Association of serum myeloperoxidase with metabolic syndrome and adverse lipid profiles in scleroderma patients

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Abstract

Objective

Plasma myeloperoxidase (MPO) levels have been associated with cardiovascular disease in the general population. However, their relationship to cardiovascular manifestations in systemic sclerosis (SSc) remains unexplored. This study aims to investigate the association between circulating MPO and SSc disease characteristics, incorporating a comprehensive assessment of lipid profiles, carotid atherosclerosis, and metabolic syndrome.

Methods

This cross-sectional study encompassed 81 individuals with confirmed systemic sclerosis (SSc). All SSc patients underwent a complete clinical evaluation. Serum MPO levels and lipid profiles were assessed. To elucidate potential associations between MPO and both SSc-specific manifestations and cardiometabolic parameters, we employed multivariable linear regression analyses.

Results

Disease characteristics, including SSc subtype (diffuse or limited), Rodnan skin score, and the presence of visceral involvement (e.g. pulmonary, or other organ involvement) and autoantibody profiles, showed no correlation with MPO levels. However, significant and positive associations were observed, after multivariable adjustment, between MPO values and the presence of metabolic syndrome, LDL: HDL cholesterol ratio, non-HDL cholesterol, apolipoprotein B levels, apolipoprotein B:A1 ratio, and the atherogenic index.

Conclusion

Circulating MPO levels do not correlate with specific SSc disease manifestations. However, higher MPO values are associated with the presence of metabolic syndrome and an unfavourable lipid profile in patients with this condition.

Key words

systemic sclerosis, scleroderma, myeloperoxidase, metabolic syndrome, lipids, cardiovascular disease

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Received on November 12, 2024; accepted in revised form on February 24, 2025

Funding: this study has been funded by a grant to S.C. by Instituto de Salud Carlos III (ISCIII) through the project PI21/01474 and co-funded by the European Union.

Competing interests: the authors declare that there are no conflicts of interest related to this study. Nevertheless, I. Ferraz-Amaro would like to acknowledge that he has received grants/research supports from Novartis, as well as consultation fees from company sponsored speakers' bureaus associated with Abbvie, Novartis and Bristol-Myers Squibb.
M.A. González-Gay received consultation fees/participation from company sponsored speakers' bureau from GSK, Sanofi, Otsuka and Amgen.

Introduction

Systemic sclerosis (SSc), also called scleroderma, is a chronic multisystem disease marked by widespread vascular dysfunction and progressive fibrosis affecting both the skin and internal organs (1). This condition is notably heterogeneous, as reflected in its diverse range of organ manifestations, variable disease progression, severity, and clinical outcomes (2). In this regard, SSc is generally classified according to the extent of skin involvement, patterns of internal organ involvement, and the presence of overlapping features with other systemic rheumatic diseases. Based on these criteria, the primary subsets of SSc include limited cutaneous, diffuse cutaneous, SSc sine scleroderma, and SSc overlap syndrome (3). Cutaneous manifestations, such as skin thickening and induration, along with Raynaud's phenomenon, are nearly universal clinical features of SSc. Additional characteristics of the disease include digital ulcers, tissue loss, musculoskeletal symptoms, and involvement of the gastrointestinal, pulmonary, and cardiac systems (4, 5). Cardiovascular disease is common but often underrecognised in patients with SSc. Contributing factors to vascular issues in SSc, which overlap with those seen in atherosclerosis, include endothelial dysfunction, a reduced number of circulating endothelial progenitor cells, and an increase in microparticles. Indicators of elevated cardiovascular risk in SSc patients include increased arterial stiffness, carotid intima-media thickening, and reduced flow-mediated dilatation (6, 7). Because of that, 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, and other vascular imaging techniques (8). The results revealed that SSc patients had significantly higher cIMT and reduced flow-mediated vasodilation, indicating a greater 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 are at an elevated risk for atherosclerosis and called for further research to clarify the underlying mechanisms (8).

Metabolic syndrome is relatively common in patients with SSc, potentially exacerbating the risk of cardiovascular disease (9). Features of metabolic syndrome, such as abnormal lipid profiles and insulin resistance, can further impair overall health outcomes and contribute to higher rates of morbidity and mortality. In this context, Atzeni *et al*. stressed the importance of routine metabolic syndrome screening as a key component of clinical care for SSc patients, emphasising the need of management of individual metabolic syndrome components to improve prognosis and reduce cardiovascular risk (9). In addition, SSc patients exhibit abnormal lipid profiles compared to healthy controls, including reduced cholesterol efflux capacity (10). Furthermore, insulin resistance has been independently linked to the presence of digital ulcers in SSc patients and may serve as a potential biomarker for microvasculopathy in these patients (11).

