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SHORT REPORT

Sex differences in cytokines and adipokines in obese patients with PsA and controls undergoing a weight loss intervention

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ABSTRACT

Objective In this post hoc analysis of a previously published study, we compared cytokines and adipokine levels in women and men with psoriatic arthritis (PsA) at baseline (BL) and 6 months (M6) following a weight loss intervention.

Methods Patients with PsA (n=41) between 25 and 75 years of age, with body mass index (BMI)≥33 kg/m^2 were included in a weight loss intervention with a very low energy diet (VLED) for 12 or 16 weeks depending on BL BMI<40 or ≥40 kg/m^2. As controls (n=39), obese individuals, already planned for VLED treatment were recruited and matched for sex, age and weight to the patients with PsA. Cytokines and adipokines were measured at BL and M6.

Results At BL, serum levels of interleukin (IL)-23, leptin and high molecular weight-adiponectin were higher in women with PsA compared with men, whereas serum levels of interferon (IFN)-γ, IL-12/IL-23 p40 and IL-13 were significantly lower in women. Serum IL-23 was significantly reduced at M6 compared with BL in women but not in men with PsA. In women with PsA, the reduction in IL-23 at M6, ΔIL-23, were positively correlated with ΔDisease Activity Score 28 C reactive protein (CRP) (Spearman's correlation (r_S)=0.486, p=0.016), ΔCRP (r_S=0.468, p=0.021), Δleptin (r_S=0.683, p<0.001) and negatively correlated with Δtotal-adiponectin (r_S=−0.433, p=0.035). Also in women, ΔDisease Activity in Psoriatic Arthritis was positively correlated with Δtumour necrosis factor-α (r_S=0.417, p=0.034), ΔIL-1β (r_S=0.550, p=0.034), ΔIFN-γ (r_S=0.414, p=0.035) and Δleptin (r_S=0.410, p=0.038). None of these correlations were significant in men with PsA.

Conclusions Women and men with PsA differed with regard to serum levels of cytokines and adipokines before and after weight loss.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Obesity is over-represented in psoriatic arthritis (PsA), weight loss is associated with improved disease activity, improved response to treatment and reduced levels of proinflammatory cytokines and adipokines.
⇒ Women with PsA frequently report worse pain, fatigue and poorer response to treatment.
⇒ Previous studies have found sex differences in cytokines and adipokines, however, no study has assessed sex differences in cytokines and adipokines in PsA.

WHAT THIS STUDY ADDS

⇒ In this study, we found significantly reduced serum interleukin (IL)-23 levels in women, but not in men with PsA after a weight loss intervention.
⇒ Reductions in IL-23, ΔIL-23, were positively correlated with ΔDisease Activity Score 28 C reactive protein (CRP), ΔCRP, Δleptin and negatively correlated with Δtotal-adiponectin, in women but not in men.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study identifies differences in cytokine and adipokine levels in women and men with PsA, that may have an impact on sex differences regarding patient-reported outcome measures and treatment response.

INTRODUCTION

Obesity is associated with increased levels of several proinflammatory cytokines and adipokines, including tumour necrosis factor (TNF)-α, interleukin (IL)−1, IL-6, IL-17, IL-23, C reactive protein (CRP) and leptin.[1 2] Weight loss in obese individuals often results in lowered levels of proinflammatory cytokines, CRP and adipokines.[3] Obesity is a known risk factor for developing psoriatic arthritis (PsA).[4] Obesity in PsA is associated with higher disease activity and reduced response to treatment,[5] whereas weight loss has been shown to improve disease activity in obese patients with PsA.[6] PsA has a similar

Table 1 Cytokines and adipokines in women and men with psoriatic arthritis at baseline and at 6 months (M6) of follow-up

