month] and/or total duration) to the multivariate model showed similar results without any significant association with glucocorticoid exposure (data not shown). Furthermore, when other confounding factors between HS and SSc patients were adjusted, again neither ever (OR 1.12, 95% CI 0.37–3.36, $P = 0.84$) nor total glucocorticoid exposure (OR 1.00, 95% CI 0.98–1.02, $P = 0.70$) were associated with subclinical atherosclerosis in SSc.

Performances of cardiovascular risk algorithms in SSc. Discriminating capacities of the 3 risk indices were poor, with AUC 0.494 (95% CI 0.355–0.634) of SCORE,

Table 3. Predictors of subclinical atherosclerosis in SSc patients*

Variables	β	OR (95% CI)	*P*
Age	0.069	1.07 (1.02–1.13)	0.013
Disease duration	−0.29	0.97 (0.89–1.06)	0.52
Pulmonary arterial hypertension	1.451	4.27 (1.37–13.27)	0.012
Elevated ESR at study entry	1.225	3.40 (1.03–11.2)	0.045
Hypertension	0.771	2.10 (0.59–7.89)	0.24
Metabolic syndrome	0.526	1.69 (0.51–5.62)	0.39

* SSc = systemic sclerosis; OR = odds ratio; 95% CI = 95% confidence interval; ESR = erythrocyte sedimentation rate.

Table 4. Sensitivity and specificity of CV risk indices in SSc with different cutoff points*

	Sensitivity	Specificity
SCORE		
≥5%	0	98.9
≥1%	52.4	80.9
QRisk II		
≥20%	14.3	100
≥10%	38.1	87.6
Modified QRisk II		
≥20%	19	96.6
≥10%	47.6	85.4
2013 ACC/AHA 10-year AS-CVD risk		
≥7.5%	28.6	87.6
≥5%	33.3	82

* Values are the percentage. CV = cardiovascular; SSc = systemic sclerosis; SCORE = Systematic Coronary Risk Evaluation; ACC/AHA = American College of Cardiology/American Heart Association; AS-CVD = atherosclerotic cardiovascular disease.

AUC 0.575 (95% CI 0.425–0.725) of QRisk II, and AUC 0.588 (95% CI 0.441–0.735) of ACC/AHA 10-year AS-CVD risk. Furthermore, the ability of identification of the patients with subclinical atherosclerosis was also not satisfactory. Sensitivity and specificity of the CV risk indices are shown in Table 4. SCORE classified none of the US+ patients as high CV risk, whereas QRisk II and 2013 ACC/AHA risk indices classified only 3 (14.2%) and 6 (28.6%) of 21 US+ patients as high CV risk. Neither the modified version of QRisk II nor the lowered cutoff values for risk indices (SCORE ≥1%, QRisk II ≥10%, and 2013 ACC/AHA 10-year AS-CVD ≥5%) significantly improved the performance of risk indices in SSc (Table 4).

DISCUSSION

Premature CVD, as a consequence of accelerated atherosclerosis, is the leading cause of mortality and morbidity in autoimmune rheumatic diseases, particularly in RA and SLE (5,6). Although increased CVD in SSc has been reported in population-based cohort studies (2–4,36), there are controversial data regarding the prevalence of atherosclerosis in SSc (9–11,13–18,37). The present study showed that SSc patients had significantly higher cIMT and more frequent carotid plaques and increased cIMT, i.e., subclinical atherosclerosis, compared to HS. This increased atherosclerosis prevalence in SSc patients was even comparable to age- and sex-matched RA patients.

cIMT and carotid plaques evaluated by US are good surrogate markers of future coronary heart disease, stroke, and death both in the general population (31) and inflammatory rheumatic diseases (18). These surrogate markers of atherosclerosis have also been investigated in SSc. Although cIMT and carotid plaque prevalence were widely varied among different studies (9–12), pooled data from meta-analyses and recent larger studies indicated that SSc patients had both a higher frequency of subclinical atherosclerosis and higher cIMT compared to HS (13,16,18). The discrepancies in the study results could be partially explained by differences in included patients and the sample sizes. Our study is one of the largest sample size studies evaluating cIMT and carotid plaques in SSc. Besides higher risk of subclinical atherosclerosis in SSc compared to HS, we also demonstrated that subclinical atherosclerosis risk in SSc is comparable to the risk in RA in which accelerated atherosclerosis is clearly defined.

