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ORIGINAL ARTICLE

Pro-inflammatory adipokine profile in psoriatic arthritis: results from a cross-sectional study comparing PsA subset with evident cutaneous involvement and subset "sine psoriasis"

Francesco Caso[1] · Loredana Postiglione[2] · Bianca Covelli[2] · Margherita Ricciardone[2] · Gaetano Di Spigna[2] · Pietro Formisano[2] · Vittoria D'Esposito[2] · Nicolò Girolimetto[1] · Marco Tasso[1] · Rosario Peluso[1] · Luca Navarini[3] · Massimo Ciccozzi[4] · Domenico Paolo Emanuele Margiotta[3] · Francesca Oliviero[5] · Antonella Afeltra[3] · Leonardo Punzi[5,6] · Antonio Del Puente[1] · Raffaele Scarpa[1] · Luisa Costa[1]

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Abstract

Objective Adipokines have been considered in the pathogenesis of the inflammatory processes of psoriatic arthritis (PsA). The main aim of the current study is to investigate possible differences and correlations between adipokines and clinical expression in PsA patients with and without clinical evident psoriasis.

Methods Serum levels of TNF-α, IL-6, leptin, resistin, visfatin, and ghrelin were measured in 80 consecutive PsA patients, 42 PsA patients with clinically evident psoriasis (group 1) and 38 PsA patients sine psoriasis (group 2), fulfilling the CASPAR criteria.

Results Patients of the two groups were not significantly different for levels of TNF-α, IL-6, leptin, resistin, visfatin, and ghrelin. In the entire cohort, a positive association has been shown between leptin levels and female gender ($\beta = 0.3$, $p = 0.001$), BMI ($\beta = 0.8$, $p < 0.0001$), tender joint count ($\beta = 0.23$, $p = 0.05$), and patient pain-VAS score ($\beta = 0.4$, $p = 0.049$). In group 1, serum concentration of leptin was associated with female gender ($\beta = 0.41$, $p < 0.0001$) and BMI ($\beta = 0.6$, $p = 0.012$), whereas in group 2, a positive association was shown between leptin levels and BMI ($\beta = 0.7$, $p = 0.003$) and CRP ($\beta = 0.35$, $p = 0.012$). With regard to resistin, in the multivariate model, only the association between resistin and IL-6 was found ($\beta = 0.33$, $p = 0.002$). The association between resistin and IL-6 was confirmed in group 1 ($\beta = 0.46$, $p = 0.004$) but not in group 2.

Conclusions Until today, the present study represents the first investigating difference in the adipokine pattern between PsA patients with psoriasis and sine psoriasis. We report a strict interplay between leptin, female gender, BMI, and inflammatory activity in overall PsA patients. In PsA patients with clinical evident psoriasis, leptin was associated with female gender and BMI, and a close association between resistin and IL-6 was found. Further, a positive association between leptin levels and BMI and CRP was found in PsA sine psoriasis patients. Further studies are also advocated for clarifying the possible role of these adipokines as laboratory findings or as disease mediators in addressing the different phenotypes of the disease.

Key Points

•Levels of TNF-α, IL-6, leptin, resistin, visfatin, and ghrelin did not differ between PsA patients with clinical evident psoriasis and PsA sine psoriasis.
•There is a strict interplay between leptin, female gender, BMI, and inflammatory activity in PsA.
•There is a close association between resistin and IL-6 in PsA patients with clinical evident psoriasis.

Keywords Adipokine · Body mass index · Leptin · PsA sine psoriasis · Psoriatic arthritis

✉ Francesco Caso
francescocaso1@yahoo.it; francesco.caso@unina.it

[1] Rheumatology Unit, Department of Clinical Medicine and Surgery, School of Medicine, University Federico II of Naples, Via S. Pansini 5, 80131 Naples, Italy

[2] Translational Medical Sciences Department, School of Medicine, University Federico II of Naples, Naples, Italy

[3] Unit of Allergology, Clinical Immunology and Rheumatology, Università Campus Bio-Medico di Roma, Rome, Italy

[4] Unit of Clinical Laboratory Science, Università Campus Bio-Medico di Roma, Rome, Italy

[5] Department of Clinical Medicine DIMED, University of Padova, Padua, Italy

[6] Centre for Gout and Metabolic Bone and Joint Diseases, Rheumatology, SS Giovanni and Paolo Hospital, Venice, Italy

Introduction

Psoriatic arthritis (PsA) is an inflammatory spondyloarthropathy associated with psoriasis [1, 2]. In addition to the phenotype with clinically evident psoriasis, the disease can also appear in patients who have never had psoriasis but with a positive history of psoriasis in a first- or second-degree relative [3–6].

