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ORIGINAL ARTICLE

Body mass index and adipokines/cytokines dysregulation in systemic sclerosis

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ABSTRACT

Body fat has regulatory functions through producing cytokines and adipokines whose role in the pathogenesis of systemic sclerosis (SSc) is currently emerging. Changes in body mass, either over- or underweight, entail a dysregulation of the cytokine/adipokine network that may impact upon SSc disease activity. We evaluated serum levels of adipokines and cytokines in SSc patients and correlated them to clinical features and body mass index (BMI) categories. The study included 89 SSc patients and 26 healthy donors (HD). Serum levels of adiponectin, leptin, resistin, visfatin, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-2, IL-10 and IL-17A were measured by multiplex immunoassay and correlated to BMI and disease-specific features. Student's *t*-test or analysis of variance (ANOVA) were used for comparisons between groups. Spearman's or Pearson's tests were used for correlation analysis. Serum levels of TNF-α, IL-2, leptin and resistin were significantly higher in SSc than in HD. Leptin levels were significantly higher in interstitial lung disease (ILD)- and pulmonary arterial hypertension (PAH)-SSc subgroups. The highest levels of IL-17A, IL-2, IL-10, leptin and visfatin were detected in SSc patients with obesity ($p < 0.01$). Conversely, underweight SSc patients showed the highest TNF-α levels ($p < 0.05$). Adipokines, IL-2, IL-10 and IL-17A were found to be increased in SSc patients with obesity, but whether or not they play a role in the pathogenesis of the disease remains to be investigated. Intriguingly, underweight patients had the highest TNF-α levels, suggesting a potential role of TNF-α in inducing the cachexia observed in long-lasting disease.

KEYWORDS

adiponectin, body weight, leptin, visfatin

INTRODUCTION

Systemic sclerosis (SSc) is a connective tissue disease characterized by small vessel vasculopathy associated with fibrosis of multiple organs. The pathogenesis is unclear, but an autoimmune dysregulation and abnormal inflammatory response seems to be involved in the early stage of the disease. Emerging evidence suggests that white

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adipose tissue (WAT), besides having the role of energy storage, is now acknowledged as a pleiotropic organ with endocrine functions and regulating immune and inflammatory responses, being a source of cytokines and adipokines (leptin, adiponectin, visfatin, resistin) [1]. Indeed, obesity may have an impact on disease activity as well as on the clinical response of patients with rheumatoid arthritis and psoriatic arthritis [2,3]. In subjects with obesity, leptin induces the expression of adhesion molecules on endothelial cells and activates macrophages, while hindering adiponectin production by adipocytes, contributing to the 'low-grade inflammatory state' associated with obesity [1].

Recently the role of cytokines/adipokines in the pathophysiology of SSc has become a matter of investigation, but studies correlating them with the clinical subsets or particular organ involvement were not always consistent. Serum leptin levels were found to be positively correlated with body mass index (BMI), negatively with disease activity in SSc patients but not increased in comparison with healthy controls [4,5]. Conversely, serum levels of leptin, resistin and tumor necrosis factor (TNF)-α were higher in a small cohort of 16 SSc patients than in control subjects, but no correlation with skin involvement, disease duration and disease activity was seen [6]. A newly discovered adipokine, adipsin, was significantly higher in limited cutaneous SSc (lcSSc) than in diffuse cutaneous SSc (dcSSc), and was strongly associated with pulmonary arterial hypertension [7]. Interestingly, adiponectin seems to play a protective role in SSc, as the levels were found to be low in dcSSc patients and inversely correlated with the extension of skin fibrosis, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [5,8–10]. However, the interweave among body mass, cytokines/adipokines and SSc clinical phenotypes has been poorly investigated.

In this study, we aimed to evaluate serum levels of adipokines (leptin, resistin, visfatin, adiponectin) and cytokines [TNF-α, interferon (IFN)-γ, interleukin (IL)-2, IL-10, IL-17A] in SSc patients according to BMI categories and disease specific characteristics.

METHODS

Participants

We evaluated 89 Caucasian patients with SSc fulfilling the 2013 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria [11] and 26 healthy blood donors (HD) as control group, including subjects not suffering from any disease and not taking medications at enrolment.