Currently, there is limited information about underlying mechanisms of atherosclerosis in SSc. Atherosclerosis is known as a dynamic process that endothelial dysfunction, inflammation, and traditional CV risk factors concurrently play roles. It is unlikely that traditional CV risk factors per se fully explain the increased prevalence of atherosclerosis in SSc, as after adjustment of confounding factors in HS and SSc patients the risk of subclinical atherosclerosis was still 3 times higher than HS. Studies of atherosclerosis and CVD in SSc, including large population-based studies, also did not suggest strong contributions of traditional CV risks on either atherosclerosis or CVD (3,4,17,38). In our study, despite the higher CRP levels, longer disease duration, and worse CV risk profile with higher systolic and diastolic BP, waist circumference, and total cholesterol levels in RA patients, the frequency of subclinical atherosclerosis in SSc patients was similar to RA patients. One of the reasons for this may be the presence of more significant endothelial dysfunction in SSc instead of the inflammation of RA. A recent study, in which serum proteins implicated in vasculopathy and fibrosis were analyzed, supports this hypothesis (16). Schiopu et al reported that SSc patients with plaques had higher levels of those proteins compared to SSc patients without plaques (16).

Another noteworthy finding of our study was the association of elevated ESR with subclinical atherosclerosis in SSc. Although inflammation plays a very important role in all stages of atherosclerosis/thrombosis and is regarded as the main reason for increased CVD in autoimmune diseases (39,40), in SSc inflammation it is not as prominent and severe as in RA or SLE. The majority of the studies of CVD or atherosclerosis in SSc either did not evaluate acute-phase reactants or did not show any difference in the levels of ESR or CRP between SSc patients with and without CVD or atherosclerosis (3,9,11,38). Besides our study, the contribution of inflammation has been shown in only 1 recent study (16). In that study, although serum ESR and CRP levels were similar in SSc patients with and without carotid plaques, serum CRP and inflammatory cytokines were found to be associated with carotid plaques but not with cIMT (16). However, this finding about ESR in our study should be interpreted cautiously as the inflammatory biomarker ESR is more variable than CRP and can be affected by age, sex, anemia, and several other factors that are not uncommon in SSc patients.

Comparison of SSc patients with and without subclinical atherosclerosis in terms of disease characteristics and traditional CV risk factors also gave additional information about the predisposing causes of atherosclerosis in SSc. In multivariable analysis, only age, PAH, and elevated ESR were found to be independently associated with subclinical atherosclerosis in SSc. Regarding traditional CV

risk factors, the previous studies with higher prevalence of atherosclerosis in SSc indicated an association with age, HT, atherogenic lipid profile (low HDL cholesterol, high triglyceride), and cigarette smoking (pack-years) (3,17,36,41). However, the effect of metabolic syndrome, a well-known CV risk factor, on atherosclerosis in SSc has not been evaluated yet. In our cohort, besides higher prevalence of metabolic syndrome in SSc patients with subclinical atherosclerosis (~52%), metabolic syndrome was also 2 times more prevalent in SSc patients than in HS (32% versus 16%). Despite metabolic syndrome not being associated with subclinical atherosclerosis in SSc in multivariate analysis, it is possible that it may have an effect on plaque stability. Considering this high frequency of metabolic syndrome in SSc and detrimental CV effects in the general population (42), evaluation of metabolic syndrome in SSc may be a part of standard care of an SSc patient.

Concerning disease characteristics, disease duration, anticentromere antibody positivity, cumulative glucocorticoid dose, and MRSS (negatively) have been reported to be associated with CVD and/or atherosclerosis in SSc (36,37,41,43). However, PAH was found to be associated with CVD only in a systematic review of the prevalence of coronary heart disease in SSc (1). In our study, the strongest association with subclinical atherosclerosis in SSc was observed with PAH (OR 4). This finding is important because it indicates that microvascular disease in SSc, like PAH with robust data about association with endothelial dysfunction (44,45), may have implications in macrovascular disease and atherosclerosis in SSc.

