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Subclinical atherosclerosis in systemic sclerosis and rheumatoid arthritis: a comparative matched-cohort study

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Abstract

Systemic autoimmune inflammatory disorders confer a higher risk of cardiovascular (CV) disease leading to increased morbidity and mortality and reduced life expectancy compared to the general population. CV risk in systemic sclerosis (SSc) has not been studied extensively but surrogate markers of atherosclerosis namely carotid intima media thickness (cIMT) and pulse wave velocity (PWV) are impaired in some but not all studies in SSc patients. The aim of this study was to investigate the prevalence of subclinical atherosclerosis assessed by cIMT and PWV between two well-characterized SSc and Rheumatoid Arthritis (RA) cohorts. Consecutive SSc patients attending the Scleroderma Clinic were compared with RA patients recruited in the Dudley Rheumatoid Arthritis Co-morbidity Cohort (DRACCO), a prospective study examining CV burden in RA. Augmentation Index (Aix75) and cIMT were measured in all participants. Propensity score matching was utilised to select patients from the two cohorts with similar demographic characteristics, CV risk factors and inflammatory load. Unpaired analysis was performed using unpaired *t* test for continuous variables and χ^2 test for dichotomous variables. Statistical analysis was repeated using paired *t* test for continuous normal variables and McNemar's test for dichotomous variables. Fifty five age- and sex-matched SSc and RA patients were included in the analysis. No difference was demonstrated between SSc and RA subjects regarding cIMT (0.66 mm vs 0.63 mm, respectively) and Aix75% measurements (33.4 vs 31.7, respectively) neither in paired ($p=0.623$ for cIMT and $p=0.204$ for Aix%) nor in unpaired *t* test analysis ($p=0.137$ for cIMT and $p=0.397$ for AIx%). The results of this comparative study show that subclinical atherosclerosis is comparable between SSc and RA, a systemic disease with well-defined high atherosclerotic burden. Such findings underscore the importance of CV risk management in SSc in parallel with other disease-related manifestations.

Keywords Systemic sclerosis · cIMT · Rheumatoid arthritis · Atherosclerosis · Augmentation index

Introduction

Systemic autoimmune inflammatory disorders confer a higher risk of cardiovascular (CV) disease leading to increased morbidity and mortality and reduced life expectancy compared to the general population [1–3]. Although cardiac involvement covers a wide spectrum of conditions such as accelerated atherosclerosis, coronary artery disease, myocardial and pericardial inflammation, heart failure, valvulopathies as well as pulmonary hypertension [4], *cerebrovascular* atherosclerotic disease also presents more frequently and poses the greatest mortality risk [5, 6]. The epidemiology and pathogenesis of CV comorbidities are well studied in rheumatoid arthritis (RA) where the excess CV risk is predominantly ascribed to disease-related factors namely cumulative systemic inflammatory burden and cardiotoxic effects of antirheumatic treatment and to a lesser extend to traditional CV disease risk factors such as arterial hypertension, glucose intolerance, sedentary life, smoking and dyslipidemia [7]. RA is now considered to be an independent predictor for early atherosclerosis with comparable CV risk to diabetes mellitus (DM) [8].

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Systemic sclerosis (SSc) is characterized by overproduction of collagen due to upregulation of fibroblasts function and endothelial activation leading to diffuse microangiopathy. While microvascular functional and structural changes represent the hallmark of SSc-related vasculopathy, an increasing amount of epidemiological data suggest that macrovascular atherosclerotic disease contributes to morbidity and mortality in SSc and further worsens the prognosis of the disease [9, 10]. Data from national registries [11], observational studies [12] and qualitative systematic reviews [13] demonstrate higher rates of coronary artery disease and CV events showing a 2.0- to 3.5-fold increased relative risk of myocardial infarction and stroke in SSc individuals compared to healthy controls [14, 15]. On the other hand, it remains unknown whether increased CV disease in SSc is attributable to disease-specific cardiac complications such as myocardial fibrosis and impaired coronary microcirculation or to accelerated atherosclerosis. Given that cardiopulmonary complications are the main determinants of unfavorable prognosis in SSc [16, 17], the clarification of the direct role of SSc in facilitating CV events is of importance regarding CV risk assessment and management in this population.

