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# Proinflammatory and anti-inflammatory cytokine profiles in psoriasis: use as laboratory biomarkers and disease predictors

Camila Cataldi[1] · Naiara Lourenço Mari[1] · Marcell Alysson Batisti Lozovoy[2] · Ligia Márcia Mário Martins[3] · Edna Maria Vissoci Reiche[2] · Michael Maes[4,5] · Isaias Dichi[6] · Andréa Name Colado Simão[2]

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## Abstract

**Objective** The objectives of this study were to delineate the pro and anti-inflammatory cytokine profiles of psoriasis and cytokine profile models that externally validate the diagnosis.

**Subjects and Methods** This study recruited 70 patients with psoriasis and 76 healthy controls. Cytokine profiles were evaluated, including pro-inflammatory M1 (IL-1 + IL-6 + TNF-α), Th1 (IL-2 + IL-12 + IFN-γ), Th17 (IL-6 + IL-17), and immune-inflammatory response system (IRS = M1 + Th1 + Th17) profiles. Moreover, the anti-inflammatory potential included Th2 (IL-4), Th2 + T regulatory (Th2 + Treg, namely IL-4 + IL-10 + TGF-β), anti-inflammatory (Th2 + Treg + adiponectin), and the pro-inflammatory/anti-inflammatory index.

**Results** There was a highly significant association between psoriasis and cytokine levels with an effect size of 0.829 and a particularly strong impact on IL-2 (0.463), IL-12 (0.451), IL-10 (0.532) and adiponectin (0.401). TGF-β and adiponectin were significantly lower while all other cytokines (except IFN-γ) were significantly higher in psoriasis than in controls. In addition, M1, Th1, Th17, Th2 + Treg, and IRS/Anti-inflammatory index were significantly higher in psoriasis patients than in controls. The IRS index, Th2 + Treg, and adiponectin predicted psoriasis with 97.1% sensitivity and 94% specificity.

**Conclusion** In conclusion, psoriasis is characterized by increased M1, Th1, Th2 and Th17 profiles together with lowered TGF-β and adiponectin. In addition, we propose a model based on a higher IRS and Th2 + Treg index coupled with lower adiponectin values, which may be used to externally validate the diagnosis of psoriasis. The most important single biomarker of psoriasis is adiponectin. Because the latter may play a role in the modulation of the chronic inflammatory response in psoriasis, adiponectin could be a new drug target to treat psoriasis.

**Keywords** Psoriasis · Cytokines · Adiponectin · Inflammation

## Introduction

Psoriasis is an autoimmune disease characterized by chronic inflammation of the skin related to innate and adaptive immune responses. Plaque-type psoriasis or psoriasis

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✉ Andréa Name Colado Simão
deianame@yahoo.com.br

[1] Laboratory of Research in Applied Immunology, University of Londrina, Londrina, PR, Brazil

[2] Laboratory of Research in Applied Immunology, Department of Pathology, Clinical Analysis and Toxicology, University of Londrina, Rua Robert Koch, n 60, Londrina, Paraná 86038-440, Brazil

[3] Department of Dermatology, University of Londrina, Londrina, PR, Brazil

[4] IMPACT Strategic Research Centre, School of Medicine, Deakin University, Geelong, VIC, Australia

[5] Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

[6] Laboratory of Research in Applied Immunology, Department of Internal Medicine, University of Londrina, Londrina, PR, Brazil

vulgaris is the most common clinical manifestation, and its features include red and scaly plaques on the elbows, knees and scalp. Along with other autoimmune diseases, psoriasis is a multifactorial disorder and can be triggered by injury, trauma, infections and medications, as well as psychological stress [1].

Histological findings demonstrate epidermis hyperkeratinisation and leukocyte infiltration into the dermis, mainly formed by activated T cells [2]. Although the recruitment and activation of T helper (Th) 1 and Th17 lymphocytes drive the pathogenesis of psoriasis, neutrophils, antigen-presentation cells (APCs), macrophages and keratinocytes contribute to the synthesis and secretion of cytokines, including those produced by Th1 and Th17 cells. The presence of pro-inflammatory cells and their cytokines creates a damaging environment leading to the development and aggravation of psoriatic lesions [3].

The cytokine profile of psoriasis is vast and complex. Interleukin (IL)–2, Tumour Necrosis Factor-alpha (TNF-α) and Interferon-gamma (IFN-γ) are produced by Th1 cells under the stimulation of IL-12. In the same way, IL-1β and IL-6 are responsible for Th17 cell differentiation, which secretes IL-6, IL-17, IL-21 and IL-22. Previous studies showed that these cytokines are present in psoriatric lesions and that their serum levels correlate with severity of illness [4]. In addition, studies show that IL-4, produced by Th2 cells, may ameliorate the aspect of psoriasis lesions [5] while suppressing pro-inflammatory responses and inhibiting IL-1β, IL-6 and Th17 producing cells [6, 7].

