Relationship Between Increased Fecal Calprotectin Levels and Interstitial Lung Disease in Systemic Sclerosis

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ABSTRACT. ***Objective.*** To evaluate the relationship between fecal calprotectin (FC) and interstitial lung disease (ILD) in systemic sclerosis (SSc).

Methods. The study enrolled 129 outpatients with SSc. Data about disease characteristics, in particular lung involvement, were collected and FC was measured.

Results. Patients with ILD (35, 27.1%) had higher values of FC ($p < 0.001$). In multivariate analysis, these variables were associated with increased risk of ILD: diffuse disease subset, higher modified Rodnan skin score, longer disease duration, higher severity scores, steroid treatment, and higher FC levels, while diverticulosis was protective.

Conclusion. ILD is independently associated with increased FC levels in SSc. (First Release November 15 2018; J Rheumatol 2019;46:274–8; doi:10.3899/jrheum.171445)

Key Indexing Terms:
SYSTEMIC SCLEROSIS INTERSTITIAL LUNG DISEASE FECAL CALPROTECTIN

Systemic sclerosis (SSc) is a connective tissue disease characterized by vasculopathy, immune activation, and progressive fibrosis of skin and internal organs such as the gastrointestinal (GI) tract and lungs.

Asymptomatic lung fibrosis has been shown in up to 90%[1] of patients with SSc, although it may be clinically relevant in only 25% of cases[2] and accounts for about 19% of deaths in the European League Against Rheumatism (EULAR) Scleroderma Trials and Research group cohort[3]. Some risk factors for interstitial lung disease (ILD) have been recognized, the most relevant being antitopoisomerase I antibodies and diffuse cutaneous subset[4].

Calprotectin is a 36 kDa calcium and zinc–binding protein mainly produced by activated monocytes and neutrophils, and its fecal levels are increased when neutrophils aggregate because of intestinal inflammation. It has been widely validated for diagnosis and management of inflammatory bowel disease (IBD)[5,6], and in SSc it has been shown to be increased[7] and that levels > 275 μg/g have a good performance in identifying patients with small intestinal bacterial overgrowth (SIBO)[8]. In addition, Andréasson, *et al*[9] have shown that SSc patients with intestinal dysbiosis have higher fecal calprotectin (FC) levels and prevalence of lung involvement.

The aim of our study was to further investigate whether there is a link between FC and lung involvement, even after correcting for other possible confounders.

MATERIALS AND METHODS

From April 2016 to December 2016, all outpatients affected by SSc were enrolled, excluding those who declined to provide written informed consent, those with concomitant untreated cancer, those with an established diagnosis of IBD, those receiving antibiotic treatment during the last month, and pregnant or breast-feeding women.

All patients fulfilled the American College of Rheumatology/EULAR classification criteria for SSc[10]. Along with a routine blood test, FC was measured using Quantum Blue Calprotectin (Bühlmann Laboratories AG; lower limit 30 μg/g). All patients underwent pulmonary function tests (PFT) with DLCO adjusted for hemoglobin. ILD was diagnosed by pulmonary high-resolution computed tomography in patients with symptoms and/or PFT suggestive of lung involvement; no cutoff of extension of lung involvement was defined.

To examine GI symptoms, the University of California, Los Angeles Scleroderma Clinical Trial Consortium GIT 2.0 (UCLA) questionnaire[11] was administered.

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The study was performed according to the Helsinki declaration and approved by Verona Medical School institutional review board (protocol number 18493). All patients provided written informed consent.

Statistical analysis. Continuous variables were expressed as mean (± SD) if normally distributed and as median (and interquartile range) if not normally distributed, and categorical variable as absolute number (percentage). Comparisons between groups were performed using Student t test, Mann-Whitney U, or chi-square tests, or Fisher's exact test, as appropriate. Determinants of ILD were studied with multivariate regression analysis including variables exhibiting a p value < 0.10 in univariate analysis, and that may affect FC levels [i.e., steroid treatment, proton pump inhibitors (PPI), diverticulosis], with logarithmic transformation of those not normally distributed. Because FC was not normally distributed, even after logarithmic transformation, it was divided into 3 categories [i.e., < 100 μg/g (normal values of our laboratory), between 100 and 275 μg/g, and higher than 275 μg/g (cutoff shown to increase the risk of SIBO[8])]. Statistical analysis was performed by SPSS 17.0 (SPSS Inc.).

RESULTS

The study cohort was composed of 129 patients. Table 1[12] summarizes their characteristics. GI tract involvement was severe/endstage in 3 cases (2.4%), moderate in 1 (0.8%), and mild in 93 (72.1%); SIBO was confirmed in only 1 patient.