In SSc, non-invasive assessment of functional and morphological markers of early endothelial dysfunction such as carotid intima-media thickness (cIMT) and pulse wave velocity have yielded conflicting results suggesting that the prevalence of subclinical atherosclerosis in SSc might be lower compared to RA and other rheumatic diseases [18, 19]. However, a systematic review and metaanalysis of 31 studies suggested that SSc persons have higher cIMT values compared to healthy controls [20]. To date, there are only a few comparative studies investigating the magnitude of macrovascular atherosclerotic disease between SSc and RA by assessing carotid intima media thickness (cIMT) [21], and prevalence of CV disease risk factors [22]. Both studies indicate that SSc has comparable CV risk to RA whistle a recent comparative study showed a lower prevalence of established coronary artery disease in SSc compared to diabetes mellitus [23]. The aim of the current study is to investigate the prevalence of subclinical atherosclerosis assessed by non-invasive techniques between two well-characterized SSc and RA cohorts.

Patients and methods

Patients

The study enrolled consecutive SSc patients attending the Scleroderma Clinic of the Fourth Department of Internal Medicine, Hippokration General Hospital, Thessaloniki, Greece, between September 2017 and October 2018. All participants fulfilled the revised EULAR/ACR criteria for the diagnosis of SS [24]. Individuals with history of cardiovascular events such as myocardial infarction and/or stroke, chronic kidney defined as per Kidney Disease Improving Global Outcomes 2012 guidelines [25] and psychiatric disease, as well as malignancy were excluded. SSc subjects were compared with RA patients recruited in the Dudley Rheumatoid Arthritis Co-morbidity Cohort (DRACCO), a prospective study examining CV burden in RA. Detailed characteristics of the participants in DRACCO have been described previously [26]. Ethical approval was provided by local institutional boards—Hippokration Hospital and Black Country Ethics Committee, respectively—and all participants gave their written informed consent according to the Declaration of Helsinki.

Protocol

All participants reported to a thermoregulated (22 ± 0.9 °C) vascular laboratory after a 12-h overnight fast. They were asked to refrain from exercise 24 h before the session and from smoking 12 h before the session. Blood tests assessing routine hematology and biochemistry, lipid profile, fasting glucose, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were performed at the same day. CV comorbidities (arterial hypertension, dyslipidemia, diabetes mellitus and obesity) were recorded. Arterial hypertension was defined as office blood pressure (BP) 140/90 mmHg, or history of anti hypertensive drug intake [27]. Dyslipidemia was defined by total cholesterol of 240 mg/dl and/or low-density lipoprotein of 130 mg/dl and/or triglycerides of 160 mg/dl and/or intake of lipid-lowering drugs. A diagnosis of DM was based on the requirement for anti diabetic drugs.

Carotid atherosclerosis

All participants were evaluated with high-resolution ultrasonography of the carotid artery AS for RA and EP for SSc individuals according to previously established guidelines [28]. Methodological details for the RA cohort have been described previously [26]. For the SSc cohort, a General Electric Vivid-7 ultra sound device equipped with a 10-MHz linear transducer was used, and at least three measurements were performed in the far proximal wall across a 5-mm segment of both right and left common carotid arteries 1 cm from distal carotid bifurcation. cIMT was defined by determining the thickness between the lines of Pignoli; with the first echogenic line representing the lumen intima interface, and the second line representing the media adventitia interface [29]. The cIMT from both sides were further averaged to give the overall cIMT. The intra-observer co-efficient of variation for AS was 8.6% and for EP 8.8%.

Arterial stiffness

Pulse wave analysis (SphygmoCor Px Pulse Wave Ana lysis, ScanMed Medical Instruments, Moreton-in-Marsh, UK) was used to determine augmentation index (AIx) as described previously [30]. Briefly, an applanation tonometer positioned over the radial artery recorded the first and second systolic peaks. AIx was calculated as the ratio of the second to the first systolic peaks from the recorded pulse waveform and is expressed as a percentage of the pulse pressure, providing a measurement of the reflected pulse wave and the arterial stiffness [31]. As there is a linear correlation between heart rate and Aix and to achieve comparable measurements, the adjusted AIx to a heart rate of 75 beats per minute (AIx-75) was recorded.