Myeloperoxidase (MPO) is an abundant heme peroxidase enzyme found in granules of neutrophils and monocytes (12). Its physiological role appears to be a critical component of phagocytic microorganism-killing activities of the innate immune system (13). In this regard, opsonised bacteria are engulfed into phagocytic cells into an intracellular compartment known as a "phagosome". Then, MPO and other antimicrobial systems stored in cytoplasmic granules fuse and are released into phagosomes containing ingested microorganisms. Hence, MPO has been proposed to be involved in the destruction of bacteria, protozoa, parasites, viruses, and even some tumour cells (14). Besides, MPO hereditary deficiency predisposes to immune deficiency (15). Also, antibodies against MPO have been implicated in various types of vasculitis, most prominently

three clinically and pathologically recognised forms: granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (16).

Recent findings suggest that beyond its established antimicrobial role, MPO can also influence immune cells and modulate tissue responses, playing a part in both healthy and pathological processes (17). In this regard, higher levels of MPO are associated with the presence of coronary disease and may be predictive of the presence of acute coronary syndrome in patients with chest pain (18-20). In a nested case-cohort study from the MONICA/KORA Augsburg involving 333 cases with CHD and 1727 controls followed for an average of nearly 11 years, patients with elevated MPO levels had significantly greater likelihood of developing coronary heart disease after adjusting for traditional major cardiovascular risk factors (hazard ratio 1.70 for top tertile versus bottom two tertiles, 95% CI 1.25-2.30) (20). Besides, among patients with chronic systolic heart failure, elevated plasma MPO levels have been associated with an increased likelihood of more advanced heart failure and may be predictive of a higher rate of adverse clinical outcomes (21). MPO has also been involved in lipid metabolism. Apolipoprotein A-1, the primary protein constituent of high-density lipoprotein (HDL), is a selective target for MPO-catalysed nitration and chlorination *in vivo*, and MPO-catalysed oxidation of HDL and apoA-I results in selective inhibition of cholesterol efflux from macrophages (22).

In this study, we aimed to determine whether MPO serum values are related to specific disease characteristics, including a comprehensive cardiovascular profile encompassing metabolic syndrome, lipid profile, and subclinical carotid atheromatosis.

Methods

Study participants

This cross-sectional study included 81 patients with SSc, all of whom were 18 years or older and met the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc (23). They had been diagnosed by rheumatologists and were periodically followed up at the rheumatology outpatient clinics of our institution. The study included unselected consecutive SSc patients with a disease duration of at least one year. Patients 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. 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 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 140 and 90 mmHg respectively, accordingly to current guidelines (24). Obesity, defined as a body mass index (BMI) equal to or greater than 30 kg/m^2 (25). Disease duration for SSc was defined as the time since the onset of the first SSc-related symptom other than Raynaud's phenomenon. The modified Rodnan Skin Score (mRSS) skin score was used to assess skin thickening (26). This score has been commonly used as an outcome measure in clinical trials. 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 (27)and scleroderma patterns were sub-graded as "early", "active" and "late"(27).

Cardiovascular risk score (SCORE2) was calculated according to the 2021 European Society of Cardiology guidelines on cardiovascular disease prevention in clinical practice (28). 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.

A carotid ultrasound examination was performed to evaluate the cIMT within the common carotid artery. 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 (29), 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 (29).

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).

Table I. Demographics of systemic sclerosis patients.