Cytokine assay

Blood samples obtained from all participants were centrifuged and serum was separated and stored in aliquots at −80°C until use. Serum levels of adipokines (adiponectin, leptin, resistin, visfatin) and cytokines (TNF-α, IFN-γ, IL-2, IL-10, IL-17A) were measured in duplicate using kits manufactured by Bio-Rad (Bioplex ProTM cytokine/chemokine and growth factor assay and Bioplex pro diabetes assay) for multiplex immunoassay (Bioplex 200 system; Bio-Rad Laboratories (Hercules, California, USA). The analyses were carried out according to the manufacturer's instructions.

Clinical data

From all patients we collected clinical, anthropometric and laboratory features, including disease duration, onset of Raynaud's phenomenon, skin involvement according to the modified Rodnan skin score (mRSS) [12] and cutaneous subset according to LeRoy criteria [13]. Moreover, the presence/absence of interstitial lung disease (ILD) defined by chest high-resolution computed tomography (HR-CT) scan, pulmonary function test (PFT) with forced vital capacity (FVC), FEV in 1 s (FEV_1/FVC, diffusing capacity of the lungs for carbon monoxide (DLCO) and right ventricle (RV) estimation, the 6-min walking distance test (6mWDT), the presence/absence of pulmonary arterial hypertension (PAH) diagnosed by right heart catheterization, the presence/absence of esophagopathy evaluated at esophageal scintigraphy or esophageal manometry or chest HR-CT scan, the presence of digital pitting-scars and/or digital ulcers (past or active), the nailfold capillaroscopic pattern 'early', 'active' and 'late' [14] and disease activity according to the ESSG (European Scleroderma Study Group) disease activity index [15] were recorded. Drugs investigated were: peripheral vasodilators, iloprost, immunosuppressive drugs, glucocorticoids, anti-hypertensive and lipid-lowering agents, targeted therapy for the treatment of PAH (bosentan, sildenafil, tadalafil, ambrisentan) and oxygen therapy. The BMI, cardiovascular risk index, acute phase proteins, cholesterol and triglyceride serum levels, smoking status, co-morbidity (such as arterial hypertension, diabetes mellitus and hyperlipidemia) were also assessed. The BMI was calculated as weight in kilograms divided by the height in square meters, and in accordance with the World Health Organization (WHO) BMI category classification, patients were considered underweight (BMI < 18.5), normal weight (BMI = 18.5–24.99), overweight (BMI = 25–29.99)

and obese (≥30). The cardiovascular (CV) risk was estimated as the ratio of total cholesterol/high-density lipoprotein (HDL) or applying the Framingham risk score (FRS).

Statistical analysis

Data were analyzed using IBM-SPSS statistics version 20 software. The comparison between two groups were performed by Student's *t*-test or c^2 test where appropriate. Comparisons among several groups were made using analysis of variance (ANOVA), as appropriate. Spearman's or Pearson's tests were used for correlations between cytokine/adipokine and clinical characteristics. Multiple linear regressions were performed for the analysis of predictors. The multivariate model was built, including different drug treatments (yes/no) (SSc-glucocorticoids, SSc-ERA, SSc-immunosuppressants, SSc-CCB, SSc-iloprost, SSc-PDE5i), cytokine/adipokine levels, BMI, age, gender, disease duration, disease activity index ≥3 ESSG (yes/no). A p value ≤ 0.05 was considered statistically significant.

RESULTS

Patient characteristics

Clinical characteristics of SSs patients are shown in Table 1. Most patients had limited cutaneous SSc (83%), and 27% had active disease (≥3 ESSG score). Of note, only five (6%) patients were obese (BMI ≥ 30), while nine (10%) were underweight (BMI ≤ 18.5). At study entry, drugs taken were calcium channel blockers (CCB) (67.4%), iloprost (48.3%) glucocorticoids (34.8%), endothelin receptor antagonists (ERA) (22.3%), methotrexate (19.5%), mycophenolate mofetil (13.5%) and phosphodiesterase-5 inhibitors (PDE5i) (tadalafil, sildenafil) (8.9%). No patient was taking non-steroidal anti-inflammatory drugs. Table 2 shows the comparison of demographics, anthropometric characteristics and serum levels of cytokines and adipokines between SSc and HD. No significant differences in anthropometric characteristics were detected, but a trend towards a lower BMI was seen in SSc patients.

Adipokines and cytokines

Table 2 shows the comparison of cytokines and adipokines between HD and the whole SSc cohort. Leptin and resistin were significantly higher in SSc than in HD.