Statistical analysis

Statistical analysis was performed using R v 3.6.2. Single value imputation was performed using nonlinear additive transformation and imputation function in the Hmisc package in R. The precision of the imputed values was checked by removing pre-existing values and comparing the imputed values to the original values. Comparison between entire RA and SSc cohorts (pre-matching comparison) was performed in two steps: an unadjusted analysis followed by a second one after adjustment for age and sex. Then, a second analysis after matching the two cohorts for demographic and CV risk factors was performed. Propensity score matching (PSM) was performed using the MatchIt package in R. Matching was performed based on the following set of covariates: sex, age and cardiovascular risk factors (smoking, hypertension, BMI, high cholesterol and diabetes), ESR and CRP. The propensity scores were estimated by running a logit model where the outcome variable was the disease state (RA vs. SSc) with covariates as the predictors in the model. Matching (1:1 ratio) was then performed using the "Nearest" method. Each patient from the SSc group was matched to its nearest observation (based on propensity score) from the RA group. Covariate balance was examined before and after PSM. For participants in the SSc group, kidney function (eGFR) was estimated using the CKD-EPI equation.

The analysis of non-matched data was performed using Mann–Whitney test for non-normal continuous data and using unpaired *t* test for normal continuous data. χ^2 test and Fisher-exact test were used to compare the distribution of nominal and categorical variables. The analysis of matched data was performed using the same approach. However, an additional approach was used to analyse the propensity matched data to take the paired nature of the data into account. The propensity matched individuals (each matched pair of RA and SSc patients) can be regarded as paired as they were matched based on propensity score. The lack of independence in the propensity score matched sample should be accounted for when performing the analysis. The analysis was also repeated using paired t test for continuous variable. McNemar's test was used to compare the distribution of dichotomous variables between matched pairs. The results of both analyses were presented. Hypothesis testing was performed at 5% level of significance.

Results

Pre-matching comparison

We included 201 patients with RA and 63 patients with SSc. Demographic data, disease-related characteristics and cardiovascular risk factors of the participants are summarized in Table 1. In general, RA patients were older compared to SSc group (72.8 vs. 58.8 years, $p<0.001$) and males were more prevalent in the RA group compared to the SSc group (22.9% vs. 3.17%, $p=0.001$). Traditional CV risk factors such as hypertension, hyperlipidemia and diabetes mellitus were more common in the RA group. Patients with RA had a significantly higher BMI and weight compared to the SSC group. Steroid use was not significantly different between groups. ESR was significantly higher in SSc patients compared to RA patients ($p=0.019$) although no significant difference was noted in CRP values.

Comparison between groups revealed that mean cIMT average, cIMT left average, and cIMT right average were significantly higher in RA patients compared to SSc patients but these differences were no longer significant after adjustment for age and sex (Table 2). Similarly, mean AIX 75% was also higher in RA patients compared to SSc patients (32.9 ± 9.11 vs. 29.7 ± 11.3, $p<0.05$) in unadjusted analysis but the comparison after adjusting for age and sex showed no difference between the two groups.

Matched data analysis

Propensity score matching was performed, as previously mentioned, to ensure that the distribution of covariates is similar between both groups. Patients with missing AIX 75% in the RA group ($n=25$) were excluded from the analysis. The matched dataset included 55 patients from each group. Observations were dropped from both groups so that the best matching is obtained. Thus, eight patients with no corresponding matching patients in the RA group were excluded. None of the demographic characteristics of cardiovascular risk factors were significantly different between both groups after the matching algorithm was executed ($p>0.05$ for all variables) (Table 3).