The chronic immune-inflammatory response observed in psoriasis patients is frequently associated with systemic comorbidities, including obesity and metabolic syndrome (MetS). MetS is a metabolic disorder generated by the combination of insulin resistance, obesity, hypertension and dyslipidemia [8]. The presence of MetS in patients with psoriasis is often reported and may be associated with the insulin resistance caused by the immune-inflammatory response that accompanies psoriasis [9]. Obese patients also have a Th1 response pattern, which adipocytes are responsible for the production of TNF-α and IL-6. The activity of these cytokines may provoke a decline in anti-inflammatory defenses, especially in adiponectin levels [10].

Adiponectin is an adipokine that has anti-inflammatory effects by inhibiting the activity and secretion of pro-inflammatory cytokines, including IL-2, IL-6, TNF-α and IFN-γ, and enhancing the production of anti-inflammatory cytokines, including IL-10 [11]. The upregulation of anti-inflammatory cytokines can help restore the imbalance between Th1/Th17 and Th2 responses that affect patients with psoriasis [12].

Our research group has examined cytokine profiles in autoimmune diseases such as systemic lupus erythematosus (SLE) and observed that the immune response is driven by pro-inflammatory cytokines, including Th1 and Th17. The evaluation of those cytokine profiles is useful to elucidate which profiles are dominant thereby characterizing the features of the disorder that influence disease activity and severity [13]. Nevertheless, studies that assessed cytokine levels in patients with psoriasis are quite scarce and these studies reported often controversial results on serum cytokine levels rather than cytokine profiles [4, 14, 15]. As such it was difficult to pinpoint the pro-inflammatory versus anti-inflammatory balance is psoriasis. Finally, studies that have concomitantly evaluated those cytokines with adiponectin in psoriasis are also scarce, while there is insufficient information whether these cytokine or cytokine profiles may be used as laboratory biomarkers for psoriasis.

Hence, the main objective of this study is to evaluate cytokine profiles and the pro and anti-inflammatory index in psoriasis as well as to determine models of cytokine profiles, which could help to predict the diagnosis of psoriasis.

## Subjects and methods

### Subjects

This study recruited 146 individuals. Seventy patients with psoriasis (56 with plaque-type psoriasis, 10 with psoriatic arthritis, 3 with guttate psoriasis) were selected from among the ambulatory of Dermatology of the University Hospital of Londrina, Paraná, Brazil and 76 were healthy controls. The diagnostic was determined by clinical features and the disease activity was measured using Psoriasis Activity Severity Index (PASI) [16]. MetS was defined following the Adult Treatment Panel III criteria [17]. Inclusion criteria were patients of both sex and aged from 18 to 70 years old. Exclusion criteria were thyroid, adrenal, renal, hepatic, gastrointestinal, infectious, and oncological, another autoimmune disease, hormone replacement therapy and antioxidant supplements. Information on lifestyle factors and medical history was obtained at clinical evaluation. The individuals of both groups self-reported that they did not drink alcohol regularly. Sample collection and laboratorial analysis, as well as data evaluation, were performed in a blinded fashion. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the Ethical Committee of the University of Londrina, Paraná, Brazil (CAAE: 51826215.0.000.5231). Written informed consent was obtained from all subjects.

### Anthropometric and blood pressure measurements

The body weight was measured using a 0.1 kg precision electronic scale. The subjects were weighed in the morning,

wearing light clothing and barefoot. Stature was measured through a stadiometer whose accuracy was 0.1 cm. The formula for dividing body weight (kg) by squared height (m) was used to calculate Body Mass Index (BMI). Waist circumference was measured with the individuals standing upright by placing a tape measure between the lower ribs and the iliac crest. Blood pressure was measured in triplicate in the left arm of seated patients using a calibrated sphygmomanometer and 1 min interval between measurements. Individuals using antihypertensive or whose blood pressure was ≥ 140–90 mmHg were considered hypertensive [18].

### Cytokines plasma levels

After fasting for 12 h, venous blood was withdrawn with ethylenediaminetetraacetic acid (EDTA) using sterile tubes (BD Vacutainer UltraTouch; Franklin Lakes, NJ, USA). Whole blood was centrifuged at 1500 rpm for 10 min and plasma samples were separated and divided into aliquots and then stored at − 80 °C for subsequent analysis. Levels of IFN-γ, TNF-α, IL-10, IL-12, IL-17, IL-1β, IL-2, IL-4 and IL-6 were performed using ProcartaPlex Human High Sensitivity Panel 9plex (Invitrogen, Thermo Fisher Scientific, Viena, Austria) and Transforming Growth Factor- beta (TGF-β) was performed using ProcartaPlex Human TGF beta 1 Simplex (Invitrogen, Thermo Fisher Scientific, Viena Austria) both techniques for Luminex® platform. Adiponectin levels were evaluated through enzyme-linked immunosorbent assay (ELISA) technique using Human Adiponectin/Acrp30 DuoSet® kit (R&D Systems, Minneapolis, USA).