PsA represents a systemic condition, and metabolic syndrome (MetS) has been reported as a related possible aspect of the heterogeneous phenotypical spectrum [7–12]. In the development of MetS, an important role is played by the chronic low-grade inflammatory state and by the white adipose tissue (WAT) [13–16]. WAT represents a tissue devoted to energy storage and a multifunctional endocrine organ able to secrete several pro- and anti-inflammatory molecules called adipokines, therefore regulating and linking inflammation and metabolic state [15, 16]. PsA has been associated with a high prevalence of MetS and its components [17, 18].

Adipokines, synthetized by WAT and at the same time acting on it, have been considered also in the pathogenesis of the inflammatory processes of PsA [19–28].

Tumor necrosis factor alpha (TNF-α), a Th1-associated and Th17-associated molecule, represents a pro-inflammatory cytokine mainly produced by monocytes and macrophages with a central role in PsA pathogenesis [19]. On the metabolic side, TNF-α is able to induce adipocyte apoptosis, promote insulin resistance, increase plasma triglycerides, and stimulate lipolysis [20–22]. Interleukin-6 (IL-6) promotes the hepatic production of many acute phase reactants, and it is able to induce hepatic insulin resistance [21–25].

Leptin is synthesized by adipose tissue and plays an important role in body energy balance and adipose tissue deposition, and its plasma levels positively correlate with body fat mass [26–28]. In PsA, leptin levels have been found higher in women with PsA compared with those with psoriasis, and they positively correlate with homeostasis model assessment of insulin resistance (Homa-IR) and BMI [29]. Leptin levels have been found higher in PsA patients compared with non-PsA control individuals [30]. Leptin concentrations have been found higher in patients with psoriasis compared with controls [31]. High levels of leptin have been found in patients with psoriasis and with MetS [32].

Resistin is another adipocyte-specific pro-inflammatory polypeptide synthesized mostly by macrophages and monocytes from fat tissue, and it is able to induce insulin resistance [33, 34]. Resistin concentrations have been found higher in patients with PsA and psoriasis compared with controls [31, 32, 35, 36].

Visfatin mediates a complex cellular signalling process stimulated by oxidative stress resulting in vascular endothelial inflammation [37]. High levels of visfatin have been found in patients with PsA [35].

Ghrelin is a peptide secreted mainly by the gastric mucosa, able to stimulate appetite, with anti-inflammatory effects [38–40]. A strong negative correlation has been reported between the Psoriasis Area and Severity Index (PASI) and serum ghrelin levels [41, 42].

In a previous study [43], we have investigated differences in clinical expression between PsA with clinical evident psoriasis and PsA sine psoriasis. Main results showed a significantly higher prevalence of MetS in PsA patients with clinical evident psoriasis. In addition, BMI resulted as an important determinant in the development of MetS in these patients [43]. We also performed cytokine pattern analysis in these PsA subjects, and data are now available. The main aim of the current study is to investigate possible differences and correlations between adipokines and clinical expression in PsA patients with and without clinical evident psoriasis.

Patients and methods

Clinical characteristics of this cohort have been previously described [43]. Briefly, eighty consecutive PsA patients fulfilling the CASPAR criteria attending the Psoriatic Arthritis Clinic at the University Federico II of Naples were enrolled in the study. Forty-two patients (52.5%) were classified as having PsA with clinically evident psoriasis (group 1) (male, 19 (45.24%); mean age 49.62 ± 12.43 years) and 38 (47.5%) as having PsA sine psoriasis (absence of psoriasis and a positive family history for psoriasis) (group 2) (male, 5 (13.16%); mean age 50.66 ± 9.32 years) [43].