Results showed that the mean IMT average, IMT left average, and IMT right average, and AIX 75% were not

Table 1 Demographic and cardiovascular risk factors of the included patients

	RA $N=201$	SSc $N=63$	p
Age	72.8 (12.1)	58.8 (13.1)	< 0.001
Gender			0.001
Female	155 (77.1%)	61 (96.8%)	
Male	46 (22.9%)	2 (3.17%)	
Disease duration (years)[a]	16 (11–25)	11 (3–18)	0.865
Serum creatinine	0.83 (0.26)	0.83 (0.32)	0.894
HDL-Cholesterol	57.2 (17.0)	57.4 (18.9)	0.934
LDL-Cholesterol	113 (34.4)	110 (37.3)	0.632
Total Cholesterol	192 (39.1)	188 (40.8)	0.472
TC/HDL	3.56 (1.01)	3.53 (1.05)	0.851
Diabetes			0.050
No	180 (89.6%)	62 (98.4%)	
Yes	21 (10.4%)	1 (1.59%)	
Hypertension			< 0.001
No	71 (35.3%)	43 (68.3%)	
Yes	130 (64.7%)	20 (31.7%)	
Hyperlipidemia			< 0.001
No	129 (64.2%)	57 (90.5%)	
Yes	72 (35.8%)	6 (9.52%)	
Smoking			0.002
No	178 (88.6%)	45 (71.4%)	
Yes	23 (11.4%)	18 (28.6%)	
Systolic BP	135 (17.3)	129 (19.8)	0.037
Diastolic BP	76.9 (10.8)	76.8 (9.04)	0.988
ESR	16.3 (15.1)	22.5 (18.7)	0.019
CRP	9.41 (20.2)	6.82 (29)	0.511
Weight (kg)	75.2 (17.3)	64.1 (10.5)	< 0.001
Height (cm)	163 (9.00)	162 (5.68)	0.547
BMI			< 0.001
Normal	60 (29.9%)	38 (60.3%)	
Overweight	74 (36.8%)	17 (27.0%)	
Obese	67 (33.3%)	8 (12.7%)	
BMI	28.3 (5.36)	24.4 (3.88)	< 0.001
Steroids			0.188
No	150 (74.6%)	41 (65.1%)	
Yes	51 (25.4%)	22 (34.9%)	
MTX	122 (60.7%)	18 (28.57%)	
HCQ	50 (25%)	14 (19.1%)	
MMF		15 (20.5%)	
AZA		5 (6.8%)	
ANTI-TNF	57 (28.3%)		

Data were summarized using mean (SD) for continuous variables and using count (%) for categorical variables

RA rheumatoid arthritis, *SSc* systemic sclerosis, *HDL* high-density lipid, *LDL* low-density lipids, *TC* triglycerides, *BP* blood pressure, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *BMI* body mass index, *MTX* methotrexate, *AZA* azathioprine, *HCQ* hydroxychloroquine, *MMF* mycophenolate mofetyl, *ANTI-TNF* tumor necrosis factor-alpha inhibitors

Table 1 (continued)

[a]Median (25th–75th) percentiles

significantly different between matched patients in both paired and unpaired analysis ($p > 0.05$) (Table 4).

Discussion

In this comparative study between two well-characterized cohorts of SSc and RA, and sub-analyses in sub-cohorts closely matched for relevant CV risk factors, we found that morphological and functional markers of atherosclerosis namely cIMT and AIx-75 respectively, were comparable between individuals suffering from these conditions. The findings of our study indicate that, in the same way that assessment of macrovascular atherosclerotic disease forms an accepted and important part of RA patient management, an anologous approach should be implemented for patients with SSc.

In contrast to other systemic rheumatic diseases the true impact of atherosclerosis on SSc has been highly debated as not all the available data are concordant in describing a higher burden of CV risk in this population [19, 32]. Given that the degree of systemic inflammation may be less profound in SSc than in, for example RA, the question whether SSc confers an increased CV burden comparable to that observed in other systemic autoimmune disorders remains to be addressed. In addition, the focus of the SSc community has been predominantly on the evaluation and management of severe internal organ complications such as pulmonary fibrosis and hypertension, with much less attention being paid on CV disease.

