Resistin: a possible biomarker of organ involvement in systemic sclerosis patients?

K. Sawicka[1], M. Michalska-Jakubus[1], M. Kowal[1], E. Potembska[2], D. Krasowska[1]

[1]*Department of Dermatology, Venereology and Paediatric Dermatology,* [2]*Department of Psychiatric Nursing, Medical University of Lublin, Poland.*

Karolina Sawicka, MD
Małgorzata Michalska-Jakubus, MD, PhD
Małgorzata Kowal, PhD
Emilia Potembska PhD, MD
Dorota Krasowska, MD, PhD, Prof.

Please address correspondence to:
Dr Karolina Sawicka,
Department of Dermatology, Venereology and Paediatric Dermatology,
Medical University of Lublin,
13 Radziwiłłowska Str.,
20-080 Lublin, Poland.
E-mail: k.sawicka10@gmail.com

Received on December 12, 2016; accepted in revised form on June 26, 2017.

Clin Exp Rheumatol 2017; 35 (Suppl. 106): S144-S150.

Key words: resistin, systemic sclerosis, interstitial lung disease, internal organ involvement

Competing interests: none declared.

ABSTRACT

Objective. *Resistin has strong pro-inflammatory and profibrotic properties, which are key pathogenetic processes in systemic sclerosis.*

We hypothesised that resistin may be associated with organ involvement and inflammatory process in SSc patients. To address this hypothesis, the aim of this study was to define serum resistin levels in SSc patients and control group and determine the correlation between this adipokine and internal organ involvement in SSc patients.

Methods. *The study enrolled 48 Caucasian female patients with SSc and 38 healthy subjects of control group. Serum concentrations of resistin were measured using commercially available ELISA Kits (Quantikine ELISA Kit R&D Systems, Minneapolis, MN, USA).*

Results. *Patients with SSc had higher resistin levels [mean (SD): 10.2, (4.87)] than the control group [7.64, (4.43)] and the difference was statistically significant ($p=0.017$, $p<0.05$). We found statistically significant association between serum resistin and ILD, arthralgia and oesophageal involvement ($r=0.31$, $p=0.042$; $r=0.48$, $p=0.001$; $r=0.32$, $p=0.034$; respectively). Moreover, the assessment of the relation between plasma concentrations of resistin and inflammatory parameters in SSc patients indicated a positive correlation between resistin and C-reactive protein levels ($r=0.37$; $p=0.011$).*

Conclusion. *The results of our study indicate that resistin levels might correlate with organ involvement and inflammatory process in SSc patients.*

Introduction

Systemic sclerosis (SSc) is a chronic multiorgan inflammatory disease characterised by immune abnormalities, vascular changes and progressive fibrosis of skin and internal organs (1). Involvement of internal organs is associated with the high morbidity and mortality in SSc. Lungs are the major target organ in SSc, with mainly two pulmonary syndromes: pulmonary arterial hypertension (PAH) and/or interstitial lung disease (ILD) which are the leading cause of mortality in patients with SSc. Lung fibrosis may results from chronic pulmonary inflammation that initiates collagen production from proliferating fibroblasts (2, 3).

Resistin is a 12.5-kDa member of cysteine-rich proteins called "resisitin-like molecules" (RELMs) or "found in inflammatory zone" (FIZZ). In mice, four members of RELMs family have been described: RELMalpha (FIZZ1), RELMbeta (FIZZ2), resisitn (FIZZ3) and RELMgamma. In humans, only two RELMs have been found: resistin and RELMs beta (4). Resistin was discovered in 2001 and initially described as one of the adipocyte-derivied protein factors (ADSF) or adipokines and as a mediator of insulin resistance based on mouse models (5-7). However, mouse resistin is mainly produced in white adipose tissue (WAT), whereas expression of resistin in human adipocytes is very low and its main source are peripheral blood immune cells – monocytes and macrophages (4, 8). It is also expressed at high level in the bone marrow and lungs (4). The presence of FIZZ within or near inflammatory areas suggests a close relationship between resistin and inflammation. Resistin gene expression in peripheral blood mononuclear cells (PBMCs) was shown to be upregulated particularly on stimulation with pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α. It has been shown recently, that plasma resistin levels correlate significantly with inflammatory markers such as C-reactive protein (CRP), IL-6 and TNF-α receptor 2 (6, 9). On the other hand, resistin has been postulated as an important molecule triggering NF-κB activation and

pro-inflammatory cytokine production in human PBMC, including TNF-α, IL-1β, IL-6 and IL-12 (4, 10). These findings may provide a novel link between elevated resistin levels and inflammatory processes (9). On clinical background, a significant positive correlation between resistin and inflammatory markers like C-reactive protein or ESR has been observed in inflammatory diseases and the role of resistin in atherosclerosis, diabetes mellitus, non-alcoholic fatty liver disease, inflammatory bowel disease, psoriasis and rheumatoid arthritis has been reported (4, 11-18). Furthermore, Almehed *et al*. described an association of resistin with general inflammation and anti-inflammatory effect of glucocorticosteroids in systemic lupus erythematosus patients (19). Additionally, it is reported that resistin enhances the expansion of regulatory T-cells which may play a role in fibrosis by producing a key profibrotic cytokine- transforming growth factor β (TGF-β) (20). What is more, it is thought that resistin stimulates proliferative response in vascular smooth muscle cells and exerts angiogenic effect on endothelial cells (21, 22). Since autoimmune inflammation, vascular abnormalities with altered angiogenesis and fibroblast activation are pathogenic hallmarks in SSc, we hypothesised that resistin may be implicated in the disease development. To address this hypothesis, the aim of this study was to define serum resistin levels in SSc patients and control group as well as correlations between resistin, inflammatory parameters and internal organ involvement in SSc patients.