Cytokines were analyzed individually and in profiles as follows: pro-inflammatory: M1 (IL-1 + IL-6 + TNF-α), Th1 (IL-2 + IL-12 + IFN-γ), Th17 (IL-6 + IL-17) and Immune-Inflammatory response system index (IRS = M1 + Th1 + Th17); anti-inflammatory: Th2 (IL-4), Th2 + T regulatory (Treg) (IL-4 + IL-10 + TGF-β) and Anti-inflammatory (IL-4 + IL-10 + TGF-β + adiponectin); and two index to verify the predominant profile (pro or anti-inflammatory): IRS/Th2Treg and IRS/anti-inflammatory.

### Statistical analysis

We used analysis of variance (ANOVA) and analysis of contingency tables ($\chi^2$ test) to assess differences in scale or nominal data (either demographic or clinical) among study groups. Pearson's product moment and Spearman's rank order correlation coefficients were used to assess relationships between variables. We used multivariate general linear model (GLM) analysis to check the effects of independent variables (e.g. diagnostic groups) on cytokine levels (dependent variables) after adjusting for extraneous variables including age, sex, and BMI. When the multivariate analysis was significant, we employed tests for between-subject effects to check the effects of the significant independent variables on the dependent variables. Model-generated estimated marginal mean values with SE were computed. We have *p*-corrected results of multiple comparisons using *p*-correction for false discovery rate (FDR) [19]. Binary logistic regression analysis was used to delineate the most important predictors of psoriasis (dependent variable) with controls as reference groups and cytokines and cytokine profiles as explanatory variables. We used Neural Networks (multilayer perceptron, MLP) to assess non-linear associations between input (cytokine levels) and output (diagnosis) variables employing an automated feedforward architecture. We considered one or two hidden layers with a variable number of nodes (max 4). We computed the rate of incorrect predictions and the partitioned confusion matrix in a training, testing and holdout set (ratio: 7/3/5, respectively). The area under the receiving operating curve (AUC ROC) was computed as well as the (relative) importance of the input variables in sensitivity analyses. All statistical analyses were performed using IBM SPSS, Windows version 24. Tests were 2-tailed, and an alpha level of 0.05 indicated a statistically significant effect.

As explained by Maes and Carvalho [20] we computed z unit weighted composite scores based on the known cytokine profiles of macrophage M1, Th1, Th2, Th17 and Treg and anti-inflammatory cytokines. All Ln-transformed cytokine data were z-transformed (z scores with a distribution with mean = 0 and SD = 1) and then used in the construction of composite scores as follows: (1) Macrophage M1 profile: z value of IL-1β (zIL-1β) + zTNF-α + zIL-6; (2) Th-17 profile: zIL-6 + zIL-17; (3) Th1 profile: zIFN-γ + zIL-12 + zIL-2; (4) IRS: z(zIL-1β + zTNF-α + zIL-6 + zIL-17 + zIFN-γ + zIL-2 + zIL-12); (5) Th2 + Treg profile: zIL-4 + zIL-10 + zTGF-β; (6) anti-inflammatory index: zIL-4 + zIL-10 + zTGF-β + zAdiponectin; (7) IRS/anti-inflammatory: z(M1 + Th17 + Th1) − z (anti-inflammatory index).

## Results

### Demographic data

Table 1 shows the socio-demographic and clinical data in both controls and patients with psoriasis. Patients with psoriasis were somewhat older, included more males and had a higher BMI than controls. Therefore, all results were adjusted for possible effects of age, sex, BMI, and other extraneous variables, using the latter as covariates in regression analyses. There were no significant differences in the ratio Caucasian versus non Caucasian, smoking behavior, diabetes mellitus type 2 and hypertension between the study groups. The frequencies of MetS was

**Table 1** Sociodemographic data in both healthy controls and patients with psoriasis

| Variables | Controls ($n=76$) | Psoriasis ($n=70$) | $F/\chi^2$ | *df* | *P* value |
|---|---|---|---|---|---|
| Age (years) | 46.0 (8.7) | 53.1 (12.6) | 15.63 | 1/144 | < 0.001 |
| Sex (F/M) | 58/18 | 31/39 | 15.71 | 1 | < 0.001 |
| BMI (kg/m$^2$) | 25.9 (4.3) | 29.7 (6.2) | 19.31 | 1/142 | < 0.001 |
| Ethnicity (C/NC) | 57/19 | 60/10 | 2.63 | 1 | 0.104 |
| Smoking (yes/no) | 08/68 | 15/55 | 3.26 | 1 | 0.071 |
| DM II (yes/no) | 11/52 | 15/55 | 0.33 | 1 | 0.564 |
| Hypertension (yes/no) | 14/47 | 25/45 | 2.54 | 1 | 0.111 |
| MetS (yes/no) | 20/55 | 31/39 | 4.93 | 1 | 0.026 |

Student *t* test. Results are shown as mean (± SEM)

*F* Female, *M* male, *BMI* body mass index, *C* Caucasian, *NC* not Caucasian, *DM* diabetes mellitus, *MetS* metabolic syndrome

somewhat higher in subjects with psoriasis than in controls. The median PASI value was 4.20 and interquatiles 25% and 75% were 1.50 and 9.50, respectively (data not shown). The frequency of drugs used in treatment of psoriasis was 25.71% for methotrexate ($n=18$), 18.6% for acitretin ($n=13$), 2.9% for ciclosporin ($n=2$), 20% for TNF-α inhibitor ($n=14$), 4.3% for anti-IL-12/IL-23 ($n=3$) and 40% for topic treatment ($n=28$) (data not shown).