Glucocorticoid use is regarded as one of the main reasons for accelerated atherosclerosis in autoimmune diseases. However, so far, only 1 study evaluated the consequences of previous glucocorticoid use on atherosclerosis in SSc patients (37). That study reported that higher cumulative glucocorticoid intake was associated with higher cIMT (OR 1.15). Interestingly, in a larger cohort of SSc patients, we found that cumulative glucocorticoid exposure duration (ever/low-/high-dose exposures) was not associated with subclinical atherosclerosis. On the other hand, in the RA group in which total glucocorticoid exposure duration was higher, glucocorticoid exposure durations were associated with subclinical atherosclerosis (OR 1.023; data not shown).

Finally, in light of these data, the assessment of CV risk in SSc patients seems to have important prognostic and therapeutic relevance. However, there are still no data about how to assess CV risk in SSc in which subclinical atherosclerosis seems to be as frequent as in RA. Therefore, in this study we also tested the performances of CV risk indices in SSc. The most widely used risk indices in the general population, SCORE, QRisk II, and ACC/AHA 10-year AS-CVD risk, perform well in predicting the 10-year risk of CVD and detecting high CV–risk patients (32–34). Although their performance is not satisfactory in RA (46), some of them are recommended by EULAR for CV risk assessment in RA (22). However, in the present study we observed that these CV risk indices were even worse in SSc than in RA (46) in detecting patients with subclinical atherosclerosis. Neither decrement of threshold for risk stratification nor assuming SSc as an RA equivalent in QRisk II improved performance of risk indices. One of the reasons for inadequacy of these risk indices in SSc, similar to RA, might be the focus entirely on traditional CV risks. Previous and the current data indicate that other factors also have more contribution to the atherosclerosis and CVD in SSc.

Several strengths and limitations of our study need to be addressed. First of all, this is one of the largest sample size studies with healthy and diseased control groups evaluating cIMT and carotid plaques in SSc patients. We also evaluated the effects of traditional CV risk factors and disease-related factors on subclinical atherosclerosis quite comprehensively. Nevertheless some of the data, such as antiphospholipid antibodies, which are thought to have a role in activation of endothelium and accelerated atherosclerosis, could not be collected. Although cumulative glucocorticoid doses could not be obtained in all patients, the total glucocorticoid exposure duration with low- and high-dose periods was determined by reviewing all the previous records of patients. Lastly, because of the cross-sectional design of the study, we also could not determine the ability of risk scores to predict CV events. Instead we used increased cIMT and/or carotid plaques as a surrogate marker for future atherosclerotic CV events.

In conclusion, SSc is associated with increased atherosclerosis that is even as frequent as RA, in which accelerated atherosclerosis is well-established. Atherosclerosis in SSc is independently associated with older age, elevated ESR, and presence of PAH. Considering the high frequency of atherosclerosis in SSc and the burden of CVD in mortality of SSc, assessment of CV risk and prevention of CVD represent an opportunity to further reduce morbidity and mortality in SSc. However, CV risk assessment tools for the general population are considerably insufficient in SSc patients. Further research is warranted to fully explain the underlying mechanisms of SSc-associated atherosclerosis and to develop better CV risk assessment tools in SSc.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Ozen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ozen, Inanc, Unal, Sunbul, Ozmen, Akar, Pamuk, Tigen, Direskeneli.

Acquisition of data. Ozen, Unal, Korkmaz, Sunbul, Ozmen, Akar, Deniz, Donmez, Pamuk, Atagunduz, Tigen.

Analysis and interpretation of data. Ozen, Inanc, Sunbul, Ozmen, Direskeneli.

REFERENCES

1. Ali H, Ng KR, Low AH. A qualitative systematic review of the prevalence of coronary artery disease in systemic sclerosis. Int J Rheum Dis 2015;18:276–86.
2. Chu SY, Chen YJ, Liu CJ, Tseng WC, Lin MW, Hwang CY, et al. Increased risk of acute myocardial infarction in