Inclusion criteria were both sexes, age ≥ 18 years, and stable medical conditions. Exclusion criteria were concomitant rheumatic diseases other than PsA, endocrinopathies, renal and liver diseases, alcohol consumption, continuous use of nonsteroidal anti-inflammatory drugs (NSAIDs) and/or steroids, use of biologic DMARDs (bDMARDs), use of two or more csDMARDs, and use of progestins and drugs that may cause dyslipidemia.

As reported in the previous work [43], no significant differences were found for tender joint count (TJC; 68 joints), swollen joint count (SJC; 66 joints), tender entheseal count (TEC), Health Assessment Questionnaire (HAQ) score, patient pain on visual analogue scale score (pt pain-VAS score), and patient global disease activity (PGA) VAS score.

An increased frequency of female gender was found in patients with psoriasis (45.24%) as compared with patients with sine psoriasis (13.16%), as well an increased frequency of MetS, identified by the use of the NCEP-ACT III criteria [14], in group 1 (40.5%) when compared with group 2 (13.2%) [43].

Serum levels of TNF-α, IL-6, leptin, resistin, visfatin, and ghrelin were measured using the fully automated enzyme-linked immunosorbent assay (ELISA) analyzer Triturus

system (GRIFOLS Italy) and R&D Systems Quantikine ELISA Kits. Blood samples were collected after 12 h of overnight fasting and analyzed for these adipokines.

The study was approved by the Local Ethics Committee (CE: NA 126/15), and all patients gave their informed consent.

Statistical analysis

Continuous data were described by median (25th–75th Pctl) and categorical variables as frequencies and percentages. The Shapiro–Wilk test has been used to check normality for each variable. Comparisons between the two categories were made using *t* tests or Mann–Whitney *U* tests for continuous variables, as appropriated, and Fisher's exact test for categorical variables. Linear regression, using standardized coefficients, has been used to assess the relationship between adipokine serum levels and demographic, clinical, and laboratory parameters. Variables associated with adipokine serum levels with $p < 0.1$ were used in the multivariate analysis. For all the analysis, STATA v.14 has been used.

Results

As reported in the "Patients and methods" section, MetS was more frequent in patients with psoriasis compared with patients without psoriasis. Intriguingly, between groups 1 and 2, results did not show significant differences regarding waist circumference (group 1, 100 (90–107) cm; group 2, 95.5 (85–110) cm; $p = 0.45$), fasting glucose (group 1, 90 (85–97) mg/dl; group 2, 87.5 (80–95) mg/dl; $p = 0.18$), HLD cholesterol (group 1, 49 (42–60) mg/dl; group 2, 52 (45–64) mg/dl; $p = 0.25$), triglycerides (group 1, 113.5 (88–146) mg/dl; group 2, 105.5 (84–140) mg/dl; $p = 0.51$), and systolic blood pressure (group 1, 127.5 (120–145) mmHg; group 2, 120 (120–130) mmHg; $p = 0.076$), while in group 1, higher levels of diastolic blood pressure (80 (80–90) mmHg) were found when compared with group 2 (80 (70–80) mmHg, $p = 0.01$).

Median values of adipokines of the entire cohort are summarized in Table 1.

Patients of the two groups were not significantly different for levels of TNF-α, IL-6, leptin, resistin, visfatin, and ghrelin (Table 1).

We then analyzed data using multiple linear regression. In the entire cohort, a positive association has been shown between leptin levels and female gender ($\beta = 0.3$, $p = 0.001$), BMI ($\beta = 0.8$, $p < 0.0001$), TJC ($\beta = 0.23$, $p = 0.05$), and pt pain-VAS score ($\beta = 0.4$, $p = 0.049$). In group 1, serum concentration of leptin was associated with female gender ($\beta = 0.41$, $p < 0.0001$) and BMI ($\beta = 0.6$, $p = 0.012$), whereas in group 2, a positive association was shown between leptin levels and BMI ($\beta = 0.7$, $p = 0.003$) and CRP ($\beta = 0.35$, $p = 0.012$) (Table 2).