ILD affected 35 patients (27.1%), and those had higher FC levels ($p < 0.001$; Table 2[12]). In addition, in univariate analysis, patients with ILD also had higher modified Rodnan skin score ($p = 0.008$), C-reactive protein (CRP; $p = 0.026$), erythrocyte sedimentation rate (ESR; $p = 0.006$), and lower forced vital capacity (FVC; $p = 0.013$ and 0.009 for absolute and predicted, respectively). They also had lower UCLA questionnaire scores ($p = 0.017$), were more frequently affected by diffuse subset ($p < 0.001$), had anti-Scl-70 antibodies positivity ($p < 0.001$), and were taking immunosuppressive drugs ($p < 0.001$; i.e., mainly mycophenolate, methotrexate, and azathioprine).

Median FC was 80 ± 157 µg/g, and in 37 patients (28.7%); it was lower than the lower limit, so it was converted to 30 μg/g. FC was found to be higher in subjects under treatment with PPI (102 ± 181 μg/g vs 38.5 ± 77 μg/g, respectively, $p = 0.001$) as well as in those with diverticulosis (191 ± 259 μg/g vs 68 ± 131 μg/g, respectively, $p = 0.026$), an increased CRP level ($p = 0.042$), a moderate/severe/endstage score for GI tract ($p = 0.046$), and those taking steroids ($p = 0.015$). In addition, it positively correlated with age (Spearman's ρ 0.380, $p < 0.001$) and negatively with absolute FVC (Spearman's ρ –0.183, $p = 0.038$), although the latter was lost after correcting for age. No other differences or correlations were found.

Then we ran a multivariate analysis as previously explained; we have excluded ESR and CRP because their correlation with FC was strongly affected by age, and when added to the multivariate model, they were not significantly associated with ILD. As shown in Table 3, FC levels were confirmed to be higher in patients with lung involvement. Diffuse disease subset and higher severity scores were associated with increased risk of ILD, while diverticulosis and steroid treatment were protective against lung involvement. In addition, we ran a second multivariate analysis considering the 110 cases with FC level < 275 μg/g, and increased FC levels were confirmed to be associated with ILD.

DISCUSSION

We have found that patients with established ILD have significantly higher values of FC, even after correcting for major determinants of lung involvement or for factors affecting FC levels. This result was confirmed even when considering patients with a mild increase in FC.

Marie, *et al*[8] found no differences in FC between patients with and without ILD, although they did not perform a comprehensive multivariate analysis. On the contrary, Andréasson, *et al*[9] demonstrated that SSc patients with dysbiosis have higher FC levels and are more often affected by ILD. As summarized by Volkman[13], recent data suggest that alterations in gut microbiota exist in SSc, although the mechanism by which these alterations perpetuate inflammation and fibrosis is still unclear. From this point of view, our result may further support a possible role of gut inflammation, probably caused by dysbiosis, in extra-GI manifestations of the disease. There is some evidence in the literature of lung-gut crosstalk[14,15,16], so a possible explanation for all these findings is that altered gut microbiome causes a pathologic immune response, or the production of molecules that pass through the lung and may mediate damage.

Other possible explanations should be kept in mind. First, increased FC may simply be a marker of more severe GI involvement and so reflect a more severe disease in general, although our results were confirmed even when analyzing only patients with a milder increase in FC (i.e., > 100 and < 275 μg/g), and no differences in the Medsger score for GI tract involvement[17] were observed between patients with and without ILD. It is noteworthy that we have further confirmed that the more severe the GI tract involvement was according to Medsger scores[17], the higher the FC levels were, as shown in previous studies[8,9]. FC may be used as a marker of severity of GI tract involvement in SSc.

Another possible explanation is that the hypothesized role of gastroesophageal reflux in ILD development in patients with SSc[18] may justify a higher use of PPI that may increase FC levels, but PPI in our multivariate analysis showed nonsignificant association with ILD.

Finally, calprotectin has been found to be increased in the lung during infections[19]. It has been hypothesized, although to the best of our knowledge never proven, that high FC levels may be found in patients with lung inflammation.

The main strength of our study is that we analyzed the link between gut inflammation and ILD in a large monocentric SSc population, accounting for the majority of the most important risk factors for lung involvement and for FC level interference.

This study has some limitations, first of all those of an

Table 1. Characteristics of the population (n = 129).