systemic sclerosis: a nationwide population-based study. Am J Med 2013;126:982–8.
3. Man A, Zhu Y, Zhang Y, Dubreuil M, Rho YH, Peloquin C, et al. The risk of cardiovascular disease in systemic sclerosis: a population-based cohort study. Ann Rheum Dis 2013; 72:1188–93.
4. Ngian GS, Sahhar J, Proudman SM, Stevens W, Wicks IP, van Doornum S. Prevalence of coronary heart disease and cardiovascular risk factors in a national cross-sectional cohort study of systemic sclerosis. Ann Rheum Dis 2012;71: 1980–3.
5. Meune C, Touze E, Trinquart L, Allanore Y. Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies. Rheumatology (Oxford) 2009;48:1309–13.
6. Nossent J, Cikes N, Kiss E, Marchesoni A, Nassonova V, Mosca M, et al. Current causes of death in systemic lupus erythematosus in Europe, 2000–2004: relation to disease activity and damage accrual. Lupus 2007;16:309–17.
7. Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation 2003;107:1303–7.
8. Solomon DH, Kremer J, Curtis JR, Hochberg MC, Reed G, Tsao P, et al. Explaining the cardiovascular risk associated with rheumatoid arthritis: traditional risk factors versus markers of rheumatoid arthritis severity. Ann Rheum Dis 2010;69:1920–5.
9. Hettema ME, Zhang D, de Leeuw K, Stienstra Y, Smit AJ, Kallenberg CG, et al. Early atherosclerosis in systemic sclerosis and its relation to disease or traditional risk factors. Arthritis Res Ther 2008;10:R49.
10. Kawasaki M, Ito Y, Yokoyama H, Arai M, Takemura G, Hara A, et al. Assessment of arterial medial characteristics in human carotid arteries using integrated backscatter ultrasound and its histological implications. Atherosclerosis 2005;180:145–54.
11. Macedo R, Andretta M, Albers C, Skare T, Ribas-Filho JM, Czeczko NG. Evaluation of carotid artery intima-media complex thickness as a marker of vascular damage secondary to accelerated atherogenesis in progressive systemic sclerosis. Rev Col Bras Cir 2012;39:10–5.
12. Szucs G, Timar O, Szekanecz Z, Der H, Kerekes G, Szamosi S, et al. Endothelial dysfunction precedes atherosclerosis in systemic sclerosis: relevance for prevention of vascular complications. Rheumatology (Oxford) 2007;46:759–62.
13. Au K, Singh MK, Bodukam V, Bae S, Maranian P, Ogawa R, et al. Atherosclerosis in systemic sclerosis: a systematic review and meta-analysis. Arthritis Rheum 2011;63:2078–90.
14. Bartoli F, Blagojevic J, Bacci M, Fiori G, Tempestini A, Conforti ML, et al. Flow-mediated vasodilation and carotid intima-media thickness in systemic sclerosis. Ann N Y Acad Sci 2007;1108:283–90.
15. Khurma V, Meyer C, Park GS, McMahon M, Lin J, Singh RR, et al. A pilot study of subclinical coronary atherosclerosis in systemic sclerosis: coronary artery calcification in cases and controls. Arthritis Rheum 2008;59:591–7.
16. Schiopu E, Au KM, McMahon MA, Kaplan MJ, Divekar A, Singh RR, et al. Prevalence of subclinical atherosclerosis is increased in systemic sclerosis and is associated with serum proteins: a cross-sectional, controlled study of carotid ultrasound. Rheumatology (Oxford) 2014;53:704–13.
17. Tsifetaki N, Georgiadis AN, Alamanos Y, Fanis S, Argyropoulou MI, Drosos AA. Subclinical atherosclerosis in scleroderma patients. Scand J Rheumatol 2010;39:326–9.
18. Tyrrell PN, Beyene J, Feldman BM, McCrindle BW, Silverman ED, Bradley TJ. Rheumatic disease and carotid intima-media thickness: a systematic review and meta-analysis. Arterioscl Thromb Vasc Biol 2010;30:1014–26.
19. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. Ann Rheum Dis 2007;66:940–4.
20. Tyndall AJ, Bannert B, Vonk M, Airo P, Cozzi F, Carreira PE, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis 2010;69: 1809–15.
21. Dave AJ, Fiorentino D, Lingala B, Krishnan E, Chung L. Atherosclerotic cardiovascular disease in hospitalized patients with systemic sclerosis: higher mortality than patients with lupus and rheumatoid arthritis. Arthritis Care Res (Hoboken) 2014;66:323–7.
22. Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis 2010;69:325–31.
23. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 1980;23:581–90.
24. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
25. Valentini G, Silman AJ, Veale D. Assessment of disease activity. Clin Exp Rheumatol 2003;21:S39–41.
26. Clements PJ, Lachenbruch PA, Ng SC, Simmons M, Sterz M, Furst DE. Skin score: a semiquantitative measure of cutaneous involvement that improves prediction of prognosis in systemic sclerosis. Arthritis Rheum 1990;33:1256–63.
27. Hoepper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kuryzna M, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 2013;62:D42–50.
28. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014;37:S81–90.
29. Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
30. Corrales A, Parra JA, Gonzalez-Juanatey C, Rueda-Gotor J, Blanco R, Llorca J, et al. Cardiovascular risk stratification in rheumatic diseases: carotid ultrasound is more sensitive than Coronary Artery Calcification Score to detect subclinical atherosclerosis in patients with rheumatoid arthritis. Ann Rheum Dis 2013;72:1764–70.
31. Nambi V, Chambless L, He M, Folsom AR, Mosley T, Boerwinkle E, et al. Common carotid artery intima-media thickness is as good as carotid intima-media thickness of all carotid artery segments in improving prediction of coronary heart disease risk in the Atherosclerosis Risk in Communities (ARIC) study. Eur Heart J 2012;33:183–90.
32. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, de Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;24:987–1003.
33. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ 2008;336:1475–82.
34. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:S49–73.
35. Arts EE, Popa C, den Broader AA, Semb AG, Toms T, Kitas GD, et al. Performance of four current risk algorithms in predicting cardiovascular events in patients with early rheumatoid arthritis. Ann Rheum Dis 2015:74;668–74.
36. Nordin A, Jensen-Urstad K, Bjornadal L, Pettersson S, Larsson A, Svenungsson E. Ischemic arterial events and atherosclerosis in patients with systemic sclerosis: a population-based case-control study. Arthritis Res Ther 2013;15:R87.
37. Vettori S, Maresca L, Cuomo G, Abbadessa S, Leonardo G, Valentini G. Clinical and subclinical atherosclerosis in systemic sclerosis: consequences of previous corticosteroid treatment. Scand J Rheumatol 2010;39:485–9.