TABLE 1 Clinical findings of systemic sclerosis (SSc) cohort (n = 89 patients)

Disease duration (years), mean ± SD	8.1 ± 6.6
Underweight (BMI < 18.5), *n* (%)	9 (10%)
Normal weight (BMI ≥ 18.5 <25), *n* (%)	49 (55%)
Overweight (BMI ≥ 25 <30), *n* (%)	26 (29%)
Obese (BMI ≥ 30), *n* (%)	5 (6%)
Diabetes mellitus, *n* (%)	1 (9%)
Dyslipidemia, *n* (%)	11 (12%)
Tot-cholesterol/HDL, mean ± SD	3.3 ± 1.0
Framingham risk score, mean ± SD	3.7 ± 2.9
Previous smokers, *n* (%)	5 (6 %)
Arterial hypertension, *n* (%)	8 (7 %)
Active patients with disease activity index ≥3 ESSG, *n* (%)	24 (27%)
Erythrocyte sedimentation rate (mm/h), mean ± SD	19 ± 14
C-reactive protein (mg/l), mean ± SD	4.3 ± 5
Limited cutaneous SSc, *n* (%)	74 (83%)
Interstitial lung disease, *n* (%)	51 (57%)
Esophageal involvement, *n* (%)	79 (89%)
Bowel incontinence, *n* (%)	2 (3%)
Active digital ulcers, *n* (%)	18 (20%)
Digital pitting scars, *n* (%)	55 (62%)
Calcinosis, *n* (%)	79 (89%)
Renal involvement, *n* (%)	5 (6%)
Pulmonary arterial hypertension, *n* (%)	7 (8%)
Capillaroscopy scleroderma pattern, *n* (%)	Early 6 (7%)
	Active 49 (55%)
	Late 34 (38%)

Abbreviations: BMI, body mass index; ESSG, European Scleroderma Study Group; HDL, high-density lipoprotein; SD, standard deviation.

Visfatin was also increased in SSc, but the difference from HD did not reach statistical significance. Adiponectin was measured only in the SSc group (see below). Remarkably, SSc patients showed significantly higher levels of TNF-α and IL-2 than HD. Because of a possible bias by drugs, patients were grouped into SSc-glucocorticoids, SSc-ERA, SSc-immunosuppressants, SSc-CCB, SSc-iloprost and SSc-PDE5i. Serum levels of cytokines and adipokines were associated with the different treatments, BMI, age, gender, disease duration and disease activity index ≥3 ESSG by multivariate analysis. Only PDE5 inhibitors were independently associated with higher levels of leptin [odds ratio (OR) = 3.27, 95% confidence interval (CI) = 12 892–52 716, p = 0.002] and visfatin (OR = 2.66, 95% CI = 4340–29 950, p = 0.009). However, this association may be biased by the presence of PAH, as serum leptin was significantly higher in SSc-PAH (CI = 25 047 ± 37 289) than in no-PAH SSc

(CI = 12 053 ± 11 576, $p = 0.03$). Also, resistin levels were significantly higher in SSc-PAH (CI = 12 641 ± 14 461) than in no-PAH SSc (CI = 7103 ± 5103, $p = 0.03$). Furthermore, leptin levels were significantly higher in SSc patients with ILD (CI = 16 155 ± 2564) than in those without (8908 ± 1507, $p = 0.02$) and IL-17 levels were significantly higher in lcSSc (2.1 ± 7.4) than in dcSSc (CI = 0.22 ± 058, $p = 0.03$).

No statistically significant difference in cytokine/adipokine levels between early SSc (<2 years of disease duration) and late disease (>2 years of disease duration) was observed. We also stratified SSc patients as high and low CV risk according to the FRS and other indices (total cholesterol /HDL ratio > 4.5). As only three patients had high/medium CV FRS statistical comparison with those showing low-risk CV FRS could not be made (data not shown). Furthermore, no significant differences were found when patients were stratified according to the presence of digital ulcers or DLCO < 75% or FVC < 70% values or disease activity index ESSG > 3.

HD and SSc were then subdivided into normal (BMI < 25) and overweight/obese (BMI ≥ 25) subjects; the comparison of cytokines and adipokines is shown in Table 3. In the normal weight group, IFN-γ, leptin and resistin levels were significantly higher in SSc than in HD, while in subjects with overweight/obesity only resistin was significantly higher in SSc and leptin levels were higher in SSc than in HD, but the difference was not significantly different.