Analytes	BL, women, n=26	BL, men, n=15	P value women vs men at BL	M6, women, n=26	P value women only BL vs M6	M6, men, n=15	P value men only BL vs M6
TNF-α, pg/mL	11.70 (9.28–16.19)	15.64 (11.66–19.32)	0.114	10.91 (8.15–13.81)	0.166	13.55 (10.91–19.85)	0.955
IL-1β, pg/mL*	10.97 (6.73–16.01)	19.69 (4.31–22.98)	0.097	9.39 (4.59–13.73)	0.331	18.37 (7.13–22.91)	0.594
IL-6, pg/mL	7.46 (5.65–10.45)	9.88 (6.74–15.80)	0.096	7.05 (5.44–8.96)	0.353	9.10 (4.72–20.07)	1.000
IL-8, pg/mL	17.14 (13.76–22.70)	19.28 (12.38–23.41)	0.862	18.23 (13.56–24.69)	0.620	16.79 (11.65–20.42)	0.256
IL-12/IL-23 p40, pg/mL†	505.38 (316.66–747.47)	905.88 (471.22–1301.95)	0.009	466.00 (280.46–778.67)	0.588	879.36 (615.56–1443.48)	0.239
IL-13, pg/mL‡	777.97 (631.20–995.22)	995.22 (813.93–1331.42)	0.030	736.54 (550.28–951.51)	0.484	951.43 (813.93–1234.44)	0.814
IL-17, pg/mL§	2.43 (0.41–4.96)	4.48 (2.58–4.65)	0.143	2.43 (0.41–4.48)	0.279	2.43 (0.41–5.13)	0.225
IL-23, ng/mL¶	0.50 (0.38–0.61)	0.15 (0.10–0.30)	<0.001	0.19 (0.12–0.32)	<0.001	0.16 (0.03–0.25)	0.213
IFN-γ, pg/mL	54.23 (40.38–65.87)	73.15 (61.98–92.19)	0.002	50.77 (39.30–62.49)	0.290	72.75 (51.08–98.47)	0.456
Resistin, ng/mL	12.51 (10.31–15.01)	13.72 (11.56–15.88)	0.495	11.75 (10.10–14.15)	0.367	13.29 (8.83–15.95)	0.570
Leptin, ng/mL**	39.35 (24.19–59.30)	14.33 (8.56–18.25)	<0.001	12.56 (7.25–22.75)	<0.001	5.56 (3.79–11.22)	<0.001
HMW adiponectin, µg/mL	4.30 (2.90–6.69)	2.87 (1.04–3.39)	0.004	6.76 (3.94–11.97)	<0.001	5.16 (2.47–7.63)	<0.001
Tot-adiponectin, µg/mL	4.71 (3.28–6.29)	3.94 (2.40–4.56)	0.076	6.54 (4.05–8.53)	<0.001	5.22 (3.47–6.81)	0.003
VAS patients' global disease activity, mm	53 (28–70)	30 (4–38)	0.002	23 (10–60)	0.007	10 (3–22)	0.090
VAS pain, mm	59 (24–71)	22 (7–30)	<0.001	29 (14–66)	0.011	8 (2–23)	0.149
VAS fatigue, mm	62 (48–72)	22 (7–58)	0.004	31 (10–56)	0.003	19 (3–40)	0.182
HAQ, score	0.75 (0.50–1.16)	0.13 (0.00–0.50)	0.001	0.38 (0.25–0.88)	0.004	0.00 (0.00–0.25)	0.017
DAS28CRP, score	3.4 (2.9–4.3)	2.1 (1.8–2.9)	<0.001	2.7 (1.9–3.5)	<0.001	2.0 (1.3–2.5)	0.140
DAPSA, score	19.9 (9.1–32.9)	6.7 (3.1–16.2)	0.003	10.9 (6.7–20.2)	<0.001	2.5 (1.6–9.7)	0.038
BMI, kg/m^2	37.0 (35.0–40.1)	34.4 (33.2–35.0)	<0.001	30.7 (27.3–32.0)	<0.001	28.1 (24.3–30.0)	<0.001
CRP, mg/L	5.0 (3.0–9.5)	3.0 (1.0–8.0)	0.097	4.0 (2.0–7.5)	0.048	2.0 (1.0–6.0)	0.446