	Scleroderma (n=81)
Myeloperoxidase, ng/ml	206 (105-556)
Demographics	
Female, n (%)	76 (94)
Age, years	60 ± 11
BMI, kg/m^2	29 ± 6
Cardiovascular comorbidity	
Hypertension, n (%)	32 (40)
Current smoking, n (%)	7 (9)
Diabetes, n (%)	7 (9)
Dyslipidaemia, n (%)	72 (89)
BMI > 30 kg/m^2, n (%)	26 (32)
Statins, n (%)	20 (25)
Aspirin, n (%)	22 (27)
Metabolic syndrome, n (%)	47 (61)
Carotid atherosclerosis	
Intima media thickness, microns	663 ± 146
Plaque	28 (34)
SCORE2 calculator, %	4 (2-7)
SCORE2 categories, n (%)	
Low to moderate	45 (56)
High	27 (33)
Very high	9 (11)
Lipid profile	
Cholesterol, mg/dl	207 ± 37
Triglycerides, mg/dl	187 ± 92
HDL-cholesterol, mg/dl	52 ± 12
LDL-cholesterol, mg/dl	118 ± 33
LDL:HDL-cholesterol ratio	2.4 ± 0.9
Non-HDL-cholesterol, mg/dl	155 ± 36
Lipoprotein A, mg/dl	36 (13-91)
Apolipoprotein A1, mg/dl	165 ± 27
Apolipoprotein B, mg/dl	105 ± 25
Apo B:Apo A1 ratio	0.7 ± 0.2
Atherogenic index	4.2 ± 1.2
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 prednisone, n (%)	13 (16)
Prednisone, mg/day	5 (5-7.5)
Methotrexate, n (%)	4 (5)
Hydroxychloroquine, 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; HDL: high density lipoprotein; LDL: low density lipoprotein; SCORE2: Systematic Coronary Risk Assessment; FVC: forced vital capacity; FEV: forced expiratory volume; DLCO: diffusion capacity of the lung for the carbon monoxide.

Table II. Disease related data association with myeloperoxidase serum levels.

	Myeloperoxidase, ng/ml, Beta coef. (95%CI), *p*			
	Univariable		Multivariable	
Demographics				
Female	32 (-350-414)	0.87		
Age, years	-7 (-16-2)	0.11		
BMI, kg/m^2	0.4 (-16-17)	0.97		
Cardiovascular comorbidity				
Hypertension	132 (-59-322)	0.17		
Current smoking	53 (-274-381)	0.75		
Diabetes	-172 (-497-153)	0.30		
Dyslipidaemia	14 (-279-307)	0.93		
BMI >30 kg/m^2	99 (-101-300)	0.33		
Statins	-8 (-223-207)	0.94		
Aspirin	51 (-167-269)	0.64		
Systemic sclerosis related data				
SSc type				
Limited	ref.			
Diffuse	-95 (-332-141)	0.43		
CRP, mg/dl	**32 (19-45)**	**<0.001**	20 (-8-48)	0.15
Disease duration, years	10 (-7-27)	0.24		
Modified Rodnan Skin Score, units	8 (-6-22)	0.27		
Raynaud's phenomenon	179 (-127-485)	0.25		
Digital ulcers	46 (-223-315)	0.73		
Calcinosis	33 (-227-292)	0.80		
Arthritis	-24 (-351-304)	0.89		
Gastric reflux	-148 (-336-40)	0.12	-154 (-339-31)	0.10
Pathological oesophageal manometry	-205 (-636-226)	0.34		
Nailfold capillaroscopy pattern				
Normal	ref.			
Pathological	-46 (-278-186)	0.69		
Interstitial lung disease	-16 (-281-250)	0.91		
FVC, %	0.7 (-4-5)	0.74		
FEV1, %	-0.9 (-7-5)	0.78		
DLCO, %	2 (-2-5)	0.34		
Pulmonary hypertension	-118 (-345-109)	0.30		
Anti-centromere antibody positivity,	59 (-160-277)	0.59		
Anti-Scl70 antibody	-133 (-407-141)	0.34		
Therapies				
Current prednisone	167 (-82-415)	0.19	169 (-77-415)	0.18
Prednisone, mg/day	-92 (-188-3)	0.056	**-137 (-249-(-25))**	**0.021**
Methotrexate	-297 (-716-121)	0.16	-2777 (-689-136)	0.19
Hydroxychloroquine	196 (-226-617)	0.36		
Bosentan	-10 (-497-476)	0.97		

In this analysis myeloperoxidase serum values are the dependent variable. Oesophageal manometry assessment was available only for 33 patients. Significant *p*-values are reported in bold.
BMI: body mass index; CRP: C reactive protein; SSc: systemic sclerosis; FVC: forced vital capacity; FEV: forced expiratory volume; DLCO: diffusion capacity of the lung for the carbon monoxide. Multivariable analysis is adjusted for age and hypertension.