TABLE 2 Demographics and cytokines/adipokines serum levels in systemic sclerosis (SSc) patients as whole cohort; data are shown as mean ± standard deviation

	SSc all ($n = 89$)	HD ($n = 6$)	p
Age (years), mean ± SD	52.1 ± 14	49.4 ± 11	0.07
Female n (%)	84 (94 %)	23 (88%)	0.37
Body mass index (kg/m^2) mean ± SD	23.6 ± 4.2	25.13 ± 4.4	0.12
IL-17A pg/ml	2.4 ± 6	1.7 ± 3.1	0.96
TNF-α pg/ml	57.2 ± 62	1.0 ± 1.1	0.02
IFN-γ pg/ml	88.9 ± 172	29.6 ± 23	0.09
IL-2 pg/ml	42 ± 162	3.57 ± 1.3	0.01
IL-10 pg/ml	40 ± 175	4.3 ± 9.8	0.29
Leptin pg/ml	15 266 ± 26 679	2822 ± 2045	0.00003
Resistin pg/ml	6146 ± 2344	1705 ± 279	0.00001
Visfatin pg/ml	4459 ± 15 177	2555 ± 12 083	0.55

Abbreviations: HD, healthy donors; IFN, interferon; IL, interleukin; SD, standard deviation; TNF, tumor necrosis factor.

BMI categories in SSc

When SSc patients were subdivided into BMI categories, some meaningful differences emerged (Table 4). As expected, leptin (Figure 1) and visfatin levels were significantly higher in obesity than in other BMI classes ($p = 0.0001$ and $p = 0.002$, respectively), while no significant changes were observed for resistin. SSc patients with obesity also had the highest serum levels of IL-17A ($p = 0.01$), IL-2 ($p = 0.001$) and IL-10 ($p = 0.01$). Adiponectin levels did not significantly change among the BMI subgroups, but the leptin/adiponectin ratio, a functional biomarker of adipose tissue inflammation, was significantly higher in patients with obesity ($p = 0.0001$). A striking finding was the increased TNF-α levels observed in underweight SSc patients. The latter had significantly higher TNF-α levels ($p = 0.01$) than the other BMI classes (Table 3, Figure 2). IL-17A,

TABLE 3 Cytokines/adipokines levels in normal weight (BMI < 25) and overweight/obese (BMI ≥ 25) systemic sclerosis (SSc) patients and healthy donors (HD); data are shown as mean = standard deviation

	BMI < 25			BMI ≥ 25		
	SSc	HD	p	SSc	HD	p
IL-17 pg/ml	1.8 ± 8.9	1.5 ± 3	0.90	1.58 ± 3.61	0.51 ± 0.94	0.41
TNF pg/ml	52.8 ± 89	1.4 ± 1.1	0.03	33.0 ± 113	1.59 ± 0.92	0.33
IFN-γ pg/ml	114 ± 298	21 ± 10	0.03	78.9 ± 332	24.0 ± 8.0	0.21
IL-2 pg/ml	13.3 ± 46	1.3 ± 2.3	0.34	70.3 ± 192	1.2 ± 0.3	0.02
IL-10 pg/ml	12.7 ± 34	4.3 ± 13	0.36	60.1 ± 203	7.4 ± 0.24	0.32
Leptin pg/ml	9530 ± 13 198	2249 ± 1591	0.04	25 655 ± 39517	3490 ± 2367	0.06
Resistin pg/ml	6248 ± 2358	1667 ± 257	0.0001	6694 ± 1711	1749 ± 308	0.0001
Visfatin pg/ml	1836 ± 3921	4694 ± 16 434	0.39	8532 ± 1711	59.9 ± 92	0.25

Abbreviations: IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

TABLE 4 Cytokines and adipokines in systemic sclerosis patients by BMI categories (mean ± SD)