The results of our study concur with previous reports demonstrating that subclinical atherosclerosis is similar between SSc and RA. Ozen et al. [21] assessed endothelial function by carotid ultrasonography in 110 SSc and RA persons as well as in healthy controls. They found that cIMT estimations were higher in SSc patients compared to controls, but this increased atherosclerotic prevalence in SSc group was comparable to age- and sex-matched RA subjects. Similar to what occurs in RA, the heightened atherosclerotic burden in SSc could not be identified with cardiovascular risk scores for general population such as SCORE and QRISK II employed in their study. We further extend these findings by adding in the evaluation of macrovascular function in SSc, the measurement of arterial stiffening, a well-established risk factor for CV disease [33].

In the context of SSc, arterial stiffness appears to reflect disease progression on both vascular and fibrotic grounds. In fact, a progressive increase of AIx-75 was correlated with worsening phases of SSc microangiopathy assessed by

Table 2 Comparison of IMT and AIX 75% between groups

	Unadjusted values			Adjusted values			
	RA	SSc	*p*	RA	SSc	*p*	*N*
	N = 201	*N* = 63		*N* = 201	*N* = 63		
cIMT right average	0.69 (0.15)	0.61 (0.12)	< 0.001	0.63 (0.15)	0.61 (0.12)	0.348	264
cIMT left average	0.69 (0.15)	0.63 (0.13)	0.003	0.64 (0.14)	0.64 (0.13)	0.767	264
cIMT average	0.69 (0.13)	0.62 (0.11)	< 0.001	0.64 (0.12)	0.63 (0.10)	0.465	264
AIx 75% (%)	32.9 (9.1)	29.7 (11.3)	0.047	31.7 (8.4)	30.8 (10.9)	0.543	239

Data were summarized using mean (SD). Adjusted values were estimated assuming all patients were females aged 60

RA rheumatoid arthritis, *SSc* systemic sclerosis, *cIMT* carotid intima media thickness, *AIx* augmentation index

Table 3 Demographic and cardiovascular risk factors of the matched patients

	RA *N* = 55	SSc *N* = 55	*p* (Paired *t*-test)	*p* (Un-paired *t*-test)
Age	63.6 (14.8)	61.3 (10.9)	0.35	0.140
Gender			0.683	0.438
Female	49 (89.1%)	53 (96.4%)		
Male	6 (10.9%)	2 (3.64%)		
BMI			0.19	0.235
Normal	26 (47.3%)	33 (60.0%)		
Overweight	18 (32.7%)	14 (25.5%)		
Obese	11 (20.0%)	8 (14.5%)		
Smoking			0.332	0.513
No	45 (81.8%)	42 (76.4%)		
Yes	10 (18.2%)	13 (23.6%)		
Diabetes			1	0.364
No	55 (100%)	54 (98.2%)		
Yes	0 (0.00%)	1 (1.82%)		
Hyperlipidemia			1	1.000
No	48 (87.3%)	49 (89.1%)		
Yes	7 (12.7%)	6 (10.9%)		
Hypertension			0.08	0.441
No	32 (58.2%)	36 (65.5%)		
Yes	23 (41.8%)	19 (34.5%)		
ESR	20.4 (18.4)	22.0 (19.1)	0.744	0.666
CRP	8.38 (11.6)	6.65 (30.2)	0.649	0.692

Data were summarized using mean (SD) for continuous variables and using count (%) for categorical variables

RA rheumatoid arthritis, *SSc* systemic sclerosis, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *BMI* body mass index

nailford videocappilaroscopy in 37 SSc patients [34], whistle arterial stiffening was inversely related to the severity of lung fibrosis in the multicenter ERAMS study [35]. To the best of our knowledge, this is the first study comparing arterial stiffness between SSc and RA suggesting that increased stiffening and impaired distensibility of large arteries do not significantly differ among individuals suffering from these diseases. Taken together, the results of the present study indicate a more generalized macrovascular endothelial dysfunction in SSc, accompanied by a degree of abnormalities in noninvasive assessments of vascular function characterizing different stages of atherosclerosis equal to that seen in RA.

The exact mechanisms of CV disease in SSc have not been determined yet but several different pathophysiological processes are involved in the development of atherosclerosis.