Material and methods

Patients

The study enrolled 48 Caucasian female patients with SSc [aged 34-84 years, mean (SD): 62 (10.6) years], fulfilling the American College of Rheumatology (ACR) and/or EULAR classification criteria (23, 24). The control group consisted of 38 healthy subjects, matched with patients for sex, age, BMI and race [aged 36-88 mean (SD): 56.3 (9.7) years]. Patients and healthy controls were voluntarily recruited and informed consent was obtained from all participants. The study was approved by the Bioethics Committee. Patients with overlap syndromes, kidney disease, diabetes mellitus, thrombosis, metabolic syndrome/hyperlipidaemia, pregnancy, neoplastic diseases and those with habitual cigarette smoking and alcohol drinking were excluded from the study.

Laboratory assessment

The material for the study was fasting peripheral blood drawn for blood clot in the morning. The samples were allowed to clot for 30 min and centrifuged for 15 min at 1000 x g. Obtained sera were stored at -70˚C immediately after collection till further analysis. Serum concentrations of resistin were measured using commercially available ELISA Kits (Quantikine ELISA Kit R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instruction. The concentration level of cytokine was calculated using appropriate a standard curve generated by the reader ELISA ELX 800 Bio-tek Instruments, USA. The minimum detectable concentration of resistin ranged from 0.010–0.055 ng/ml.

Statistical analysis

A statistical analysis was performed by using Statistica 9.1 package (Stasoft, Poland). First, the numerical variables distribution was assessed by the Shapiro-Wilk test. Comparisons of numerical values between patients with SSc and healthy controls and within the patient group were performed by the Student's *t*-test. The relationship between resistin and patient characteristics were correlated by Spearman's rank correlation test, where $p<0.05$ was considered as statistically significant. The results obtained by Rho Spearman's rank correlation test were checked by the difference test for the independent groups- the Mann-Whitney U-test. Three or more independent groups were compared using the Kruskal-Wallis test with post-hoc assays available for this test.

Clinical assessments

The clinical and laboratory data were obtained at the same hospitalisation as the blood sampling. Skin thickness was evaluated using a modified Rodnan skin score (mRSS) (25). Patients were divided onto two groups classified as having either lcSSc or dcSSc, according to the criteria proposed by LeRoy *et al*. (26). The disease duration was measured from the onset of the first symptom, other than Raynaud's phenomenon, consistent with SSc. The disease activity was assessed according to the European Scleroderma Study Group (EScSG) disease activity score for SSc (Valentini disease activity index) as active or inactive (27). Microvascular abnormalities such as digital ulcers and osteolysis of the distal phalanges of the fingers (acroosteolysis) were also evaluated. Nailfold capillaroscopy was performed to estimate SSc microangiopathy and patients were classified into three groups presenting as an early, active or late pattern, according to the criteria proposed by Cutolo *et al*. (28). Patients were evaluated with respiratory function tests and high-resolution computed tomography (HRCT). Patients with ground glass opacification, centrilobular nodules or honeycomb picture were regarded to have lung involvement. Pulmonary artery pressure and valvular insufficiency were assessed by colour Doppler echocardiography (ECO). The pulmonary arterial hypertension was defined as systolic pulmonary arterial pressure (sPAP) ≥35 mm Hg in Doppler echocardiography and was determined only at rest (29). The presence of ANAs and their specificity including anticentromere antibodies (ACAs), anti-topo I (Scl-70) antibodies, anti-RNA polymerase I or III antibodies, anti- U3- and U1-RNP, PM-Scl and anti-Ku antibodies was determined by means of IIF on HEp-2 cells and/ or immunoblot analysis.

Results

Detailed clinical and laboratory characteristics of the study population are summarised in Table I. Mean disease duration was 12.85 years (±7.63). Scleroderma-related interstitial lung disease, defined based on HRCT findings, was present in 43 patients (89.5%) and 11 (22.9%) of SSc patients had elevated pulmonary artery pressure on ECO. In patients group, 35 (72.9%) had oesophageal involvement and 41 (85.6%) had arthralgia, while 10 (20.8%) presented

Table I. Clinical and laboratory characteristics of patients with systemic sclerosis (SSc) and healthy control group.