With regard to resistin, in the multivariate model, only the association between resistin and IL-6 was found in the overall cohort ($\beta = 0.33$, $p = 0.002$). The association between resistin and IL-6 was confirmed in group 1 ($\beta = 0.46$, $p = 0.004$) but not in group 2.

For ghrelin and visfatin, no association was found in the multivariate model. When using the univariate analysis, the only variable associated with ghrelin serum levels was BMI ($\beta = 0.3$, $p = 0.007$) and no variable was significantly associated with visfatin.

Discussion

Different studies have investigated the role of adipokines in PsA [29–32, 35, 36]. Until today, the present study represents the first to investigate the difference in the cytokine pattern between PsA patients with psoriasis and sine psoriasis.

In the present study, we found that PsA patients with psoriasis and sine psoriasis are not significantly different for mean levels of TNF-α, IL-6, leptin, resistin, visfatin, and ghrelin.

With regard to leptin, in the entire PsA cohort, results from multiple linear regression showed a positive association between its levels and female gender, BMI, TJC, and pt pain-VAS score. In patients with psoriasis, serum concentrations of leptin were associated with female gender and BMI. Among patients without psoriasis, we found a positive association between leptin levels, BMI, and CRP.

Leptin is a pleiotropic cytokine able to sustain inflammatory responses, by stimulating several cellular activities [26–28, 44, 45]. Moreover, evidences are increasing on a possible role of leptin as a modulator of pain [46–48] and its possible role in influencing disease activity in inflammatory arthropathies [49–51]. In particular, in a recent Mexican study, in RA, circulating leptin correlated with clinical activity in a manner independent of the patient's BMI [51].

Actually, in the overall cohort, serum leptin levels were correlated with pain aspects, as represented by TJC and patient pain-VAS score, which are frequently considered markers of inflammation [52]. In patients without psoriasis, we found that leptin levels were also correlated with the inflammatory marker, CRP. Correlation of leptin with CRP could be explained at the light of the fact that leptin activates monocytes and macrophages to sustain inflammatory response [28].

Our study confirms also results from other studies in which higher leptin levels have been found in PsA women with clinically evident psoriasis, and these are correlated with BMI [29, 30].

Different from RA, in which leptin has been recently found not correlated with BMI [50], in our PsA population, this adipokine was found to be associated with this anthropometric

Table 1 Median values (25th–75th Pctl) of adipokines in the two groups of the study

	Entire population	Group 1 Patients with PsA and psoriasis clinically evident ($n = 42$)	Group 2 Patients with PsA sine psoriasis	p value
TNF-α (pg/mL)	15.1 (8.96–28.45)	15.35 (10.7–29.7)	14.8 (8.83–27.2)	0.64
IL-6 (pg/mL)	4.825 (1.8–21.25)	6.195 (2.04–22.6)	2.96 (1.34–11.7)	0.25
Leptin (ng/mL)	15.34 (9.39–32.84)	14.48 (10.14–29.9)	20.19 (9.25–39.19)	0.29
Resistin (ng/mL)	8.48 (5.67–14.3)	9.47 (5.6–12.3)	8.19 (5.65–17.95)	0.98
Visfatin (ng/mL)	8.30 (7.06–11.52)	8.35 (7.38–10.1)	8.3 (6.21–11.9)	0.52
Ghrelin (ng/mL)	24.44 (20.66–32.1)	23.48 (19.81–32.32)	25.9 (22.4–31.27)	0.26

IL-6 interleukin-6, *TNF-α* tumor necrosis factor alpha

measure. This aspect suggests the need to clarify leptin's possible role in determining differences in the metabolic status of these two diseases.

Moreover, our data showed that in PsA patients with psoriasis, serum concentrations of leptin were associated with BMI. These are consistent with the results of Kyriakou and coworkers, who found high levels of leptin in PsA patients with evident psoriasis and MetS [31].

Further studies are needed to confirm a possible role of this adipokine on metabolic aspects in PsA and as marker of pain and inflammation.

Our study shows that resistin is associated with IL-6, and this association is confirmed in patients with psoriasis, suggesting a possible combined role of these two adipokines in addressing a phenotype associated with cutaneous manifestations. The complex role of resistin in PsA remains still not clarified; a recent study has demonstrated that a 6-month treatment with the anti-IL-17 agent, secukinumab, has little influence on the levels of resistin within the first 6 months of therapy. However, this study has shown that resistin might exert a different influence between males and females from a metabolic perspective. In particular, a significant decrease in the levels of resistin (about − 24%) was found on male PsA patients [53].