Table 4 Comparison of IMT and AIX 75%, between matched patients

	RA $N=55$	SSc $N=55$	Unpaired p	Paired p	Pairs
IMT R average	0.65 (0.17)	0.61 (0.12)	0.175	0.575	110
IMT L average	0.67 (0.15)	0.64 (0.13)	0.214	0.628	110
IMT average	0.66 (0.14)	0.63 (0.10)	0.137	0.623	110
AIX 75% (%)	33.4 (9.23)	31.7 (10.8)	0.397	0.204	103

Data were summarized using mean (SD) for continuous variables and using count (%) for categorical variables

RA rheumatoid arthritis, *SSc* systemic sclerosis, *cIMT* carotid intima media thickness, *AIx* augmentation index, *R* right, *L* left

SS microvasculopathy is characterized by ischemia–reperfusion and free radical injury culminating in endothelial dysfunction, immune activation and impaired vascular remodeling all of which promote macrovascular injury [36]. Traditional CV risk factors could not explain vascular disease as a number of studies of limited size reported a similar [37] or even lower prevalence [38] of these parameters in SSc compared to the general population. In contrast, a recent Danish nationwide cohort study including 2778 SSc patients reported higher rates of hypertension and treated dyslipidemia amongst SSc than their respective controls at baseline, indicating for the first time that classical CV risk factors may be significant players in subclinical atherosclerosis in the SSc setting [39]. Last but not least, inflammation—albeit to a lesser extend compared to other autoimmune disorders—contributes to vascular abnormalities as suggested by the increased risk of myocardial infarction and stroke during the first year after the diagnosis when the systemic inflammatory burden tends to reach higher levels [14].

It is worth noting that a comparative study including 408 age and sex-matched SSc and RA patients revealed no difference in the occurrence of CV events between the two diseases, despite higher prevalence of diabetes mellitus and dyslipidemia in the RA group [22]. Besides age and sex matching, we took particular care to compare individuals with similar prevalence of traditional CV risk factors—matched analysis—to minimize the influence of such parameters on the markers of preclinical atherosclerosis assessed in our study. Although the two conditions may share some (e.g. autoimmune activation) but not all (e.g. high- vs low-grade inflammation, microvasculopathy) mechanisms, the current findings add to the few previous studies by confirming that atherosclerotic burden in SSc seems to be comparable with RA. Clearly, further studies comparing endothelial function between these diseases and exploring the relative contribution of classical CV risk and inflammation in the progression of functional and morphological vascular abnormalities predominantly in SSc patients will shed more light in this complex puzzle.

Our study included a relatively small number of participants which may limit the power of our findings. In addition, we were not able to employ more methods for the evaluation of global endothelial function such as flow-mediated dilatation and assessments of microvascular function namely iontophoresis of 1% acetylcholine and 1% sodium-nitroprusside which could provide a more sensitive indication of vascular impairment particularly in the first stages of atherosclerosis. The different origin of our cohorts (RA patients recruited in United Kingdom and SSc in Greece) represents a limitation of the study. However, we compared two well-characterized cohorts of RA and SSc patients representative of the individuals attending clinics in daily clinical practice in Europe and comparable in terms of demographic and disease characteristics to patients included in previous studies.

Conclusion

In conclusion, our comparative study showed equal prevalence of macrovascular atherosclerotic disease evaluated by cIMT and arterial stiffness between SSc and RA. Such observations underline the significant and—until recently—underappreciated magnitude of CV disease in SSc and support the implementation of preventive strategies for the identification and management of patients at higher risk. More research is required for the determination of mechanisms behind CV disease in SSc and the validation of the current findings in large longitudinal studies.

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Availability of data and material Available on request.

Conflict of interest Authors declare no conflict of interest.

Ethics approval Ethics approval provided by Hippokration Hospital and Black Country Ethics Committee and all participants gave their written informed consent according to the Declaration of Helsinki.

Consent to participate All participants gave their written informed consent according to the Declaration of Helsinki.

Consent for publication The authors have consented to the publication of the paper.

Code availability Available on request.

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