Parameters	SSc patients (n=48)	Healthy controls (n=38)
Gender, female:male ratio	48:0	38:0
Age, mean (SD) (range), years	62.6 (10.5), 34-84*	56.3 (9.7) 36-88*
BMI, mean (SD)	28.07 (11.49)	25.51 (3.38)*
Disease duration (years), (SD)	12.85 (7.6)	
Duration of Raynaud's phenomenon (years), (SD)	16.91 (9.3)	
Disease type, n (%)		
lcSSc	42 (87.5)	
dcSSc	6 (12.5)	
EScSG disease activity score, mean (SD) (range)		
Active disease, n (%)	9 (18.7)	
Inactive disease, n (%)	39 (81.25)	
History of digital ulcers, n (%)		
Active digital ulcers	13 (27)	
No active digital ulcers	35 (73)	
Acroosteolysis, n (%)	13 (27)	
Early pattern of microangiopathy, n (%)	10 (20.8)	
Active pattern of microangiopathy, n (%)	8 (16.6)	
Late pattern of microangiopathy, n (%)	20 (41.6)	
mRSS, mean (SD), (range)	10 (6.2), (2-28)	
Antinuclear antibodies, n (%)		
ACA	26 (54.1)	
Topo-1	17 (35.4)	
Anti-RNA polymerase III	2 (4.1)	
Other (anti-fibrillarin, ANA-speckled pattern)	3 (6.25)	
ILD, n (%)	43 (89.5)	
DLCO, mean (SD), (range);	84.4 (19.1), (41-114)	
$DCO_{SB} \geq 80\%$	17	
$DCO_{SB} < 80\%$	9	
FVC, mean (SD), (range);	97.9 (23.2), (50-142); [6/35]	
FVC≥ 80%	35	
FVC <80%	6	
TLC, mean (SD), (range);	92.2 (21.7), (55-141); [12/26]	
TLC ≥ 80%	26	
TLC <80%	12	
PAH (sPAP ≥35 mm Hg), n (%)	11 (22.9)	
Oesophageal involvement, n (%)	35 (72.9)	
ECG changes, n (%)	6 (12.5)	
Heart valves abnormalities, n (%)	31 (64.5)	
Myalgia (n%)	10 (20.8)	
Arthralgia (n%)	41 (85.6)	
ESR, mean (SD) (range), mm/h	26,065 (15,6), (7-80)	
CRP, mean (SD) (range), mg/l	7,94 (17,2), (0,5-88,6)	
Complement C3, (low level) [n], / (in normal range) [n]	11/37	
Complement C4, (low level) [n], / (in normal range) [n]	4/44	
RF positive, (n%)	11 (22.9)	
NT-proBNP, mean (SD) range, pg/ml	367.78 (598.1), (10-3586)	
CK mean (S.D.) range, U/l	116.14 (166), (25-1092)	92.6 (67.1), (19-271)

lcSSc: limited cutaneous systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis; ACA: anticentromere antibodies; Topo-1: antitopoizomerase antibodies; ANA: antinuclear antibodies; mRSS: modified Rodnan skin score; ILD: Interstitial lung disease; DLCO: diffusing capacity for carbon monoxide; FVC: forced vital capacity; TLC: total lung capacity; PAH: pulmonary arterial pressure; ECG: electrocardiogram; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; CK: creatine kinase; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; SD: standard deviation.

*There were significant differences between the age of patients with systemic sclerosis and the control group, although there was no statistically significant relationship between age and the serum resistin levels (p=0.34 for SSc patients and p=0.39 for control group).

*There was no significant difference between BMI of SSc patients and BMI of control group, p=0.212.

myalgia symptoms. Concerning cardiac involvement, 6 (12.5%) SSc patients had ECG changes and 31 (64.5%) had heart valves abnormalities. Only in 11 (22.9%) patients the rheumatoid factor was positive. The mean CK was 116.14 (±166.013), (range 25-1092). Significant difference was found in NT-proBNP value: mean NT-proBNP in patients group was 367.78 (±598.09), (range 10-3586) compared to 92.6 (±67.1), (range 19-271) in healthy controls.

Resistin serum levels and clinical correlations

Patients with SSc had higher serum resistin levels [mean (S.D.), (range): 10.18 (±4.87), (4.8–31.7)] than the control group [7.64 (±4.43), (0.9-18.1)] and the difference was statistically significant (p=0.017, p<0.05). Furthermore, the mean value of serum resistin concentrations in dcSSc patients was 11.2 ng/ml and 10.01ng/ml in patients with lcSSc (Fig. 1). Concerning organ involvement we found statistically significant association between resistin levels and ILD (rho=0.31, p=0.042) and serum resistin concentrations were higher in SSc patients with ILD [mean (SD), (range): 10.5 (±5.01), (4.8-31.7)] than in those without lung fibrosis [mean (SD), (range): 6.8 (±2.18), (5.29-9.9)]. Moreover, we found also statistically significant association between resistin levels and arthralgia in systemic sclerosis group (rho=0.48, p=0.001). Serum concentrations of resistin were higher in SS patients with arthralgia [mean (SD), (range): 10.63 (±4.9), (4.8–31.7)] comparing to those without [mean (SD), (range): 6.16 (±1.47), (4.9–8.48)]. Finally, we showed statistically significant association between resistin levels and oesophageal involvement (rho=0.32, p=0.034) and higher resistin levels were reported in SSc patients with oesophageal involvement [mean (SD), (range): 10.85(±5.3), (4.8–31.7)] than in those without affected oesophagus function [mean (SD), (range): 8.1 (±2.3), (4.9–12.7)], (Table II). Interestingly, serum concentration of resistin positively correlated with C-reactive protein levels (r=0.37; p=0.011). Close to statistically significant association was found between serum resistin lev-