Characteristics	Values	Characteristics	Values
Age, yrs[#]	63 (13)	DLCO/AV, ml/mmHg/min/l[#]	3.49 (0.97)
Sex (female)*	109 (84.5)	DLCO/AV, predicted %[#]	77 (19)
Disease duration, yrs[#]	13 (7)	Medsger severity score for GI tract[§]	1 (1)
Raynaud phenomenon duration, yrs[#]	18 (12)	Medsger severity score for skin[§]	1 (0)
BMI, kg/m^2 [#]	24.4 (4.5)	Medsger severity score for joint tendon[§]	0 (1)
Disease subset*		Medsger severity score for muscle[§]	0 (0)
Limited	87 (67.4)	Medsger severity score for lung[§]	1 (2)
Diffuse	42 (32.6)	Medsger severity score for heart[§]	0 (1)
Autoantibodies*		Medsger severity score for kidney[§]	0 (0)
Anti-Scl-70	35 (27.1)	Total Medsger severity score[§]	5 (3)
Anticentromere	70 (54.3)	Active disease according to Valentini, *et al*[12] *	24 (18.6)
ANA	22 (17.1)	Diverticulosis*	21 (16.3)
Anti-RNA polymerase III	2 (1.5)	Endothelin receptor antagonist*	13 (10.1)
Videocapillaroscopy*		Prostanoid (any)*	124 (96.1)
Normal	12 (10.4)	Calcium channel blocker*	38 (70.5)
Early scleroderma pattern	24 (20.9)	Steroid*	22 (17.1)
Active scleroderma pattern	49 (42.6)	Immunosuppressive treatment*	34 (26.4)
Late scleroderma pattern	29 (25.2)	Previous immunosuppressive treatment*	47 (36.4)
Aspecific	1 (0.9)	PPI*	87 (67.4)
mRSS[§]	8 (7)	Hb, g/dl[#]	13.0 (1.2)
Active digital ulcers*	3 (2.3)	Creatinine, mg/dl[#]	0.81 (0.28)
Previous digital ulcers*	40 (31.0)	eGFR, CKD-EPI[#]	86 (23)
Renal crisis*	1 (0.8)	Vitamin D, nmol/l #	77 (34)
ILD*	35 (27.1)	ESR, mm/h[#]	26 (16)
PAH*	7 (5.4)	CRP, mg/l[§]	3 (1)
FVC[#]	2.7 (0.8)	Calprotectin, µg/g[§]	80 (157)
FVC predicted, %[#]	103 (24)	Log-calprotectin, µg/g[§]	4.38 (1.83)
DLCO, ml/mmHg/min[#]	14.9 (5.2)	UCLA-SCTC-GIT 2.0 total[§]	0.27 (0.54)
DLCO predicted, %[#]	68 (20)		

[#] Expressed as mean (SD). [§] Expressed as median (interquartile range). * Expressed as n (%). ANA: antinuclear antibodies without other specificities; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; FVC: forced vital capacity; DLCO/AV: DLCO corrected for alveolar volume; mRSS: modified Rodnan skin score; GI: gastrointestinal tract; BMI: body mass index; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; UCLA-SCTC-GIT 2.0: University of California, Los Angeles Scleroderma Clinical Trial Consortium GIT 2.0 questionnaire; PPI: proton pump inhibitor; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration.

observational study. In addition, ILD is a disease that needs time to develop, and most of our patients had a stable and mild disease, while FC was measured at only 1 point; it has been previously demonstrated to be very stable during about 400 days of followup[20], so the increase may reflect a longstanding process. Another limit is that no correlation between PFT and FC was found. It is possible that gut inflammation is a trigger of ILD and does not affect its evolution over time as measured by PFT; also, treatment may influence outcomes and thus obscure this correlation. Finally, no data on nonsteroidal antiinflammatory drugs, which may influence FC levels, have been systematically collected.

Patients with established ILD have increased FC levels, even after correcting for possible confounders. Further studies may clarify whether FC may be considered a marker of aberrant immune response caused by dysbiosis that may increase the risk of ILD, in particular in early disease, and whether microbiome alterations and gut dysbiosis may play roles in the development of ILD in SSc.

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Table 2. Comparison between patients with lung involvement and those without.