Inspection of the intercorrelation matrix between all cytokines showed that (without p correction): (a) IL-1β, IL-6, TNF-α, IL-12, IL-2, IL-17, IL-4 and IL-10 were strongly intercorrelated (all $r>0.312$, $p<0.001$, but most correlation coefficients were > 0.450, n = 139); (b) IFN-γ was significantly related with IL-1β ($r=0.285$, $p=0.001$, $n=139$), IL-6 ($r=0.193$, $p=0.021$), IL-12 ($r=0.200$, $p=0.018$), IL-2 ($r=0.294$, $p<0.001$), IL-17 (0.237, $p=0.005$) and IL-4 ($r=0.184$, $p=0.030$); (c) TGF-β was not associated with any of the other cytokines; and (d) adiponectin levels were significantly and inversely related with TNF-α ($r=-0.426$, $p<0.001$, $n=138$), IL-12 ($r=-0.520$, $p<0.001$), IL-2 ($r=-0.286$, $p=0.001$), IL-17 ($r=-0.256$, $p=0.002$), IL-4 ($r=-0.286$, $p=0.001$) and IL-10 ($r=-0.518$, $p<0.001$). The intercorrelation matrix between the *z* unit composite scores showed (again without *p* correction) that (a) M1 is correlated with Th1 ($r=0.673$, $p<0.001$), Th17 ($r=0.831$, $p<0.001$), Th2 + Treg ($r=0.638$, $p<0.001$) and anti-inflammatory index ($r=0.498$, $p<0.001$, all $n=139$); (b) Th1 with Th17 ($r=0.618$, $p<0.001$), Th2 + Treg ($r=0.560$, $p<0.001$) and anti-inflammatory index ($r=0.387$, $p<0.001$); and (c) Th17 with Th2 + Treg ($r=0.632$, $p<0.001$, all $n=137$) and anti-inflammatory index ($r=0.554$, $p<0.001$). Likewise, the IRS index was significantly correlated with Th2 + Treg ($r=0.664$, $p<0.001$) and with the anti-inflammatory index ($r=0.474$, $p<0.001$, all $n=137$).

## Association between psoriasis and cytokine levels

Table 2 shows the outcome of a multivariate GLM analysis with the 11 cytokines levels as dependent variables and psoriasis, age, sex and BMI as covariates. The results show that there was a highly significant effect of psoriasis explaining 82.9% of the variance in the cytokine levels. Age, sex and BMI had no significant impact on cytokine levels in this analysis. Tests for between-subject effects show highly significant effects (all $p<0.001$) of psoriasis on all cytokines (except IFN-γ and TGF-β), with a particularly strong impact on IL-2, IL-12, IL-10, and adiponectin explaining 46.3, 45.1, 53.2, and 40.1% of the variance, respectively. There was a modest association between TGF-β and psoriasis, explaining only 3.7% of the variance in TGF-β levels. There was no significant difference in IFN-γ levels between both study groups. All these differences remained significant after p-correction for FDR.

Table 3 shows the model-derived estimated marginal mean values of the 11 cytokines in controls and patients. Figure 1 shows the z transformed values of the 11 cytokines in both study groups. TGF-β and adiponectin were significantly lower in psoriasis than in controls, while all other cytokines (except IFN-γ) were significantly higher in psoriasis than in controls.

We have also examined the putative effects of other extraneous variables by entering these in the multivariate GLM analysis shown in Table 2. Thus, there were no significant effects of smoking ($F=1.05$, $df=11/120$, $p=0.411$), MetS ($F=1.46$, $df=11/120$, $p=0.156$), diabetes mellitus type 2 ($F=0.76$, $df=11/107$, $p=0.680$) and hypertension ($F=0.80$, $df=11/107$, $p=0.636$). Moreover, there were no significant effects of topical treatments ($F=0.35$, $df=11/119$, $p=0.971$) and immunomodulatory treatments (methotrexate, cyclosporine and anti-TNF) and acitretin ($F=0.75$, $df=11/119$, $p=0.691$) on the 11