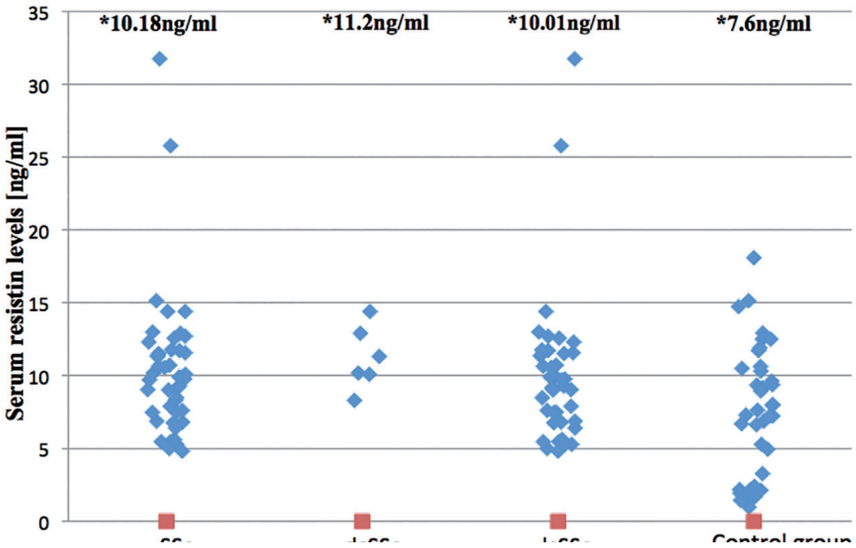

Fig. 1. Serum resistin levels in SSc, dcSSc, lcSSc patients and control group. *= mean value.

Table II. Statistically significant associations between serum resistin levels and clinical and laboratory parameters in SSc patients with use of Spearman's rank test and Mann-Whitney U-test.

Resistin	Spearman's rank test		Mann-Whitney U-test			
	Rho	*p*-value	Internal organ involvement (-) median	Internal organ involvement (+) median	z	*p*-value
Arthralgia	0.48	0.001	5.29	9.91	-2.87	0.004
Oesophageal involvement	0.32	0.034	8.48	10.37	-2.1	0.036
ILD	0.31	0.042	6.03	9.84	-2.02	0.043
CRP	0.37	0.011				

ILD: interstitial lung disease, CRP: C-reactive protein, SD: standard deviation.

Table III. Correlation analysis between serum resistin levels and clinical and laboratory parameters in SSc patients without statistical significance.

Resistin	Rho	
	Spearman	*p*-value
Disease activity	0.23	0.135
Digital ulcers	-0.01	0.931
Acroosteolysis	-0.10	0.511
Raynaud's phenomenon	0.08	0.585
mRSS	0.08	0.601
RF	0.27	0.074
PAH	0.15	0.342
Heart valve involvement	0.00	0.991
ECG	-0.23	0.135
DLCO	0.13	0.539
FVC%NAT	0.009	0.611
TLC	-0.29	0.09
C3	0.16	0.315
C4	0.09	0.578
ESR	0.28	0.061
NT-proBNP	-0.04	0.796
CK	0.01	0.962
Myalgia	0.08	0.610

mRSS: modified Rodnan skin score; ESR: erythrocyte sedimentation rate; ECG: electrocardiogram; RF: rheumatoid factor; PAH: pulmonary arterial hypertension; DLCO: diffusing capacity for carbon monoxide; FVC: forced vital capacity; TLC: total lung capacity; CK: creatine kinase; NT-proBNP: N-terminal prohormone of brain natriuretic peptide. *p>0.05.

els and ESR levels (r=0.28, p=0.061). However, we did not find any association between resistin and nailfold capillaroscopy characteristics, digital ulcers, acroosteolysis (Tables III and IV). Although nine SSc patients had decreased values of DLCO <80%, six patients had decreased FVC <80% and eight TLC<80%, we did not find and statistically significant associations between serum resistin levels and pulmonary function tests. Mutual correlations of resistin with clinical profile of SSc patients are presented in Tables II and III.