38. Mok MY, Lau CS, Chiu SS, Tso AW, Lo Y, Law LS, et al. Systemic sclerosis is an independent risk factor for increased coronary artery calcium deposition. Arthritis Rheum 2011;63:1387–95.
39. Gonzalez-Gay MA, Gonzalez-Juanatey C, Pineiro A, Garcia-Porrua C, Testa A, Llorca J. High-grade C-reactive protein elevation correlates with accelerated atherogenesis in patients with rheumatoid arthritis. J Rheumatol 2005;32: 1219–23.
40. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO III, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice. A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499–511.
41. Frerix M, Stegbauer J, Kreuter A, Weiner SM. Atherosclerotic plaques occur in absence of intima-media thickening in both systemic sclerosis and systemic lupus erythematosus: a duplex sonography study of carotid and femoral arteries and follow-up for cardiovascular events. Arthritis Res Ther 2014; 16:R54.
42. Fitchett D. The metabolic syndrome is an important concept in therapeutic decision-making. Can J Cardiol 2015;31:596–600.
43. Zeng Y, Li M, Xu D, Hou Y, Wang Q, Fang Q, et al. Macrovascular involvement in systemic sclerosis: evidence of correlation with disease activity. Clin Exp Rheumatol 2012;30:S76–80.
44. Hofstee HM, Voskuyl AE, Vonk Noordegraaf A, Smulders YM, Postmus PE, Dijkmans BA, et al. Pulmonary arterial hypertension in systemic sclerosis is associated with profound impairment of microvascular endothelium-dependent vasodilatation. J Rheumatol 2012;39:100–5.
45. Peled N, Shitrit D, Fox BD, Shlomi D, Amital A, Bendayan D, et al. Peripheral arterial stiffness and endothelial dysfunction in idiopathic and scleroderma associated pulmonary arterial hypertension. J Rheumatol 2009;36:970–5.
46. Ozen G, Sunbul M, Atagunduz P, Direskeneli H, Tigen K, Inanc N. The 2013 ACC/AHA 10-year atherosclerotic cardiovascular risk index is better than SCORE and QRisk II in rheumatoid arthritis: is it enough? Rheumatology (Oxford) 2016;55:513–22.