**Table 2** Outcome of a multivariate GLM analysis with the 11 cytokines levels as dependent variables and psoriasis, age, sex and body mass index (BMI) as covariates

| Type tests | Dependent variables | Explanatory variables | *F* | *df* | *P* value | Partial eta squared |
|---|---|---|---|---|---|---|
| Multivariate | All 11 cytokines | Psoriasis | 53.34 | 11/121 | < 0.001 | 0.829 |
| | | Age | 0.80 | 11/121 | 0.639 | 0.068 |
| | | Sex | 0.69 | 11/121 | 0.747 | 0.059 |
| | | BMI | 0.59 | 11/121 | 0.838 | 0.050 |
| Between-subject effects | IL-1β | Psoriasis | 14.91 | 1/131 | < 0.001 | 0.102 |
| | IL-6 | Psoriasis | 6.13 | 1/131 | 0.015 | 0.045 |
| | TNF-α | Psoriasis | 6.89 | 1/131 | 0.010 | 0.050 |
| | IL-12 | Psoriasis | 107.71 | 1/131 | < 0.001 | 0.451 |
| | IFN-γ | Psoriasis | 0.01 | 1/131 | 0.915 | 0.001 |
| | IL-2 | Psoriasis | 113.16 | 1/131 | < 0.001 | 0.463 |
| | IL-17 | Psoriasis | 12.24 | 1/131 | 0.001 | 0.085 |
| | IL-4 | Psoriasis | 25.89 | 1/131 | < 0.001 | 0.165 |
| | IL-10 | Psoriasis | 148.81 | 1/131 | < 0.001 | 0.532 |
| | TGF-β | Psoriasis | 5.00 | 1/131 | 0.027 | 0.037 |
| | Adiponectin | Psoriasis | 87.86 | 1/131 | < 0.001 | 0.401 |

All cytokine data are processed in Ln transformation

*BMI* Body mass index, *IL* interleukin, *TNF-α* tumor necrosis factor alpha, *IFN-γ* interferon gamma, *TGF-β* transforming growth factor beta

**Table 3** Model-derived estimated marginal mean values of the 11 cytokines in controls and patients with psoriasis

| Variables | Controls | Psoriasis |
|---|---|---|
| IL-1β | −0.367 (0.130) | +0.360 (0.119) |
| IL-6 | −0.233 (0.134) | +0.250 (0.123) |
| TNF-α | −0.246 (0.132) | +0.259 (0.122) |
| IL-12 | −0.706 (0.094) | +0.719 (0.087) |
| IFN-γ | +0.022 (0.139) | +0.044 (0.128) |
| IL-2 | −0.745 (0.095) | +0.728 (0.088) |
| IL-17 | −0.322 (0.133) | +0.356 (0.123) |
| IL-4 | −0.474 (0.124) | +0.446 (0.114) |
| IL-10 | −0.771 (0.087) | +0.776 (0.080) |
| TGF-β | +0.230 (0.139) | −0.221 (0.128) |
| Adiponectin | +0.684 (0.102) | −0.701 (0.093) |

*IL* Interleukin, *TNF-α* tumor necrosis factor alpha, *IFN-γ* interferon gamma, *TGF-β* transforming growth factor beta

cytokines levels. As such, the effects of the drug state of the patients on the results can be ruled out.

## Association between psoriasis and composite scores

Table 4 shows the outcome of a multivariate GLM analysis with the 8 composite scores as dependent variables and psoriasis, age, sex, and BMI as covariates. The results show that there was a high effect of psoriasis explaining 56.8% of the variance in the composite scores. Tests for between-subject effects showed that all composite scores, except the anti-inflammatory index and IRS/Th2 + Treg, were significantly different between both study groups. *P*-correction for FDR showed that those differences remained significant after *p*-correction (all $p < 0.001$).

Table 5 shows the model-generated estimated marginal mean values in both study groups and that M1, Th1, Th17, Th2 + Treg and IRS/Anti-inflammatory index were significantly higher in psoriasis patients than in controls. Figure 2 shows the z transformed values of the different composite scores and shows the group means of the composite scores in both controls and patients with psoriasis in a distribution with mean 0 and SD = 1.

## Best prediction of psoriasis

In order to examine which combination of cytokines or composite score best predict psoriasis, we have carried out binary logistic regression analyses with psoriasis as the dependent variable (and controls as the reference group). All cytokines or all composite scores (with adiponectin) were entered as explanatory variables. We found that 4 cytokines predicted psoriasis with a 100% sensitivity and specificity ($\chi^2 = 191.28$, $df = 4$, $p < 0.001$, Nagelkerke = 1.00), namely IL-17, IL-12, IL-2 and adiponectin. Unfortunately, the program does not allow to compute OR and CI intervals when there is a 100% prediction. Table 6 shows the results of the second logistic regression analysis with the composite scores and adiponectin as input variables. We found that 3 variables predicted psoriasis with a 97.1% sensitivity and 94.0% specificity ($\chi^2 = 142.34$, $df = 3$, $p < 0.001$, Nagelkerke = 0.862),