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 low-density lipoprotein cholesterol (LDL) >130 mg/dl. A standard technique was used to measure high-sensitivity C-reactive protein (CRP). MPO serum levels were measured by electrochemiluminescence immunoassay method (MERCK® MILLIPLEX map Multiplex Detection). Both the intra- and inter-coefficients of variability were <10% for these 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 MPO was examined using multivariable

Table III. Relationship of cardiometabolic features to myeloperoxidase values in SSc patients.

	Myeloperoxidase, ng/ml Beta coef. (95%CI), *p*			
	Univariable		Multivariable	
Metabolic syndrome	181 (-13-375)	0.067	**203 (12-395)**	**0.038**
Carotid atherosclerosis				
Intima media thickness, microns	-0.3 (-0.9-0.4)	0.39		
Plaque	-41 (-298-216)	0.75		
SCORE2 calculator, %	-14 (-36-7)	0.18		
SCORE2 categories				
Low to moderate	ref.			
High	-99 (-307-109)	0.35		
Very high	-199 (-514-117)	0.21		
Lipid profile				
Cholesterol, mg/dl	2 (-0.4-5)	0.095	3 (-0.02-5)	0.052
Triglycerides, mg/dl	0.7 (-0.4-2)	0.20		
HDL-cholesterol, mg/dl	-6 (-14-2)	0.13	-5 (-13-3)	0.19
LDL-cholesterol, mg/dl	3 (-0.4-6)	0.088	3 (-0.003-6)	0.050
LDL:HDL-cholesterol ratio	**167 (51-283)**	**0.005**	**161 (48-273)**	**0.006**
Non-HDL-cholesterol, mg/dl	**3 (0.4-6)**	**0.023**	**3 (0.7-6)**	**0.013**
Lipoprotein A, mg/dl	-0.5 (-2-0.8)	0.42		
Apolipoprotein A1, mg/dl	-3 (-6-0.7)	0.12	-2 (-6-1)	0.20
Apolipoprotein B, mg/dl	**6 (2-10)**	**0.002**	**6 (2-9)**	**0.003**
Apo B:Apo A1 ratio	**879 (433-1326)**	**<0.001**	**816 (379-1254)**	**<0.001**
Atherogenic index	**116 (34-197)**	**0.006**	**109 (30-189)**	**0.008**

In this analysis myeloperoxidase serum values are the dependent variable. SCORE2: Systematic Coronary Risk Assessment. Multivariable analysis is adjusted for age and hypertension.
Significant *p*-values are reported in bold.

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 MPO. All analyses were conducted using Stata software, version 17/SE (StataCorp, College Station, TX, USA), with a two-sided 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 with SSc

The characteristics of the SSc population are described in Table I. 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.

Cardiovascular risk factors were prevalent in the patient sample: 40% had hypertension, 9% were smokers, 9% had diabetes, and 89% met criteria for dyslipidaemia. Additionally, 25% were on statins and 25% on aspirin. Furthermore, 61% met criteria for metabolic syndrome, 34% had carotid plaques on carotid ultrasound, and the median SCORE2 was 4 (IQR 2–7). The lipid profile is also shown in Table I.

Relationship of disease characteristics to MPO levels

Demographic characteristics, including age, sex, and BMI, along with various cardiovascular risk factors, showed no significant association with MPO levels (Table II). Regarding disease-related parameters, CRP levels were positively associated with MPO; however, this significance was lost after multivariable adjustment. Additionally, disease characteristics such as SSc subtype (diffuse or limited), Rodnan skin score, presence of visceral involvement (pulmonary, or other), and autoantibody profile did not correlate with MPO levels. Besides, ILD and smoking were not related to MPO values. Notably, prednisone use was significantly linked to lower MPO levels (beta coef. -137,95%CI: -249-(-25) ng/ml, *p*=0.021) (Table II).

Association of cardiometabolic features with myeloperoxidase values in SSc

The relationship between cardiovascular disease characteristics and MPO levels is shown in Table III. In univariable analysis, patients with metabolic syndrome had higher MPO values, though this was not statistically significant. However, after adjusting for covariates, the association became significant (beta coef. 203, 95%CI: 12–395 ng/ml, *p*=0.038). Conversely, cardiovascular risk calculator SCORE2, cIMT, and the presence of carotid plaque showed no significant associations with MPO levels. Additionally, when a specific assessment of the different lipid fractions was performed, we observed that many lipid-related markers were significantly and positively associated with MPO levels. Specifically, the LDL:HDL ratio, non-HDL cholesterol, apolipoprotein B levels, the apolipoprotein B:A1 ratio, and the atherogenic index showed significant positive associations after multivariable adjustment (Table III). While total cholesterol and LDL showed a near-significant positive trend, statistical significance was not achieved in these cases.