Values are median (IQR).
P value for comparison between BL and M6 are based on cytokine levels above detection level, present in.
*18 women and 13 men.
†21 women and 14 men.
‡25 women and 15 men.
§10 women and 10 men.
¶24 women and 11 men.
**26 women and 14 men.
BL, baseline; BMI, body mass index; CRP, C reactive protein; DAPSA, Disease Activity in Psoriatic Arthritis; DAS28CRP, Disease Activity Score; HAQ, Health Assessment Questionnaire; HMW, high molecular weight; IFN, interferon; IL, interleukin; M6, month 6 after baseline; TNF, tumour necrosis factor; Tot, total; VAS, Visual Analogue Scale.

Table 2 Cytokines and adipokines in controls, stratified by sex, at baseline and at 6 months of follow-up

Analytes	BL, women, n=28	BL, men, n=11	P value women vs men at BL	M6, women, n=28	P value women only BL vs M6	M6, men, n=11	P value men only BL vs M6
TNF-α, pg/mL	10.66 (7.36–12.99)	13.54 (11.66–16.17)	0.009	9.13 (7.09–11.18)	0.015	13.01 (9.60–14.48)	0.130
IL-1β, pg/mL*	9.88 (5.30–13.85)	14.28 (4.80–19.35)	0.313	8.35 (5.16–14.28)	0.158	9.90 (5.30–14.28)	0.091
IL-6, pg/mL†	7.23 (5.54–8.72)	7.98 (6.74–11.70)	0.091	5.74 (4.65–8.12)	0.008	7.83 (7.36–8.44)	0.202
IL-8, pg/mL‡	18.52 (12.51–27.26)	20.04 (15.82–27.32)	0.310	13.46 (11.51–19.03)	0.070	18.36 (16.60–28.71)	0.790
IL-12/IL-23 p40, pg/mL§	434.64 (299.93–602.65)	729.51 (570.13–1039.57)	0.018	299.93 (185.07–606.95)	0.035	729.91 (466.00–982.41)	0.674
IL-13, pg/mL¶	828.95 (650.51–1000.24)	966.28 (885.07–1132.26)	0.103	617.56 (551.40–966.28)	0.031	1023.60 (813.93–1132.26)	0.767
IL-17, pg/mL**	0.41 (0.41–2.94)	2.43 (0.41–3.90)	0.352	1.42 (0.41–2.63)	0.655	0.41 (0.41–2.63)	0.180
IL-23, ng/mL††	0.59 (0.41–0.82)	0.26 (0.17–0.54)	0.004	0.24 (0.11–0.45)	<0.001	0.21 (0.12–0.27)	0.011
IFN-γ, pg/mL	50.77 (42.34–58.02)	63.50 (58.36–76.35)	0.005	43.73 (36.50–60.26)	0.031	58.36 (54.73–69.95)	0.086
Resistin, ng/mL	12.75 (10.54–16.83)	9.35 (7.48–13.44)	0.142	12.80 (9.54–15.21)	0.425	11.15 (8.43–13.04)	0.424
Leptin, ng/mL‡‡	49.31 (31.57–68.47)	17.76 (12.56–32.83)	0.002	14.11 (9.76–32.39)	<0.001	13.40 (9.10–16.21)	0.007
HMW adiponectin, µg/mL	4.31 (2.14–7.86)	3.19 (1.63–5.85)	0.261	5.86 (4.57–8.75)	<0.001	5.78 (3.46–6.80)	0.003
Tot-adiponectin, µg/mL	4.37 (3.56–5.97)	3.70 (2.56–4.16)	0.119	5.80 (4.31–7.33)	<0.001	4.99 (3.88–6.01)	0.004
BMI, kg/m^2	37.16 (36.25–39.25)	41.52 (37.73–42.92)	0.002	29.19 (27.55–31.63)	<0.001	34.66 (31.25–37.66)	0.003
CRP, mg/L	4.0 (2.0–6.0)	4.0 (2.0–8.0)	0.706	2.0 (1.0–3.8)	<0.001	2.0 (1.0–4.0)	0.108