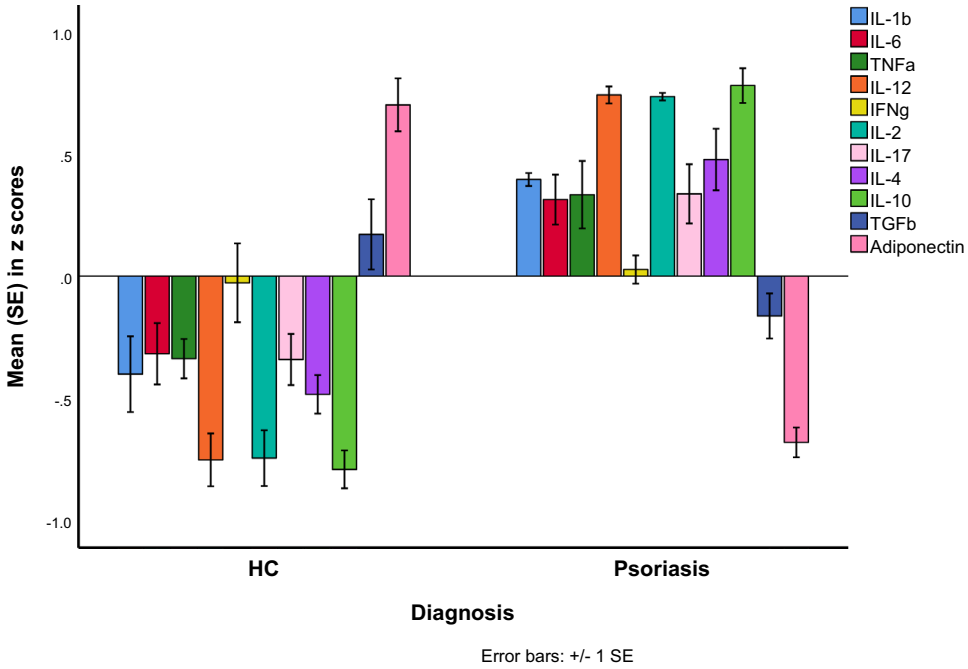


**Fig. 1** Z transformed values of 11 cytokines in patients with psoriasis and healthy controls (HC). *IL* Interleukin, *TNFα* tumour necrosis factor-alpha, *IFNg* interferon-gamma, *TGFb* transforming growth factor-beta. All cytokines are significantly higher in psoriasis patients than in controls ($p < 0.05$), except IFNg (see Table 2 for exact $p$ values and effect sizes)

**Table 4** Outcome of a multivariate GLM analysis with the 8 composite scores as dependent variables and psoriasis, age, sex and BMI as covariates

| Type tests | Dependent variables | Explanatory variables | *F* | *DF* | *P* value | Partial eta squared |
|---|---|---|---|---|---|---|
| Multivariate | All 8 scores | Psoriasis | 27.64 | 6/126 | < 0.001 | 0.568 |
| | | Age | 1.20 | 6/126 | 0.309 | 0.054 |
| | | Sex | 0.39 | 6/126 | 0.887 | 0.018 |
| | | BMI | 0.73 | 6/126 | 0.624 | 0.034 |
| Between-subject effect | M1 | Psoriasis | 17.49 | 1/131 | < 0.001 | 0.118 |
| | Th1 | Psoriasis | 54.20 | 1/131 | < 0.001 | 0.293 |
| | Th17 | Psoriasis | 12.65 | 1/131 | 0.001 | 0.088 |
| | IRS | Psoriasis | 40.94 | 1/131 | < 0.001 | 0.238 |
| | Th2 + Treg | Psoriasis | 39.79 | 1/131 | < 0.001 | 0.233 |
| | Anti-inflamatory | Psoriasis | 3.08 | 1/131 | 0.082 | 0.023 |
| | IRS/Th2 + Treg | Psoriasis | 0.01 | 1/131 | 0.924 | 0.000 |
| | IRS/Anti-inflamatory | Psoriasis | 14.56 | 1/131 | < 0.001 | 0.100 |

*BMI* Body mass index, *M1* macrophage type 1, *Th* lymphocyte T helper, *IRS* immune-inflammatory response system, *Treg* regulatory T cells

M1: computed as z interleukin-1 (zIL-1) + zIL-6 + zTNF-α

Th1: zIL-2 + zIL-12 + zINF-γ

Th17: computed as zIL-6 + IL-17

IRS: computed as z(sum of all cytokines in M1 + Th1 + zTh17 profiles)

Th2 + Treg: computed as zIL-4 + zIL-10 + zTGF-β

Anti-inflammatory computed as: zIL-4 + zIL-10 + zTGF-β + zAdiponectin

IRS/Th2 + Treg: zIRS - z(zIL-4 + zIL-10 + zTGF-β)

IRS/Anti-inflammatory: zIRS - z(zIL-4 + zIL-10 + zTGF-β + zAdiponectin)

namely IRS index, Th2 + Treg (both positively associated) and adiponectin (negatively associated).