Other studies have reported that resistin levels were increased in patients with severe cutaneous psoriasis [31, 32, 35, 36] and were correlated with RA clinical activity in a manner independent of the patient's BMI [51].

Furthermore, results from our study are in line with other evidences describing that resistin levels can be regulated by the pro-inflammatory cytokine IL-6 [34].

Larger studies could clarify the possible role of resistin and IL-6 serum levels, as potential markers of cutaneous involvement, also useful to discriminate PsA with clinical evident psoriasis from PsA sine psoriasis.

Not coincidentally, in our study, despite IL-6 serum levels did not reach a significant difference between the two groups, IL-6 concentrations were higher in PsA patients with clinical evident psoriasis as compared with those in PsA sine psoriasis patients.

Limitations of our study are represented by its cross-sectional nature. Therefore, we cannot suggest any causal relationship.

Previous studies already showed that MetS and pro-inflammatory cytokine pattern are increased in patients with both PsA and psoriasis compared with healthy individuals and are increased in PsA when compared with psoriasis alone [29–32, 35, 36, 41]. For this reason, we aimed at focusing on patients with arthritis.

Table 2 Multiple linear regression results reaching statistical significance for the outcome of leptin serum levels in the entire cohort of the study, group 1 and group 2

	Overall cohort Beta	p	Group 1 Beta	p	Group 2 Beta	p
Female	0.3	0.001	0.41	< 0.0001	ns	ns
BMI	0.8	< 0.0001	0.6	0.012	0.7	0.003
TJC	0.23	0.05	ns	ns	ns	ns
Pt pain-VAS score	0.4	0.049	ns	ns	ns	ns
CRP	ns	ns	ns	ns	0.35	0.012

Analyzed variables not reaching statistical significance: age, WC, MetS, PASI, disease duration, hypertension, SJC, TEC, presence of dactylitis, PGA, BASDAI, BASFI, HAQ, ESR, fibrinogen, IL-6, and TNF-α

BMI body mass index, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Function Index, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *HAQ* Health Assessment Questionnaire, *IL-6* interleukin-6, *MetS* metabolic syndrome, *PGA* physician's global assessment, *Pt* patient, *SJC* swollen joint count, *TEC* tender entheseal count, *TJC* tender joint count, *TNF-α* tumor necrosis factor-α, *VAS* visual analogue scale, *WC* waist circumference

Strengths of our study are represented by its relatively large sample size, especially when considering sine psoriasis patients and the extensive description of clinical characteristics of the two groups.

In summary, our results show mainly a strict interplay between leptin, female gender, BMI, and inflammatory activity in overall PsA patients, as well as between resistin and IL-6 mainly in patients with psoriasis.

These findings highlight the importance of further studies on larger cohorts. They could be useful in understanding the complex pattern of adipokines which in PsA patients underlines the heterogeneous phenotypical expression of these subjects. Further studies are also advocated for clarifying possible role of these adipokines as laboratory findings or as disease mediators in addressing the different phenotypes of the disease.

Compliance with ethical standards

The study was approved by the Local Ethics Committee (CE: NA 126/15), and all patients gave their informed consent.

Disclosures None.