Discussion

Although most reports concerning resistin focused on its function in the metabolic syndrome, obesity and insulin resistance, the involvement of resistin in the regulation of inflammatory and autoimmune process in light of still unclear pathogenesis of connective tissue diseases drew the attention of the investigators through the last decade. There is some evidence on its role in RA, SLE, Sjögren's syndrome and other inflammatory diseases (30). In the literature there is still no agreement as for serum levels and correlations of resistin in SSc, mainly because of limited number of studies. Some reports have suggested that increased levels of resistin may modulate immune responses in SSc and correlate with some laboratory as well as clinical data, however, results are divergent (18). In the present study we detected higher resistin levels in SSc patients than in the control group, and the difference was statistically significant. This is an agreement with the results of Pehlivan *et al*. and Olewicz-Gawlik *et al*. who reported higher resitin levels in SSc patients (31, 32). However, the authors did not find a significant relationship between serum levels of resistin and organ involvement including skin score and lung involvement as well as with laboratory parameters such as CRP, ESR, C3 and C4 (31, 32). To the best of our knowledge, the present study is the first to show a significant association between serum levels of resistin and ILD, oesophageal involvement and arthralgia. We also found a positive correlation of resistin levels and CRP values. However, we did not find any

Table IV. Comparison between serum resistin levels in systemic sclerosis patients and early, active or late pattern of microangiopathy. The Kruskal-Wallis test.

	Microangiopathy pattern				H	*p*-value
	no microangiopathy	early	active	late		
	Median					
Resistin	10.63	9.77	10.55	9.05	1.13	0.77

association between serum levels of resistin and clinical type of SSc as well as disease activity what corresponds with results obtained by Lee *et al*. and Olewicz-Gawlik *et al*. (18, 33).

We believe that the major finding of this study is the association between resistin serum levels and the presence of ILD on HRCT scans in SSc patients. It may point out a link between resistin and ILD development, especially in the light of evidence that human resistin is expressed at high level in lung tissue (4). SSc-related lung fibrosis presents as a mixed pattern of fibrosis and inflammation. It is presumed to be related to abnormal interactions between endothelial cells, lymphocytes/monocytes and fibroblasts with myofibroblast activation and collagen overproduction as the most important characteristics. A pivotal role seems to be played by transforming growth factor (TGF)-β (34, 35). The role of resistin in fibrotic processes and the mechanism behind this effect is currently closely investigated. Among probable mechanisms, the enhancement of regulatory T cells expansion, being an important source of TGF-β is taken into consideration (36). Importantly, in lung and skin biopsies of SSc patients, increased expression of Toll-like receptor-4 (TLR4) has been demonstrated which activation potentiates TGF-β signaling (35), and a recent study demonstrated that the resistin binds to TLR-4. Moreover, resistin induces proliferation of vascular smooth muscle cells and has proinflammatory and angiogenic impact on endothelial cells which may lead to vascular remodelling (37, 38). It has been found, that resistin takes part in promotion of endothelial cells activation by promoting endothelin-1 (ET-1) release which has also a potent impact on vascular smooth muscle cells, promotes the differentiation of quiescent fibroblast into myofibroblast and prevents fibroblast apoptosis (31, 33, 39-41). Moreover, FIZZ1/RELM alpha, another member of RELMs family, has recently been found to be highly induced in animal model of lung fibrosis and shown to activate fibroblasts with promotion of myofibroblast differentiation and enhancing their resistance to apoptotic stimuli (42). It has been found to be highly induced in lung allergic inflammation as well as bleomycin induced lung fibrosis and expressed by airways and type II alveolar epithelial cells (43). *In vitro* FIZZ1 stimulates type I collagen and alpha-smooth-muscle actin (alpha-SMA) expression in lung fibroblasts as well as has an anti-apoptotic effect on these cells (42). Similarly, FIZZ2 (RELM beta) is also shown to promote lung collagen deposition (42). On clinical background, it has been reported in the literature that increased concentrations of resistin may be a probable cause of pancreatic fibrosis in the course of chronic pancreatitis (4). Moreover, potential contribution of resistin in fibrosis of myocardium was reported by Chemaly *et al*. (44). The authors demonstrated that resistin upregulation was associated with increased myocardial fibrosis with subsequent cardiac hypertrophy and heart failure in rats *in vivo* (44). What is more, the authors reported that the higher local expression of resistin reflected replacement fibrosis in chronic ischaemia in animal myocardium and found that increased fibrosis was followed by resistin overexpression in left heart ventricle of rats (45). Resistin-induced TGFbeta1 from Kupfer cells enhaced hepatic stellate cells collagen I expression (46). The results of Yang *et al*. showed that resistin exert the effect on hepatic fibrosis in non-alcoholic liver disease in rats (47). Additionally, there is an evidence of the role of resistin in the pathogenesis of PAH in SSc patients. Masui *et al*. reported significantly increased serum resistin levels in SSc patients with elevated RVSP (right ventricular systolic pressure) on echocardiogram compared to those with normal RVSP (40). The authors suggested that elevated resistin levels were associated with the progression of proliferative vasculopathy, affecting pulmonary arterial vessels leading to PAH (40).

