

**Serum chemerin in systemic sclerosis: a novel marker of early diffuse disease?**

Sirs,  
the adipocytokine chemerin exerts a chemotactic function for immune cells, promotes cellular migration under inflammatory conditions and mediates dysregulated angiogenesis (1). Chemerin expression is induced by peroxisome proliferator-activated receptor  $\gamma$  (PPAR- $\gamma$ ), a transcription factor that, besides modulating glucose and lipid homeostasis, displays potent anti-fibrotic effects (2). PPAR- $\gamma$  expression and activity are impaired in SSc lesional tissues, being inversely related to TGF- $\beta$  (3). We evaluated the serum levels of chemerin in a cohort including: i) 57 patients with systemic sclerosis (SSc) (4) (25 with diffuse cutaneous SSc [dcSSc] and 32 with limited cutaneous SSc [lcSSc] (5)), ii) 60 patients with Raynaud's phenomenon (RP, 29 with primary RP (pRP) and 31 with secondary RP (sRP) associated with undifferentiated connective tissue disease and iii) 21 healthy subjects (NHS) (Table I). At study inclusion, patients underwent: i) autoantibody profiling using the commercial "EUROLINE-SSc profile" kit (Euroimmun, Lubeck, Germany); ii) nailfold capillaroscopy; iii) echocardiography; iv) lung function tests and v) blood withdrawal. Chemerin levels were measured by Quantikine ELISA, R&D Systems, Minneapolis, MN, USA. Enrolled subjects had a BMI below 30 Kg/m<sup>2</sup> and an estimated GFR greater than 60 ml/min/1.73m<sup>2</sup>, since obesity and impaired renal function are associated with increased chemerin (2). Participants provided written informed consent; the study was approved by the local ethical committee.

dcSSc patients displayed significantly lower chemerin levels compared to NHS (median [interquartile range (IQR)] 87ng/mL [48] and 113ng/mL [44], respectively;  $p=0.049$ ), while subjects with lcSSc, pRP and sRP presented similar serum chemerin to controls (103ng/mL [35], 90ng/mL [52] and 92ng/mL [53], respectively). Chemerin levels were positively related with disease duration ( $p=0.024$ ,  $r=0.224$ ). Such correlation was particularly significant when considering patients with dcSSc ( $p=0.003$ ,  $r=0.553$ ). In this group, individuals with a disease duration below 36 months presented lower levels of serum chemerin compared to those with a dcSSc diagnosis longer than 36 months ( $p=0.004$ ). Chemerin levels were similar when patients were subgrouped upon autoantibody specificities (anti-centromere antibodies median 106.8ng/mL [40], anti-DNA topoisomerase I 85.75ng/mL [49], other specificities 98.3ng/mL [54];  $p=0.912$ ) and capillaroscopic patterns (normal capillaroscopic pattern 94.9ng/mL [54.22], scleroderma pattern early 93.5ng/mL [49.6], active

**Table I.** Demographic and clinical data of enrolled patients.

	dcSSc (N=25)	lcSSc (N=32)	pRP (N=29)	sRP (N=31)	NHS (N=21)
Age (years)	50 [19]	57.5 [18.5]	47 [17]	51 [16]	48 [15]
Females (%)	19 (76%)	26 (81.3%)	28 (96.5%)	29 (93.5%)	15 (71%)
Disease duration (months)*	48 [114]	32 [79]	24 [105]	72 [96]	/
Autoantibodies					
ACA	/	28 (87.5%)	/	2 (6.4%)	/
ATA	20 (80%)	/	/	2 (6.4%)	/
ARA	/	/	/	/	/
Anti-U <sub>3</sub> RNP	1 (4%)	/	/	1 (3.2%)	/
Anti-Th/To	/	3 (9.4%)	/	/	/
ILD <sup>g</sup>	18 (72%)	4 (12.5%)	/	/	/
PAH <sup>h</sup>	1 (4%)	3 (9%)	/	/	/
Joint involvement	6 (24%)	3 (9.3%)	/	6 (19.3%)	/
SRC <sup>i</sup>	1 (4%)	/	/	/	/
Muscle involvement <sup>k</sup>	/	2 (6.2%)	/	/	/
Severe GI involvement <sup>l</sup>	2 (6.8%)	2 (6.2%)	/	/	/
Heart involvement <sup>m</sup>	6 (24%)	3 (9.3%)	/	/	/
Digital ulcers	17 (68%)	13 (40.6%)	/	/	/
Capillaroscopic pattern <sup>o</sup>					
Normal Scleroderma pattern	/	3 (9.3%)	29 (100%)	26 (84%)	/
Early	4 (16%)	8 (25%)	/	5 (16%)	/
Active	9 (36%)	10 (31.3%)	/	/	/
Late	12 (48%)	11 (34.4%)	/	/	/