Values are median (IQR).
P value for comparison between BL and M6 are based on cytokine levels above detection level, present in.
*17 women and 10 men.
†28 women and 10 men.
‡27 women and 11 men.
§20 women and 9 men.
¶26 women and 11 men.
**14 women and 5 men.
††28 women and 10 men.
‡‡ 28 women and 10 men.
BL, baseline; BMI, body mass index; CRP, C reactive protein; HMW, high molecular weight; IFN, interferon; IL, interleukin; M6, month 6 after baseline; TNF, tumour necrosis factor; Tot, total.

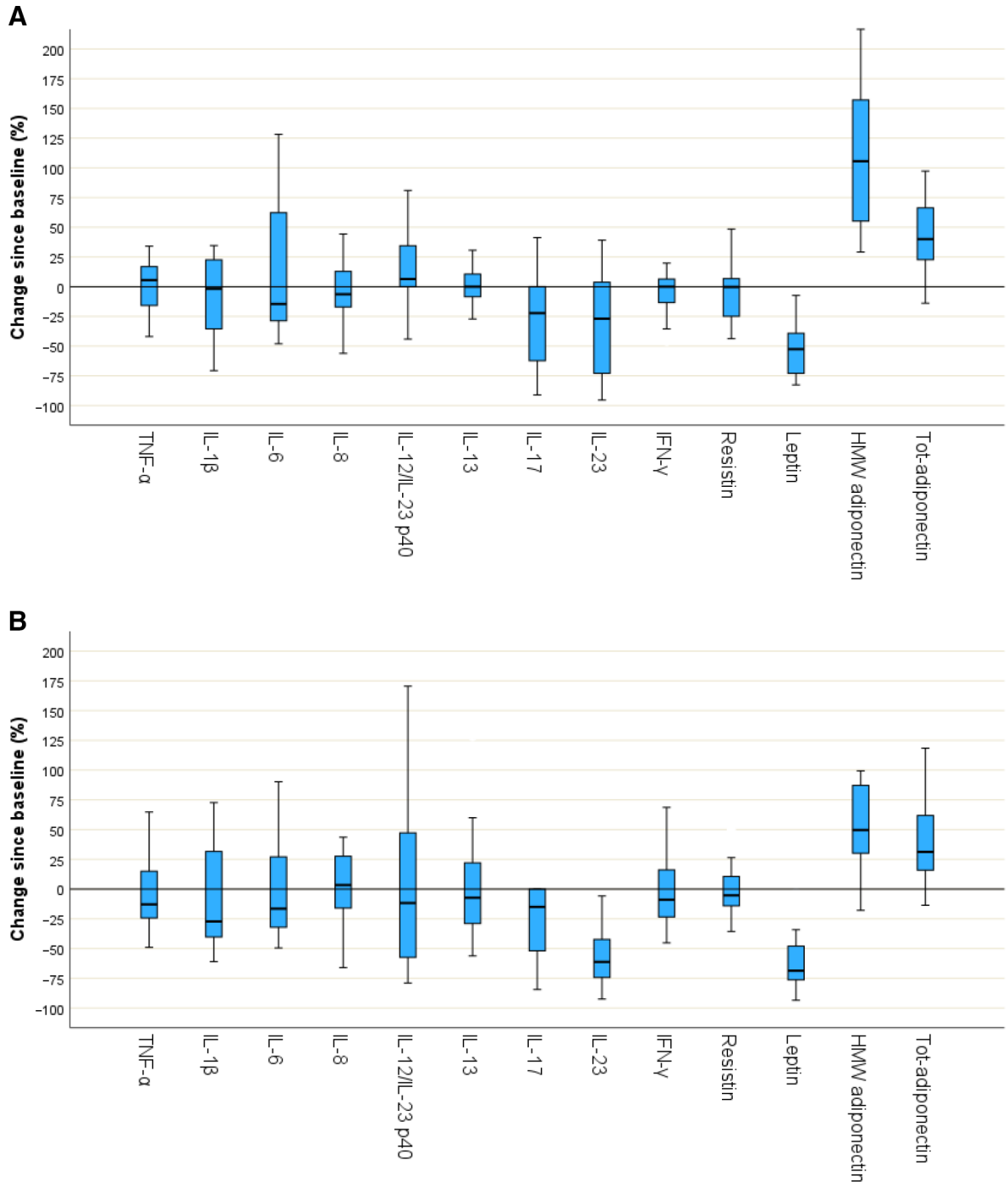

Figure 1 Boxplots for cytokines and adipokines, showing the distribution of change (median and IQR) in %, comparing BL and M6. **(A)** Baseline (BL) to month 6 (M6) change (%) in women with psoriatic arthritis (PsA), n=26; number of patients with missing data values (cytokine or adipokine levels below detection limit); IL- 1β, n=11; IL- 12/IL- 23 p40, n=5; IL- 13, n=1; IL- 17, n=18; IL- 23, n=2. **(B)** BL to M6 change (%) in men with PsA, n=15; number of patients with missing data values (cytokine or adipokine levels below detection limit); IL- 1β, n=3; IL- 12/IL- 23 p40, n=1; IL-17, n=8; IL- 23, n=4; leptin, n=1. HMW, high molecular weight; IFN, interferon; IL, interleukin; TNF tumour necrosis factor; Tot total.

sex distribution between women and men, although important sex differences relating to disease characteristics, pain, fatigue and response to treatment[7 8] have been reported. Others have reported sex differences in proinflammatory cytokines,[9 10] although not assessing patients with PsA. To our knowledge no previous study has investigated sex differences in cytokine levels in PsA.

We have previously reported on the effects of weight loss by a very low energy diet (VLED) on cytokine levels in obese patients with PsA and matched controls that underwent a weight loss intervention.[11] Here we report on sex differences in cytokine levels at baseline (BL) and at 6 months (M6) from the same study, in which 41 patients with PsA (26 women and 15 men) and 39 controls (28