In the present study we observed the positive correlation between resistin and CRP levels in SSc patients. Similar results were obtained by Masui *et al*. (40). Further, we also found almost statistically significant association between serum resistin levels and ESR. This positive correlation between resistin and inflammatory markers in SSc patients suggest that the increased resistin concentrations found in SSc could be linked to general or connective tissue inflammation. Resistin as a pro-inflammatory cytokine has also been shown to positively correlate with the inflammation markers, CRP and/or ESR, in the course of rheumatoid arthritis and SLE, and importantly had no significant correlation with markers of insulin resistance or BMI (9, 14, 16, 19, 48-53). Migita *et al*. suggested that in RA patients hyperresistinaemia might be associated with systemic inflammation via TNF-α (14). Resistin may bind to TLR-4 and thus may act as pro-inflammatory cytokine in human monocytes (54). Resisitin has been shown to induce expression and to stimulate secretion of pro-inflammatory cytokines including IL-1, IL-6, IL-12 and TNF-α through activation of nuclear transcription factor NF-κB in human peripheral blood mononuclear cells (55). In SLE patients' serum resistin levels positively correlated with elevated values of these pro-inflammatory cytokines – IL-1beta, IL-6 and TNF-α (52). The association between elevated serum resistin levels and arthralgia, as revealed in our study, may be supported by close to statistically significance relationship between resistin and rheumatoid factor (RF) values showed in our SSc patients group. In RA models, resistin has been described to colocalise with inflammatory cells in synovial tissue and upregulates cytokine production – synovial

fluid expresses IL-6 and TNF-α when stimulated by resistin (6, 56). Elevated levels of resistin have also been shown in the synovial fluid from patients with RA and correlated strongly with inflammatory markers such as erythrocyte sedimentation rate (ESR) and CRP (9). Moreover, administration of recombinant mouse resistin into the knee joints of healthy mice induced arthritis-like syndrome in mice in a dose dependent manner with leucocyte infiltration and hyperplasia of the synovia (9, 55). Importantly, resisitin was increased in patients with arthritis independent of metabolic syndrome or abdominal obesity (55).

Conclusions

In summary, we herein reported the first study demonstrating the association of serum resistin levels with ILD, oesophageal involvement and arthralgia in SSc patients. Moreover, the positive correlation between serum resistin levels and CRP observed in our SSc patients group may point out a possible contribution of increased resistin concentration to inflammation in the disease process. However, it still remains to clarify whether the observed hyperresistinaemia in subject with SSc or other connective tissue diseases contribute to their development or only reflects the activity of inflammatory response.

Additionally, it has to be noted that our study has several limitations. The first of them is a small and homogenous sample size. Another potential drawback of the study may be a selection bias. Finally, further studies are needed to explore the biological mechanisms of the relationship between resistin and SSc and to test its predictive value.

Key messages

- The obtained data suggest that resistin may act as a useful maker of lung involvement in SSc patients.
- The positive correlation of resistin serum levels with C-reactive protein and association with arthralgia may indicate its role in inflammatory process in SSc patients.
- Further studies are needed to confirm the role of resistin in the pathogenesis of SSc.