Discussion

The present study highlights the significant role of MPO in the metabolic syndrome of patients with SSc, which may greatly influence the development of cardiovascular disease.

MPO, an enzyme produced by neutrophils and macrophages during inflammation, contributes to oxidative stress, endothelial dysfunction, and vascular damage, all of which are central to the development of atherosclerosis and coronary artery disease in SSc patients. One of the key mechanisms by which MPO exacerbates cardiovascular risk is

its interaction with nitric oxide (NO). While NO is crucial for maintaining vascular health by promoting vasodilation and reducing oxidative stress, MPO can counteract these protective effects by consuming NO and forming MPO-NO complexes. This interaction inhibits the activity of endothelial nitric oxide synthase (eNOS), the enzyme responsible for producing NO, further contributing to endothelial dysfunction. This disruption of NO metabolism is a hallmark of endothelial dysfunction, which is a critical event in the progression of cardiovascular diseases, especially those associated with metabolic syndrome (30).

Interestingly, in a meta-analysis by Au *et al*., the decreased FMD observed in SSc patients was similar to that found in other high-risk populations, such as those with familial hypercholesterolemia and familial combined hyperlipidaemia (8). This finding is consistent with other studies showing that premature atherosclerosis in SSc patients is associated with significant impairment in flow-mediated vasodilation, which correlates with traditional cardiovascular risk factors such as age, dyslipidaemia, and obesity (31). Furthermore, the increased cardiovascular risk in SSc patients is well-documented, with studies highlighting the adverse impact of the disease on the vascular bed across various organs, thereby increasing the likelihood of cardiovascular complications (32).

In our study, we observed a significant association between elevated MPO levels, an abnormal lipid profile, and the presence of metabolic syndrome in SSc patients. Specifically, MPO appears to promote oxidative modification of LDL, a key factor in atherosclerosis. Elevated MPO levels can transform normal LDL into oxidised LDL, a more proatherogenic form that is more readily taken up by macrophages, leading to foam cell formation and plaque development in arterial walls. This process contributes to the vascular damage seen in SSc patients and may explain the observed abnormal lipid profile, characterised by increased levels of oxidised LDL.

While we found an association between MPO values and lipid profile as well as the presence of metabolic syndrome, we did not observe a relation of cIMT or the presence of carotid plaque to MPO levels. This finding is not unexpected, as the impact of traditional cardiovascular risk factors on subclinical atherosclerosis may be generally more significant than that of a single serological marker. Moreover, our findings showed an association between MPO and CRP, further highlighting the relationship between oxidative stress and inflammation in SSc. Both MPO and CRP are markers of inflammation, but they reflect different aspects of the inflammatory response. The positive correlation between MPO and CRP suggests that local oxidative damage, mediated by MPO, and systemic inflammation, indicated by CRP, both contribute to the elevated cardiovascular risk in SSc patients. Together, these findings emphasise the complex interplay between oxidative stress, inflammation, and endothelial d*ys*function in the development of cardiovascular disease in SSc.

Finally in our study we observed a negative association between prednisone and MPO that could be attributed to the anti-inflammatory effects of prednisone. This glucocorticoid suppresses inflammation by inhibiting the activation of immune cells, such as neutrophils and macrophages, which are primary sources of MPO. By reducing the inflammatory response, prednisone can lower MPO production and release, leading to decreased serum levels. Additionally, prednisone's immunosuppressive effects may result in reduced neutrophil and macrophage activity, further contributing to lower MPO levels.

We acknowledge the limitation of not including a control population in our study. However, our hypothesis was not to compare MPO levels between patients and controls, but rather to investigate the relationship between these levels and disease characteristics. For this reason, the relationship between MPO values and metabolic syndrome or lipid profile in healthy subjects cannot be concluded from our study.

In conclusion, MPO levels are associated with the presence of metabolic syndrome and an unfavourable lipid profile in patients with SSc. Whether MPO can be used in routine clinical practice as a marker of cardiovascular risk in these patients warrants further investigation and collaboration among research groups interested in this condition.

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