women and 11 men), matched by sex, age and weight, were followed-up to M6.

METHODS

The 12-month weight loss intervention and study design have been described in detail previously.[6 11] Patients with PsA between 25 and 75 years of age, with body mass index (BMI)≥33 kg/m^2 and meeting the ClASsification criteria for Psoriatic ARthritis criteria[12] were eligible. Exclusion criteria for both patients and controls were epilepsy, pregnancy, porphyria, type 1 diabetes, severe kidney, heart or catabolic disease, binge eating disorder, current treatment with lithium, phenytoin or warfarin, having mental imbalance affecting participation or a history of stroke, myocardial infarction, major surgery or trauma during the last 3 months or cancer treatment during the last 5 years. Treatment with conventional synthetical or biological disease-modifying anti-rheumatic drugs was held unchanged from 3 months before BL until M6. Patients with PsA and controls were given VLED (640 kcal/day) for 12 or 16 weeks, depending on BL BMI<40 or ≥40 kg/m^2. Food was gradually reintroduced thereafter and every patient was given an individual diet advise and followed during 12 months at the obesity department. As controls, obese individuals, already planned for VLED treatment were recruited from the Regional Obesity Centre at Sahlgrenska University Hospital and matched for sex, age and weight to the patients with PsA. In addition to the exclusion criteria for patients with PsA, controls with a diagnosis of psoriasis, PsA or any inflammatory rheumatic disease were not eligible for the study. Serum levels of cytokines and adipokines were analysed at BL and M6 using Human Magnetic Luminex Assays (R&D Systems). The analysis and quantification were performed using a Bio-Plex 200 system (Bio-Rad) with five-parameter logistic standard curves. Samples with analyte levels below the detection level were excluded from the analysis.

Statistical analyses

Descriptive statistics are presented as numbers (%), median and IQR.