Although the cytokines yielded a 100% correct prediction we have also performed a Neural Network analysis in order to examine the most significant features of psoriasis. Psoriasis and control groups were the output variables, while all 11 cytokines were the input variables. Automatic architecture training of the network delineated the best model using 2

**Table 5** Model-generated estimated marginal mean values of macrophagic M1, T helper (Th)1, Th17, Th2 + T regulatory (Treg), anti-inflammatory profiles and their ratios in patients with psoriasis and controls

| Variables | Controls | Psoriasis |
|---|---|---|
| M1 | −0.375 (0.125) | +0.384 (0.115) |
| Th1 | −0.582 (0.111) | +0.606 (0.102) |
| Th17 | −0.325 (0.131) | +0.354 (0.121) |
| IRS | −0.523 (0.115) | +0.547 (0.106) |
| Th2 + Treg | −0.542 (0.115) | +0.512 (0.106) |
| Anti-inflammatory | −0.331 (0.247) | +0.300 (0.227) |
| IRS/Th2 + Treg | +0.00 (0.141) | +0.021 (0.130) |
| IRS/Anti-inflamatory | −0.334 (0.130) | +0.389 (0.120) |

*M1* Macrophage type 1, *Th* lymphocyte T helper, *IRS* immune-inflammatory response system, *Treg* regulatory T cells

M1: computed as z interleukin-1 (zIL-1) + zIL-6 + zTNF-α

Th1: zIL-2 + zIL-12 + zINF-γ

Th17: computed as zIL-6 + IL-17

IRS: computed as z(sum of all cytokines in M1 + Th1 + zTh17 profiles)

Th2 + Treg: computed as zIL-4 + zIL-10 + zTGF-β

Anti-inflammatory computed as: zIL-4 + zIL-10 + zTGF-β + zAdiponectin

IRS/Th2 + Treg: zIRS − z(zIL-4 + zIL-10 + zTGF-β)

IRS/anti-inflammatory: zIRS − z(zIL-4 + zIL-10 + zTGF-β + zAdiponectin)

hidden layers. Hidden layer 1 contained 4 units and hidden layer 2 contained 3 units, and hyperbolic tangent was the activation function for the hidden layer, whereas identity was the activation function for the output layer. The sum of squares was used as the error function. The latter was lower in the testing set (0.238) as compared with the training set (0.533). The *per cent* incorrect predictions were 0% in the training, testing and holdout samples. Figure 3 shows the importance chart with the importance and normalized importance of the 11 cytokines for psoriasis and controls. This figure shows that adiponectin is by far the dominant variable, followed at a distance by IL-10, IL-12 and IL-17.

## Discussion

The major finding of the present study is that there was a highly significant association between psoriasis and cytokine levels explaining 82.9% of their variance, with a particularly strong impact on IL-2 (46.3%), IL-12 (45.1%), IL-10 (53.2%), and adiponectin (40.1%). Of the 11 cytokines evaluated, TGF-β and adiponectin were significantly lower in psoriasis than in controls, while all other cytokines (except IFN-γ) were significantly higher in psoriasis than in controls. Our data demonstrated that lowered adiponectin is the most dominant feature of psoriasis followed at a distance by IL-10, IL-12 and IL-17. In addition, we propose a laboratory biomarker model to predict psoriasis with 97.1% sensitivity and 94% specificity.

Macrophages type 1 (M1) are characterized by the production of pro-inflammatory cytokines as IL-1, IL-6 and TNF-α [21]. In the present study, serum levels of IL-1β, TNF-α and IL-6 in patients with psoriasis were significantly higher when compared with healthy controls. Our data are in agreement with the previous studies, which demonstrated increased TNF-α and IL-6 levels [14, 22]. No other studies reported on increased IL-1β serum levels in patients as compared to controls. However, Skendros et al. (2017) found that IL-1β inhibition therapy reduced the activity of the disease, suggesting that IL-1β may play a role in generalized pustular psoriasis [23]. Hence, our outcome confirms the robust impact of Th1 and Th17 profile cytokines in the pathophysiology of psoriasis.

In the present study, IL-12 and IL-2, both Th1 cytokines, were increased in psoriasis patients. Macrophages and dendritic cells produce IL-12, which stimulates T effector cell differentiation into a pro-inflammatory Th1 response. Once activated, Th1 cells secrete cytokines which play a role in psoriasis pathophysiology, such as IFN-γ, TNF-α and IL-2 [24]. IL-12 not only promotes a pro-inflammatory response but also aggravates psoriatic lesions [25]. Our data are in agreement with a previous study showing that IL-12 levels are increased in patients with psoriasis [26]. In contrast, the data on IL-2 are controversial. Th1 cells produce and secrete IL-2 under the influence of IL-12. The major function of IL-2 is induction of the Th1 phenotype thereby producing IFN-γ, TNF-α and other pro-inflammatory cytokines, and activating Natural Killers (NK) cells [27]. Increased levels of IL-2 in peripheral blood of patients with psoriasis were reported before [28, 29], although Takahashi et al. (2010) showed no significant differences in the levels of IL-2 between psoriasis patients and healthy controls in a Japanese population. Genetic differences in study populations can explain, in part, the controversial data between our study and Takahashi's [25].