References

1. Caso F, Costa L, Atteno M, Del Puente A, Cantarini L, Lubrano E, Scarpa R (2014) Simple clinical indicators for early psoriatic arthritis detection. Springerplus 3:759
2. Napolitano M, Caso F, Scarpa R, Megna M, Patrì A, Balato N, Costa L (2016) Psoriatic arthritis and psoriasis: differential diagnosis. Clin Rheumatol 35:1893–1901
3. Lapadula G, Marchesoni A, Salaffi F, Ramonda R, Salvarani C, Punzi L, Costa L, Caso F, Simone D, Baiocchi G, Scioscia C, Di Carlo M, Scarpa R, Ferraccioli G (2016) Evidence-based algorithm for diagnosis and assessment in psoriatic arthritis: results by Italian DElphi in psoriatic Arthritis (IDEA). Reumatismo 68:126–136
4. Olivieri I, Padula A, D'Angelo S, Cutro MS (2009) Psoriatic arthritis sine psoriasis. J Rheumatol Suppl 83:28–29
5. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, CASPAR Study Group (2006) Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 54:2665–2673
6. Tillett W, Costa L, Jadon D, Wallis D, Cavill C, McHugh J, Korendowych E, McHugh N (2012) The ClASsification for Psoriatic ARthritis (CASPAR) criteria—a retrospective feasibility, sensitivity, and specificity study. J Rheumatol 39:154–156
7. Scarpa R, Caso F, Costa L, Peluso R, Del Puente A, Olivieri I (2017) Psoriatic disease 10 years later. J Rheumatol 44:1298–1301
8. Costa L, Caso F, D'Elia L, Atteno M, Peluso R, Del Puente A, Strazzullo P, Scarpa R (2012) Psoriatic arthritis is associated with increased arterial stiffness in the absence of known cardiovascular risk factors: a case control study. Clin Rheumatol 31:711–715
9. Peluso R, Caso F, Tasso M, Ambrosino P, Dario Di Minno MN, Lupoli R, Criscuolo L, Caso P, Ursini F, Puente AD, Scarpa R, Costa L, On Behalf Of CaRRDs Study Group (2018) Cardiovascular risk markers and major adverse cardiovascular events in psoriatic arthritis patients. Rev Recent Clin Trials 13:199–209
10. Costa L, Caso F, Atteno M, Del Puente A, Darda MA, Caso P, Ortolan A, Fiocco U, Ramonda R, Punzi L, Scarpa R (2014) Impact of 24-month treatment with etanercept, adalimumab, or methotrexate on metabolic syndrome components in a cohort of 210 psoriatic arthritis patients. Clin Rheumatol 33:833–839
11. Costa L, Caso F, Ramonda R, Del Puente A, Cantarini L, Darda MA, Caso P, Lorenzin M, Fiocco U, Punzi L, Scarpa R (2015) Metabolic syndrome and its relationship with the achievement of minimal disease activity state in psoriatic arthritis patients: an observational study. Immunol Res 61:147–153
12. Chimenti MS, Caso F, Alivernini S, De Martino E, Costa L, Tolusso B, Triggianese P, Conigliaro P, Gremese E, Scarpa R, Perricone R (2019) Amplifying the concept of psoriatic arthritis: the role of autoimmunity in systemic psoriatic disease. Autoimmun Rev 18:565–575. https://doi.org/10.1016/j.autrev.2018.11.007
13. Eckel RH, Alberti KG, Grundy SM, Zimmet PZ (2010) The metabolic syndrome. Lancet 375:181–183
14. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001) Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 85:2486–2497
15. Hotamisligil GS (2006) Inflammation and metabolic disorders. Nature. 444:860–867
16. Hutcheson J (2015) Adipokines influence the inflammatory balance in autoimmunity. Cytokine 75:272–279
17. Gentile M, Peluso R, Di Minno MND, Costa L, Caso F, de Simone B, Iannuzzo G, Scarpa R, Rubba P (2016) Association between small dense LDL and sub-clinical atherosclerosis in patients with psoriatic arthritis. Clin Rheumatol 35:2023–2029
18. Tam LS, Tomlinson B, Chu TT, Li M, Leung YY, Kwok LW, Li TK, Yu T, Zhu YE, Wong KC, Kun EW, Li EK (2008) Cardiovascular risk profile of patients with psoriatic arthritis compared to controls–the role of inflammation. Rheumatology (Oxford) 47:718–723
19. Caso F, Lubrano E, Del Puente A, Caso P, Peluso R, Foglia F, Benigno C, Girolimetto N, Bottiglieri P, Scarpa R, Costa L (2016) Progress in understanding and utilizing TNF-α inhibition for the treatment of psoriatic arthritis. Expert Rev Clin Immunol 12:315–331
20. Sethi JK, Hotamisligil GS (1999) The role of TNF alpha in adipocyte metabolism. Semin Cell Dev Biol 10:19–29
21. Trayhurn P, Wood IS (2004) Adipokines: inflammation and the pleiotropic role of white adipose tissue. Br J Nutr 92:347–355
22. Gremese E, Ferraccioli G (2011) The metabolic syndrome: the crossroads between rheumatoid arthritis and cardiovascular risk. Autoimmun Rev 10:582–589
23. Choi KM, Ryu OH, Lee KW, Kim HY, Seo JA, Kim SG, Kim NH, Choi DS, Baik SH (2007) Serum adiponectin, interleukin-10 levels and inflammatory markers in the metabolic syndrome. Diabetes Res Clin Pract 75:235–240
24. Fonseca JE, Santos MJ, Canha˜o H, Choy E (2009) Interleukin-6 as a key player in systemic inflammation and joint destruction. Autoimmun Rev 8:538–542
25. Caso F, Costa L, Nucera V, Barilaro G, Masala IF, Talotta R, Caso P, Scarpa R, Sarzi-Puttini P, Atzeni F (2018) From autoinflammation to autoimmunity: old and recent findings. Clin Rheumatol 37:2305–2321
26. Scrivo R, Vasile M, Bartosiewicz I, Valesini G (2011) Inflammation as "common soil" of the multifactorial diseases. Autoimmun Rev 10:369–374
27. Dutheil F, Gordon BA, Naughton G, Crendal E, Courteix D, Chaplais E, Thivel D, Lac G, Benson AC (2018) Cardiovascular risk of adipokines: a review. J Int Med Res 46:2082–2095