	Underweight	Normal weight	Overweight	Obese	*p*
IL-17A pg/ml	0.05 ± 0.1	2.24 ± 9.1	0.8 ± 1.5	6.9 ± 6.7 versus UW, NW, OW	0.01
TNF-α pg/ml	144.2 ± 271 versus NW, OW, Ob	12.1 ± 43	31.1 ± 121	42 ± 71	0.03
IFN-γ pg/ml	76.4 ± 125	83.7 ± 251	105.0 ± 303	91.5 ± 249	0.97
IL-2 pg/ml	23.4 ± 85	11.4 ± 45	35.9 ± 129	233 ± 350 versus UW, NW, OW	0.001
IL-10 pg/ml	12.0 ± 31	12.8 ± 35	30.1 ± 112	204 ± 431 versus UW, NW, OW	0.01
Leptin pg/ml	9033 ± 7181	9623 ± 14 097	17 465 ± 10335	64 970 ± 89346 versus UW, NW, OW	0.0001
Visfatin pg/ml	127 ± 234	2154 ± 4199	4340 ± 7900	28 551 ± 58672 versus UW, NW, OW	0.002
Resistin pg/ml	6997 ± 956	6109 ± 2519	6637 ± 1727	6964 ± 1800	0.57
Adiponectin ng/ml	9 829 075 ± 66 275	6 582 923 ± 53 445	7 459 125 ± 65 585	3 248 520 ± 10 425	0.22
Leptin/adiponectin	0.002 ± 0.002	0.002 ± 0.004	0.003 ± 0.0006	0.02 ± 0.04 versus UW, NW, OW	0.0001

Abbreviations: NW, normal weight; Ob, obese; OW, overweight; UW = underweight.

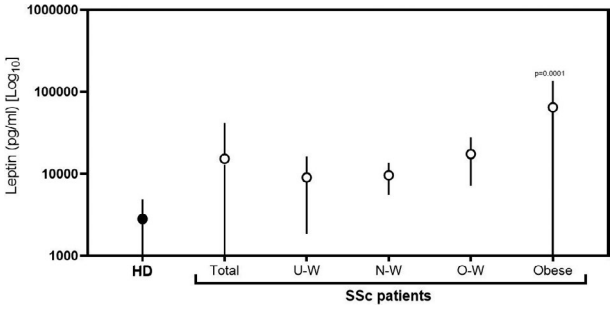

FIGURE 1 Serum leptin levels in healthy donors (HD) and systemic sclerosis (SSc) patients with different categories of body mass index. U-W = underweight; N-W = normal weight; O-W = overweight. Mean (95% confidence interval)

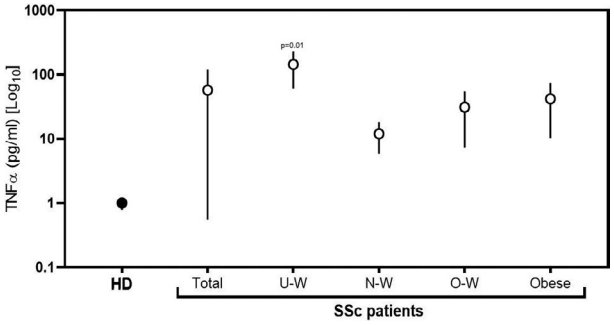

FIGURE 2 Serum tumor necrosis factor (TNF)-α levels in healthy donors (HD) and systemic sclerosis (SSc) patients with different categories of body mass index. U-W = underweight; N-W = normal weight; O-W = overweight. Mean (95% confidence interval)

leptin and visfatin levels were found to be positively correlated, and TNF-α negatively, with increasing BMI values. BMI was also correlated with ESR, CRP, triglycerides and cholesterol levels (Supporting information, Table S1).

DISCUSSION

In this study, we investigated the serum levels of different adipokines (adiponectin, leptin, resistin, visfatin) and cytokines (TNF-α, IFN, IL-12, IL-10, IL-17A) in SSc patients and searched for possible correlations with BMI and specific clinical manifestations of the disease. TNF-α, IL-2, leptin and resistin were higher in SSc patients than in HD. These findings are globally consistent with the literature reporting an increase in cytokines/adipokines in SSc to different extents [4,8,9,16–24]. However, attempts to correlate each cytokine/adipokine to the disease activity of SSc and to BMI have yielded conflicting results. Therefore, expression, role and function and each adipokine in SSc are not yet fully unveiled (Supporting information, Table S2). All the studies but one [25] showed increased serum levels of leptin in SSc, sometimes correlating with BMI. We found a slight but significant increase of leptin levels in SSc in comparison with HD and a positive correlation of leptin with BMI. However, leptin and resistin levels were found to be higher in SSc patients with PAH than in those without. Consistently, a previous study has demonstrated that leptin serum levels were higher in idiopathic PHA and SSc-PAH patients than healthy controls and that dysfunctional endothelial cells from SSc-PAH lung produced leptin *in vitro*, although a link with BMI was not investigated [26]. We also detected increased leptin levels in SSc patients affected with ILD. Furthermore, we detected significantly higher resistin levels in SSc patients than in HD, but unlike a previous study it was not regulated by BMI [6]. Conversely, we found that visfatin levels rose with BMI increases in SSc patients, but were still statistically comparable to HD. Masui *et al.* [22] had detected similar levels of visfatin in SSc patients and controls, but noticed higher visfatin levels in dsSSc patients with late disease without exploring BMI status.