Variables	ILD		
	No (94)	Yes (35)	p
Age, yrs[#]	62.3 (12.9)	64.6 (12.7)	0.365
Sex (M)*	13 (13.8)	7 (20.0)	0.389
Smoke (former + active)*	35 (37.2)	14 (40.0)	0.773
Disease duration, yrs[#]	13.9 (7.4)	11.6 (6.1)	0.088
Raynaud phenomenon duration, yrs[#]	19 (13)	15 (11)	**0.042**
BMI, kg/m^2 [#]	24.4 (4.2)	24.6 (5.2)	0.815
Diffuse disease subset*	14 (14.9)	28 (80)	**< 0.001**
Anti-Scl-70 antibody vs ANA or ACA*	12 (12.8)	23 (65.7)	**< 0.001**
mRSS[§]	7 (7)	11 (9)	**0.008**
Active digital ulcers*	1 (1.1)	2 (5.7)	0.179
Previous digital ulcers*	30 (31.9)	10 (28.6)	0.715
FVC[#]	2.8 (0.8)	2.5 (0.9)	**0.013**
FVC predicted, %[#]	106 (23)	94 (25)	**0.009**
DLCO, ml/mmHg/min[#]	15.2 (5.2)	13.9 (5.1)	0.138
DLCO predicted, %[#]	69 (20)	64 (20)	0.216
DLCO/AV, ml/mmHg/min/l[#]	3.44 (1.04)	3.64 (0.73)	0.055
DLCO/AV predicted, %[#]	76 (21)	82 (23)	0.418
Total Medsger severity score[§]	5 (2)	6 (4)	**0.028**
Medsger severity score for GI tract[§]	1 (1)	1 (0)	0.265
Valentini, *et al* activity score[12] [§]	1.5 (1.6)	2 (1.5)	**0.007**
Active disease according to Valentini, *et al*[12] *	15 (16)	9 (25.7)	0.205
Diverticulosis*	20 (21.3)	1 (2.9)	**0.012**
Endothelin receptor antagonist*	8 (8.5)	5 (14.3)	0.338
Prostanoid (any)*	91 (96.8)	33 (94.3)	0.612
Calcium channel blocker*	28 (29.8)	10 (28.6)	1.000
Vasodilators*	92 (97.9)	33 (94.3)	0.297
Steroid*	18 (19.1)	4 (11.4)	0.300
Immunosuppressive treatment*	16 (17.0)	18 (51.4)	**< 0.001**
Previous immunosuppresive treatment*	21 (22.3)	26 (74.3)	**< 0.001**
PPI*	64 (68.1)	23 (65.7)	0.798
Creatinine, mg/dl[#]	0.79 (0.27)	0.82 (0.32)	0.853
eGFR, CKD-EPI[#]	88 (23)	82 (22)	0.222
Vitamin D, nmol/l[#]	77 (35)	78 (32)	0.889
ESR, mm/h[#]	24 (23)	33 (15)	**0.006**
CRP, mg/l[§]	3 (0)	3 (2)	**0.026**
Calprotectin, µg/g[§]	56 (117)	172 (253)	**< 0.001**
UCLA-SCTC-GIT 2.0 total[§]	0.50 (0.75)	0.25 (0.75)	**0.017**

[#] Expressed as mean (SD). [§] Expressed as median (interquartile range). * Expressed as n (%). Values in bold face are statistically significant. ILD: interstitial lung disease; FVC: forced vital capacity; DLCO/AV: DLCO corrected for alveolar volume; mRSS: modified Rodnan skin score; BMI: body mass index; ANA: antinuclear antibodies; ACA: anticentromere antibodies; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; UCLA-SCTC-GIT 2.0: University of California, Los Angeles Scleroderma Clinical Trial Consortium GIT 2.0 questionnaire; GI: gastrointestinal; PPI: proton pump inhibitor; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration.

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Table 3. Multivariate analysis for the risk of interstitial lung disease according to different possible determinants.

Variables	B	p	OR (95% CI)
Whole population, n = 129			
Disease duration	–0.067	0.214	0.9 (0.8–1.0)
mRSS	–0.176	0.051	0.8 (0.7–1.0)
Valentini activity score[12]	0.433	0.102	1.5 (0.9–2.6)
Total Medsger severity score	0.301	**0.049**	1.4 (1.0–1.8)
Proton pump inhibitor	0.689	0.331	0.5 (0.1–2.0)
Anti-Scl-70 antibody	1.187	0.169	0.3 (0.1–1.7)
Diverticulosis	–4.221	**0.008**	0.0 (0.0–0.3)
Limited cutaneous subset	–2.980	**0.001**	0.1 (0.0–0.3)
FC levels		0.002	
< 100 vs > 275 μg/g	–3.959	**0.001**	0.0 (0.0–0.2)
100–275 vs > 275 μg/g	–1.805	0.099	0.2 (0.0–1.4)
Steroid treatment	–2.278	**0.048**	0.1 (0.0–1.0)
Patients with FC level < 275 μg/g, n = 110			
Disease duration	–0.048	0.395	1.0 (0.9–1.1)
mRSS	–0.120	0.179	0.9 (0.7–1.1)
Valentini activity score[12]	0.361	0.172	1.4 (0.9–2.4)
Total Medsger severity score	0.319	**0.039**	1.4 (1.0–1.9)
Proton pump inhibitor	0.813	0.260	2.3 (0.5–9.3)
Anti-Scl-70 antibody	0.695	0.455	2.0 (0.3–12.3)
Diverticulosis	–22.031	0.998	0.0 (0.0 to > 100.0)
Limited cutaneous subset	–2.908	**0.002**	0.1 (0.0–0.4)
FC < 100 μg/g	–1.935	**0.011**	0.1 (0.0–0.6)
Steroid treatment	–1.983	0.118	0.1 (0.0–1.7)

Data in bold face are statistically significant. mRSS: modified Rodnan skin score; FC: fecal calprotectin.

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