28. Chiricozzi A, Raimondo A, Lembo S, Fausti F, Dini V, Costanzo A, Monfrecola G, Balato N, Ayala F, Romanelli M, Balato A (2016) Crosstalk between skin inflammation and adipose tissue-derived products: pathogenic evidence linking psoriasis to increased adiposity. Expert Rev Clin Immunol 12:1299–1308
29. Eder L, Jayakar J, Pollock R, Pellett F, Thavaneswaran A, Chandran V, Rosen CF, Gladman DD (2013) Serum adipokines in patients with psoriatic arthritis and psoriasis alone and their correlation with disease activity. Ann Rheum Dis 72:1956–1961
30. Feld J, Nissan S, Eder L, Rahat MA, Elias M, Rimar D, Laor A, Bitterman H, Zisman D (2018) Increased prevalence of metabolic syndrome and adipocytokine levels in a psoriatic arthritis cohort. J Clin Rheumatol 24:302–307
31. Kyriakou A, Patsatsi A, Sotiriadis D, Goulis DG (2017) Serum leptin, resistin, and adiponectin concentrations in psoriasis: a meta-analysis of observational studies. Dermatology 233:378–389
32. Vachatova S, Andrys C, Krejsek J, Salavec M, Ettler K, Rehacek V, Cermakova E, Malkova A, Fiala Z, Borska L (2016) Metabolic syndrome and selective inflammatory markers in psoriatic patients. J Immunol Res 2016:5380792
33. Wolk K, Sabat R (2016) Adipokines in psoriasis: an important link between skin inflammation and metabolic alterations. Rev Endocr Metab Disord 17:305–317
34. Reilly MP, Lehrke M, Wolfe ML, Rohatgi A, Lazar MA, Rader DJ (2005) Resistin is an inflammatory marker of atherosclerosis in humans. Circulation 111:932–939
35. Dikbas O, Tosun M, Bes C, Tonuk SB, Aksehirli OY, Soy M (2016) Serum levels of visfatin, resistin and adiponectin in patients with psoriatic arthritis and associations with disease severity. Int J Rheum Dis 19:672–677
36. Kyriakou A, Patsatsi A, Sotiriadis D, Goulis DG (2018) Effects of treatment for psoriasis on circulating levels of leptin, adiponectin and resistin: a systematic review and meta-analysis. Br J Dermatol 179:273–281
37. Mattu HS, Randeva HS (2013) Role of adipokines in cardiovascular disease. J Endocrinol 216:T17–T36
38. Makris MC, Alexandrou A, Papatsoutsos EG, Malietzis G, Tsilimigras DI, Guerron AD, Moris D (2017) Ghrelin and obesity: identifying gaps and dispelling myths. A reappraisal. In Vivo 31: 1047–1050
39. Baatar D, Patel K, Taub DD (2011) The effects of ghrelin on inflammation and the immune system. Mol Cell Endocrinol 340:44–58
40. Dixit VD, Schaffer EM, Pyle RS, Collins GD, Sakthivel SK, Palaniappan R, Lillard JW Jr, Taub DD (2004) Ghrelin inhibits leptin- and activation-induced proinflammatory cytokine expression by human monocytes and T cells. J Clin Invest 114:57–66
41. Ozdemir M, Yüksel M, Gökbel H, Okudan N, Mevlitoğlu I (2012) Serum leptin, adiponectin, resistin and ghrelin levels in psoriatic patients treated with cyclosporin. J Dermatol 39:443–448