References

1. BARNES J, MAYERS MD: Epidemiology of systemic sclerosis: incidence, prevalence, survival, risk factors, malignancy, and enviromental triggers. *Curr Opin Rheumatol* 2012; 24: 165-70.
2. ABRAHAM DJ, VARGA J: Scleroderma: from cell and molecular mechanisms to disease models. *Trends Immunol* 2005; 26: 587-95.
3. HASSOUN PM: Lung involvement in systemic sclerosis. *Presse Med* 2011; 40: e3-e17.
4. ADRYCH K, SMOCZYNSKI M, SLEDZINSKI T, DETTLAFF-POKORA A, GOYKE E, SWIERCZYNSKI J: Increased serum resistin concentration in patients with chronic pancreatitis: possible cause of pancreatic fibrosis. *J Clin Gastroenterol* 2009; 43: 63-8.
5. STEPPAN CM, BAILEY ST, BHAT S *et al*.: The hormone resistin links obesity to diabetes. *Nature* 2001; 409: 307-12.
6. KRYSIAK R, HANDZLIK-ORLIK G, OKOPIEN B: The role of adipokines in connective tissue diseases. *Eur J Natur* 2012; 51: 513-28.
7. LI HM, ZHANG TP, LENG RX *et al*.: Emerging role of adipokines in systemic lupus erythematyosus. *Immunol Res* 2016; 64: 820-30.
8. ZHAO JH, HUANG XL, DUAN Y, WANG YJ, CHEN SY, WANG J: Serum adipokines levels in patients with systemic sclerosis: A meta-analysis. *Mod Rheumatol* 2017; 27: 298-305.
9. ŠENOLT L, HOUSA D, VERNEROVÁ Z *et al*.: Resistin in rheumatoid arthritis synovial tissue, synovial fluid and serum. *Ann Rheum Dis* 2007; 66: 458-63.
10. BOKAREWA M, NAGAEV I, DAHLBERG L, SMITH U, TARKOWSKI A: Resistin, an adipokine with potent proinflammatory properties. *J Immunol* 2005; 174: 5789-95.
11. KARBOWSKA A, BORATYŃSKA M, KLINGER M: Resistin: A pathogenic factor or a biomarker of metabolic disorders and inflammation? *Postepy Hig Med Dosw* 2009; 63: 485-91.
12. TARKOWSKI A, BJERSING J, SHESTAKOV A, BOKAREWA MI: Resistin competes with lipopolysaccharide for binding to Toll-like receptor 4. *J Cell Mol Med* 2010; 14: 1419-31.
13. YOSHINO T, KUSUNOKI N, TANAKA N *et al*.: Elevated serum levels of resistin, leptin, and adiponectin are associated with C-reactive protein and also other clinical conditions in rheumatoid arthritis. *Intern Med* 2011; 50: 269-75.
14. MIGITA K, MAEDA Y, MIYASHITA T *et al*.: The serum levels of resistin in rheumatoid arthritis patients. *Clin Exp Rheumatol* 2006; 24: 698-701.
15. FORSBLAD d'ELIA H, PULLERITS R, CARLSTEN H, BOKAREWA M: Resistin in serum is associated with higher levels of IL-1Ra in post-menopausal women with rheumatoid arthritis. *Rheumatology* (Oxford) 2008; 47: 1082-7.
16. SCHÄFFLER A, EHLING A, NEUMANN E *et al*.: Adipocytokines in synovial fluid. *JAMA* 2003; 290: 1709-10.
17. JOHNSTON A, ARNADOTTIR S, GUDJONSSON JE *et al*.: Obesity in psoriasis: leptin and resistin as mediators of cutaneous inflammation. *Br J Dermatol* 2008; 159: 342-50.
18. LEE YH, SONG GG: Meta-analysis of circulating adiponectin, leptin, and resistin levels in systemic sclerosis. *Z Rheumatol* 2016; Aug 11 [Epub ahead of print].
19. ALMEHED K, d'ELIA HF, BOKAREWA M, CARLSTEN H: Role of resistin as a marker of inflammation in systemic lupus erythematosus. *Arthritis Res Ther* 2008; 10: R15.
20. SON YM, AHN SM, KIM GR *et al*.: Resistin enhances the expansion of regulatory T cells through modulation of dendritic cells. *BMC Immunol* 2010; 11: 33.
21. CALABRO P, SAMUDIO I, WILLERSON JT *et al*.: Resistin promotes smooth muscle cell proliferation through activation of extracellular signal-regulated kinase ½ and phosphatidylinositol 3-kinase pathways. *Circulation* 2004; 110: 3335-40.
22. DI SIMONE N, DI NICUOLO F, SANGUINETTI M *et al*.: Resistin regulates human choriocarcinoma cell invasive behavior and endothelial cell angiogenic processes. *J Endocrinol* 2006; 189: 691-9.
23. MASI AT, RODNAN GP, MEDSGER TA *et al*.: Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980; 23: 581-90.
24. VAN DER HOOGEN F, KHANNA D, FRANSEN J *et al*.: 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Ann Rheum Dis* 2013; 72: 1747-55.
25. CLEMENTS P, LACHENBRUCH P, SEIBOLD J *et al*.: Inter and intraobserver variability of total skin thickness score (modified Rodnan TSS) in systemic sclerosis. *J Rheumatol* 1995; 22: 1281-5.
26. LEROY EC, BLACK C, FLEISCHMAJER R *et al*.: Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988; 15: 202-5.
27. VALENTINI G, DELLA ROSSA A, BOMBARDIERI S *et al*.: European multicentre study to define disease activity criteria for systemic sclerosis. II. Identification of disease activity variables and development of preliminary activity indexes. *Ann Rheum Dis* 2001; 60: 592-8.
28. CUTOLO M, PIZZORNI C, SULLI A: Nailfold video-capillaroscopy in systemic sclerosis. *Z Rheumatol* 2004; 63: 457-62.
29. VOILLIOT D, MAGNE J, DULGHERU R *et al*.: Determinants of exercise- induced pulmonary arterial hypertension in systemic sclerosis. *Int J Cardiol* 2014; 173: 373-9.
30. BOSTRÖM EA, D'ELIA HF, DAHLGREN U *et al*.: Salivary resistin reflects local inflammation in Sjögren's syndrome. *J Rheumatol* 2008; 35: 2005-11.
31. PEHLIVAN Y, ONAT AM, CEYLAN N *et al*.: Serum leptin, resistin and TNF-α levels in patients with systemic sclerosis: the role of adipokines in scleroderma. *Int J Rheum Dis* 2012; 15: 374-9.
32. OLEWICZ-GAWLIK A, DAŃCZAK-PAZDROWSKA A, KLAMA K, MACKIEWICZ S, SILNY W, HRYCAJ P: The role of adipokines in pathogenesis of systemic sclerosis- original results and short literature review. *Reumatologia* 2009; 47: 329-31.
33. OLEWICZ-GAWLIK A, DAŃCZAK-PAZDROWSKA A, KUZNAR-KAMIŃSKA B *et al*.: Circulating adipokines and organ involvement in patients with systemic sclerosis. *Acta Reu-*