Continuous variables are expressed as median [interquartile range].

\* from the onset of the first non-Raynaud's phenomenon symptom to study inclusion.

<sup>g</sup> forced vital capacity (FVC) or carbon monoxide diffusing capacity of the lung (DL<sub>CO</sub>) <55% of predicted or a 15% decline from baseline in FVC or DL<sub>CO</sub>, with evidence of fibrosis on high-resolution CT.

<sup>h</sup> mean pulmonary arterial pressure >25 mmHg at right heart catheterisation.

<sup>i</sup> new-onset systemic hypertension >150/85 mmHg with a decrease in estimated glomerular filtration rate >30%.

<sup>k</sup> objective muscle weakness (score <4 on a 5-point Likert scale) and an elevated total creatine kinase level (>4-fold the upper limit of normal).

<sup>l</sup> at least 3 episodes of intestinal pseudoobstruction requiring hospitalisation or requiring >6 weeks of enteral or parental nutritional support.

<sup>m</sup> haemodynamically significant arrhythmias, pericardial effusion or congestive heart failure.

<sup>o</sup> according to (10).

dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; pRP: primary Raynaud's phenomenon; sRP: secondary Raynaud's phenomenon; NHS: normal healthy subjects; N: number; ACA: antibodies against centromeric proteins; ATA: antibodies against DNA topoisomerase I; ARA: antibodies against RNA polymerase III; anti-U<sub>3</sub>RNP: antibodies against U<sub>3</sub>RNP; anti-Th/To: antibodies against Th/To; ILD: interstitial lung disease; SRC: scleroderma renal crisis; GI: gastrointestinal.

94.4ng/mL [41.2], late 107.8ng/mL [42.3];  $p=0.421$ ). Similarly, no significant difference emerged when chemerin levels were compared between patients with and those without interstitial lung disease (102.6ng/mL [46.95] and 95.2ng/mL [40.7], respectively;  $p=0.572$ ), heart involvement (113ng/mL [45] and 95ng/mL [44.55], respectively;  $p=0.211$ ), joint involvement (93ng/mL [33.87] and 96.7ng/mL [49.17], respectively;  $p=0.104$ ) and digital ulcers (88ng/ml [40.4] and 97ng/mL [46.5], respectively;  $p=0.131$ ).

These data suggest that SSc patients with diffuse disease display lower serum chemerin compared to NHS. In particular, chemerin is reduced in the early phase, when cutaneous disease is most active and fibrotic changes are rapidly progressive, with serum levels increasing over time, once the disease activity is stable (6). This observation fits well with the single previous study investigating

chemerin in SSc: in a cohort of 64 scleroderma patients, chemerin correlated with disease duration (2). The potential implication of chemerin in the first phase of SSc might reflect the bridge between metabolism and fibrogenesis: the loss of intradermal adipose tissue occurs very early, with adipocyte progenitors directly contributing to myofibroblast accumulation in fibrotic tissues (7). Consistently, PPAR- $\gamma$ , a master regulator of adipogenesis and the main modulator of chemerin expression, is increasingly acknowledged to be involved in SSc aetiopathogenesis, as suggested by consistent genetic, *in vitro* and *in vivo* data (3, 8).

Despite the many efforts promoted by the scientific community, SSc—in particular the early diffuse subset—is still an incurable disease (9). The identification of a biomarker to early identify patients with dcSSc would be valuable: chemerin might be a candidate fibrosis surrogate in SSc.

# Letters to the Editors

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