42. Ucak H, Demir B, Cicek D, Erden I, Aydin S, Dertlioglu SB, Arica M (2014) Metabolic changes and serum ghrelin level in patients with psoriasis. Dermatol Res Pract 2014:175693
43. Caso F, Del Puente A, Oliviero F, Peluso R, Girolimetto N, Bottiglieri P, Foglia F, Benigno C, Tasso M, Punzi L, Scarpa R, Costa L (2018) Metabolic syndrome in psoriatic arthritis: the interplay with cutaneous involvement. Evidences from literature and a recent cross-sectional study. Clin Rheumatol 37:579–586
44. La Cava A, Matarese G (2004) The weight of leptin in immunity. Nat Rev Immunol 4:371–379
45. Carniglia L, Ramírez D, Durand D, Saba J, Turati J, Caruso C, Scimonelli TN, Lasaga M (2017) Neuropeptides and microglial activation in inflammation, pain, and neurodegenerative diseases. Mediat Inflamm 2017:5048616
46. Lim G, Wang S, Zhang Y, Tian Y, Mao J (2009) Spinal leptin contributes to the pathogenesis of neuropathic pain in rodents. J Clin Invest 119:295–304
47. Tian Y, Wang S, Ma Y, Lim G, Kim H, Mao J (2011) Leptin enhances NMDA-induced spinal excitation in rats: a functional link between adipocytokine and neuropathic pain. Pain 152:1263–1271
48. Hu F, Cui Y, Guo R, Chen J, Guo R, Shen N, Hua X, Mo L, Feng J (2014) Spinal leptin contributes to the development of morphine antinociceptive tolerance by activating the STAT3-NMDA receptor pathway in rats. Mol Med Rep 10:923–930
49. Fatel ECS, Rosa FT, Simão ANC, Dichi I (2018) Adipokines in rheumatoid arthritis. Adv Rheumatol 58:25
50. Dervišević A, Resić H, Sokolović Š, Babić N, Avdagić N, Začiragić A, Bečiragić A, Fajkić A, Lepara O, Hadžović-Dzuvo A (2018) Leptin is associated with disease activity but not with anthropometric indices in rheumatoid arthritis patients. Arch Med Sci 14:1080–1086
51. Bustos Rivera-Bahena C, Xibillé-Friedmann DX, González-Christen J, Carrillo-Vázquez SM, Montiel-Hernández JL (2016) Peripheral blood leptin and resistin levels as clinical activity biomarkers in Mexican rheumatoid arthritis patients. Reumatol Clin 12:323–326
52. Khan NA, Spencer HJ, Abda E, Aggarwal A, Alten R, Ancuta C, Andersone D, Bergman M, Craig-Muller J, Detert J, Georgescu L, Gossec L, Hamoud H, Jacobs JW, Laurindo IM, Majdan M, Naranjo A, Pandya S, Pohl C, Schett G, Selim ZI, Toloza S, Yamanaka H, Sokka T (2012) Determinants of discordance in patients' and physicians' rating of rheumatoid arthritis disease activity. Arthritis Care Res (Hoboken) 64:206–214
53. Fassio A, Gatti D, Gisondi P, Girolomoni G, Viapiana O, Giollo A, Zamboni M, Rossini M, Idolazzi L (2017) Effects of secukinumab on serum adipocytokines: preliminary data. Reumatismo 69:105–110