Adiponectin can generally be accounted as a leptin antagonist with anti-inflammatory properties and decreases in obesity [27]. Adiponectin has been suggested to also have anti-fibrotic activities and seems to be regulated in SSc, depending on the skin fibrosis extension and disease duration. Adiponectin is an anti-fibrotic signal and reduces type II collagen production by scleroderma fibroblasts *in vitro* [28]. Some studies have demonstrated that adiponectin is low in dcSSc patients both in serum and lesional skin, but increases in dcSSc patients with a disease duration longer than 5 years, when skin thickness reduces [9,20,21,29]. We found low, although not statistically significant, levels of adiponectin in SSc with obesity, but we could not confirm previous data as we studied only 15 patients with dcSSc. At this point, a critical question to be addressed is: 'why is leptin increased in SSc patients as their BMI was similar to that of HD'? Indeed, no study has ever demonstrated an increased frequency of obesity among SSc patients. We may speculate that the leptin increase in SSc might be due to some adipocyte dysfunction rather than to an over-production by visceral fat, or arises from different cellular sources [26].

Among the investigated cytokines, we found significantly higher levels of TNF-α and IL-2 in SSc compared to HD, presumably linked to the biological activity of the disease, despite no correlation with the clinical manifestations or with the global disease activity being found. Within the SSc cohort, patients with obesity had significantly higher levels of IL-17A and IL-10. A correlation between IL-17A and obesity was expected, as high IL-17 mRNA expression has been found in visceral fat of women with obesity [30]. Conversely, the significantly higher IL-10 levels in SSc patients with obesity were unexpected, as in subjects with obesity IL-10 tends to be low and increases with exercise and weight loss [31]. Perhaps the most intriguing finding in our analysis was the strikingly high levels of TNF-α in underweight SSc patients, approximately 10-fold higher than in normal-weight patients. Increased levels of TNF-α in SSc have already been reported [6,18,19,32] although a link with a particular phenotype was not shown. Only one study had demonstrated a correlation of TNF-α levels with lung fibrosis and impairment of pulmonary vital capacity [32]. Of note, TNF-α blocking agents have been successfully used in SSc patients with arthritis [33], and further investigations should focus upon this possible pathogenic association. In our study, 10% of SSc patients were underweight, and loss of body mass has been associated mainly with malabsorption [34]. Over-expression of TNF may also be considered as a further mechanism involved in the chachexia-like status of SSc. During the 1980s, TNF-α and cachectin were demonstrated to be the two faces of the same coin [35]. In an experimental model, TNF-α induced weight loss directly proportional to the decreased food and water intake [36]. Moreover, it is known that anti-TNF-α drugs may increase body weight, and it has been reported that etanercept treatment promoted weight gain and reduced chachexia in patients with rheumatoid arthritis [37].

In conclusion, despite some limitations such as the cross-sectional design and the relatively small sample size of our SSc cohort, this study suggests that an abnormal twist between cytokines, adipokines and BMI takes place in SSc. These changes in adipokines may be related to a disfunction of adipocytes or other, different, sources, as SSc patients with PAH or ILD showed high leptin levels. Further investigation is warranted to establish whether these findings may represent the pathogenetic background of specific clinical manifestations of SSc.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICAL APPROVAL

The study obtained the approval of the local ethics committee (Azienda Policlinico Bari, no. 5351 14/09/2017). The study was conducted in compliance with the Helsinki Declaration, and all patients gave their written informed consent to participate and for use of their data for publication, with explicit protection of their identity

AUTHOR CONTRIBUTIONS

F.I. and E.P. conceived the study, were the major participants in its design, coordination, interpretation of results and statistical analysis; they also prepared the draft manuscript. D.N., R.B. and N.L. carried out biological assays, R.C., M.F. and F.C. collected clinical data and participated in study design coordination. All authors were involved in draft manuscript modifications and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

Data are available on request due to privacy/ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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