The Mann-Whitney U test was used for comparisons of continuous variables between groups. The χ^2 test was used for categorical variables. Wilcoxon signed-rank test was used to compare continuous-related samples. Correlations were calculated using Spearman's correlation (r_S). Two-tailed tests were used and p≤0.05 was considered statistically significant. Statistical analyses were made using SPSS Statistics V.29 (IBM, Chicago, USA).

RESULTS

At BL, women versus men with PsA had higher BMI, Disease Activity in Psoriatic Arthritis (DAPSA) score, Disease Activity Score 28 joints using CRP (DAS28-CRP), Health Assessment Questionnaire (HAQ) scores and also higher Visual Analogue Scales for patient's global disease activity, pain and fatigue. Serum IL-23, leptin and high molecular weight (HMW)-adiponectin were also higher in women with PsA, whereas serum levels of interferon (IFN)-γ, IL-12/IL-23 p40 and IL-13 were significantly lower in women compared with men table 1. In controls, serum levels of IL-23 and leptin were also higher in women, whereas BMI, TNF-α, IL-12/IL-23 p40 and IFN-γ were lower in women than in men (table 2).

Serum IL-23 was significantly reduced at M6 compared with BL in women but not in men with PsA (table 1). In female controls, significant reductions in TNF-α, IL-6, IL-12/IL-23 p40, IL-13, IL-23, IFN-γ, leptin and significant increases in HMW-adiponectin and total-adiponectin at M6 compared with BL were observed (table 2). In male controls, IL-23 and leptin were significantly reduced whereas HMW-adiponectin and total-adiponectin were significantly increased at M6 compared with BL. Changes in cytokines and adipokines comparing BL and M6 in women and men with PsA are further displayed in figure 1. In women with PsA, the reduction in IL-23 at M6, ΔIL-23, was positively correlated with ΔDAS28CRP (r_S=0.486, p=0.016), ΔCRP (r_S=0.468, p=0.021), Δleptin (r_S=0.683, p<0.001) and negatively correlated with Δtotal-adiponectin (r_S=−0.433, p=0.035). In addition, in women, ΔDAPSA was positively correlated with ΔTNF-α (r_S=0.417, p=0.034), ΔIL-1β (r_S=0.550, p=0.034), ΔIFN-γ (r_S=0.414, p=0.035) and Δleptin (r_S=0.410, p=0.038). In men with PsA, these correlations were weaker and non-significant.

DISCUSSION

Sex differences in serum cytokines levels in patients with PsA have not previously been studied. However, previous studies have reported higher levels of leptin and adiponectin in healthy women compared with men,[10] but higher levels of IL-1β, IL-6 and TNF-α in healthy men compared with healthy women.[9] The worse HAQ, pain and fatigue scores in women with PsA in the current study are consistent with a recent review by Coates *et al*.[8] Although hampered by a small sample size, multiple testing and fewer men, as well as differences in BMI between women and men, the results from the current study suggest that there are sex differences in cytokine levels in patients with PsA and obesity. This should be further explored in a larger study. These sex differences may play a role in the sex-specific differences in patient-reported outcomes and in treatment response.

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Contributors AJL participated in interpretation of data and was responsible for statistical analyses and drafting of the article. CAJ was responsible for the serum analyses of cytokines and adipokines and participated in interpretation of the data and drafting of the article. AB participated in the study design, recruitment and examination of patients, collection, analysis and interpretation of data. BE participated in the study design, recruitment and examination of patients, collection and interpretation of data and was responsible for the weight loss treatment and follow-up. LT participated in interpretation of data and drafting of the article. MD participated in interpretation of data and drafting of the article. LJ participated in interpretation of data and drafting of the article. IG participated in the study design, in interpretation of data and drafting of the article. IL participated in the study design, recruitment and examination of patients, collection and interpretation of data and was responsible for the weight loss treatment and follow-up. EK was responsible for the study design, recruitment of patients, rheumatological evaluations, data collection, interpretation of data and participated in drafting of the article. All authors have critically reviewed the manuscript, approved the final version to be published and agreed to be accountable for all aspects of the work.

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Competing interests None declared.

Patient consent for publication Not applicable.

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