matol Port 2015: 40: 156-62.
34. SOLOMON JJ, OLSON AJ, FISCHER A, BULL T, BROWN KK, RAGHU G: Scleroderma lung disease. *Eur Respir Rev* 2013; 22: 6-19.
35. CAPPELLI S, BELLANDO RANDONE S, CAMICIOTTOLI G, DE PAULIS A, GUIDUCCI S, MATUCCI-CERINIC M: Interstitial lung disease in systemic sclerosis: where we stand? *Eur Respir Rev* 2015; 24: 411-19.
36. SON YM, AHN SM, KIM GR *et al*.: Resistin enhances the expansion of regulatory T cells through modulation of dendritic cells. *BMC Immunol* 2010; 11: 33.
37. CALABRO P, SAMUDIO I, WILLERSON JT *et al*.: Resistin promotes smooth muscle cell proliferation through activation of extracellular signal-regulated kinase ½ and phosphatidylinositol 3-kinase pathways. *Circulation* 2004; 110: 3335-40.
38. DI SIMONE N, DI NICUOLO F, SANGUINETTI M *et al*.: Resistin regulates human choriocarcinoma cell invasive behavior and endothelial cell angiogenic processes. *J Endocrinol* 2006; 189: 691-9.
39. KIM HS, PARK MK, KIM HY, PARK SH: Capillary dimension measured by computer-based digitalized image correlated with plasma endothelin-1 levels in patients with systemic sclerosis. *Clin Rheumatol* 2010; 29: 247-54.
40. MASUI Y, ASANO Y, AKAMATA K *et al*.: Serum resistin levels: a possible correlation with pulmonary vascular involvement in patients with systemic sclerosis. *Rheumatol Int* 2014; 34: 1165-70.
41. VERMA S, LI SH, WANG CH *et al*.: Resistin promotes endothelial cell activation: further evidence of adipokine-endothelial interaction. *Circulation* 2003; 108: 736-40.
42. LIU T, AH BAEK H, YU H *et al*.: FIZZ2/RELM-β Induction and Role in Pulmonary Fibrosis. *J Immunol* 2011; 187: 450-61.
43. PHAN SH, VARANI J, SMITH D: Rat lung fibroblast collagen metabolism in bleomycin-induced pulmonary fibrosis. *J Clin Invest* 1985; 76: 241-7.
44. CHEMALY ER, HADRI L, ZHANG S *et al*.: Long-term in vivo resistin overexpression induces myocardial dysfunction and remodeling in rats. *J Mol Cell Cardiol* 2011; 51: 144-55.
45. CHEMALY ER, KANG S, ZHANG S *et al*.: Differential patterns of replacement and reactive fibrosis in pressure and volume overload are related to the propensity for ischaemia and involve resistin. *J Physiol* 2013; 591: 5337-55.
46. KAJDANIUK D, BOGDAN M, BORGIEL-MAREK H, KOS-KUDŁA B: Transforming growth factor beta1 (TGFbeta1) in physiology and pathology. *Endokrynol Pol* 2013; 64: 384-96.
47. YANG YP, GUAN XQ, QI MM, ZHU LR: Effects of resistin on hepatic fibrosis: possible mechanisms in non-alcoholic fatty liver disease in *in vitro* and *in vivo*. *Dongwuxue Yanjiu* 2012; 33: 367-72.
48. SCHAFFLER A, EHLING A, NEUMANN E *et al*.: Adipocytokines in synovial fluid. *J Am Med Assoc* 2003; 290: 1790-10.
49. KUNNARI A, UKKOLA O, PÄIVÄNSALO M, KESÄNIEMI YA: High plasma resistin level is associated with enhanced highly sensitive C-reactive protein and leukocytes. *J Clin Endocrinol Metab* 2006; 91: 2755-60.
50. GONZALEZ-GAY MA, GARCIA-UNZUETA MT, GONZALEZ-JUANATEY C *et al*.: Anti-TNF-alpha therapy modulates resistin in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2008; 26: 311-6.
51. BAKER JF, MORALES M, QATANANI M *et al*.: Resistin levels in lupus and association with disease-specific measures, insulin resistance, and coronary calcification. *J Rheumatol* 2011; 38: 2369-75.
52. CHUNG CP, LONG AG, SOLUS JF *et al*.: Adipocytokines in systemic lupus erythematosus: relationship to inflammation, insulin resistance and coronary atherosclerosis. *Lupus* 2009; 18: 799-806.
53. YOSHINO T, KUSUNOKI N, TANAKA N *et al*.: Elevated serum levels of resistin, leptin, and adiponectin are associated with C-reactive protein and also other clinical conditions in rheumatoid arthritis. *Intern Med* 2011; 50: 269-75.
54. WISŁOWSKA M, ROK M, JASZCZYK B, STEPIEŃ K, CICHA M: Serum leptin in rheumatoid arthritis. *Rheumatol Int* 2007; 27: 947-54.
55. KONTUNEN P, VUOLTEENAHO K, NIEMINEN L *et al*.: Resistin is linked to inflammation, and leptin to metabolic syndrome, in women with inflammatory arthritis. *Scand J Rheumatol* 2011; 40: 256-62.
56. DESSEIN PH, NORTON GR, WOODIWISS AJ, SOLOMON A: Independent relationship between circulating resistin concentrations and endothelial activation in rheumatoid arthritis. *Ann Rheum Dis* 2013; 72: 1568-88.