The pathophysiological role of Th1 and Th17 phenotypes in psoriasis has been described previously [1]. The differentiation of Th17 cells is mediated by IL- 6 in an environment containing IL-23. Th17 is a pro-inflammatory phenotype that produces mainly IL-17 and stimulates the proliferation of keratinocytes and may worsen psoriatic lesions [30]. Our study demonstrated that IL-17 levels are higher in patients than in healthy controls, corroborating the results of previous studies [25, 31, 32]. Nevertheless, Nakajima et al. (2013) and Yilmaz et al. (2012) did not find significant differences in the levels of IL-17 between patients and controls [33, 34]. These contradictory results may be explained, in part, by differences in cytokine assays, namely ELISA test versus

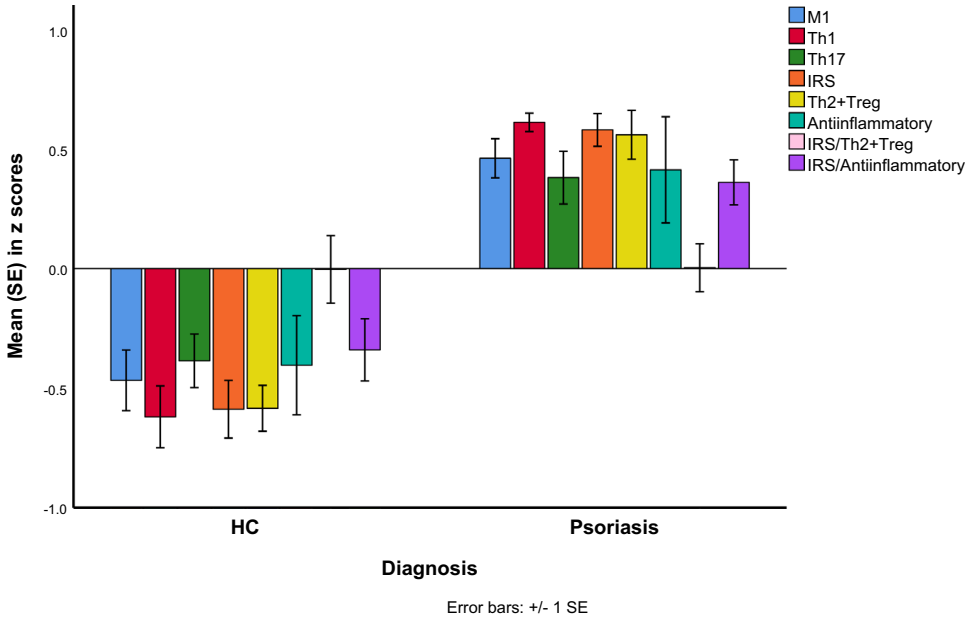


**Fig. 2** Eight z unit weighted composite scores based on cytokine assays in patients with psoriasis and healthy controls (HC). M1: index of macrophage 1 function, computed as z interleukin-1 (zIL-1) + zIL-6 + zTNF-α; Th1: index of T helper cell function, computed as zIL-2 + zIL-12 + zINF-γ; Th17: index of Th17 cell function, computed as zIL-6 + zIL-17; IRS: index of the immune-inflammatory Response System, computed as z(sum of all cytokines in the M1 + Th1 + zTh17 profiles); Th2 + Treg: index of Th2 and Tregulatory functions, computed as zIL-4 + zIL-10 + zTGF-β. Antiinflammatory: index of anti-inflammatory activities, computed as zIL-4 + zIL-10 + zTGF-β + zAdiponectin; IRS/Th2 + Treg: ratio of IRS/Th2 + Treg, computed as z(sum of all z scores of M1 + Th1 + Th17 cytokines) − z(zIL-4 + zIL-10 + zTGF-β); IRS/Antiinflammatory: computed as zIRS − z(zIL-4 + zIL-10 + zTGF-β + zAdiponectin); IL, Interleukin; TNF-α, Tumour Necrosis Factor-alpha; IFN-γ, Interferon-gamma; TGF-β, Transforming Growth Factor-beta. All indices are significantly different between psoriasis patients and controls ($p < 0.05$), except the antiinflammatory and IRS/Th2 + Treg indices (see Table 4 for exact p-values and effect sizes)

**Table 6** Binary logistic regression analyses with psoriasis as the dependent variable (and controls as the reference group) and the composite scores and adiponectin as input variables

| Explanatory variables | Wald | *df* | *P* | OR | 95% CI |
|---|---|---|---|---|---|
| IRS | 8.32 | 1 | 0.004 | 1.68 | 1.68–15.20 |
| Th2 + Treg | 5.53 | 1 | 0.019 | 1.27 | 1.28–14.44 |
| Adiponectin | 22.66 | 1 | <0.001 | 0.002 | 0.002–0.072 |

*IRS* Immune-inflammatory response system, *Th* lymphocyte T helper, *Treg* regulatory T cells

IRS: computed as z(sum of all cytokines in M1 + Th1 + zTh17 profiles)

M1: computed as z interleukin-1 (zIL-1) + zIL-6 + zTNF-α

Th1: zIL-2 + zIL-12 + zINF-γ

Th17: computed as zIL-6 + IL-17

Th2 + Treg: computed as zIL-4 + zIL-10 + zTGF-β

Predicted psoriasis with a 97.1% sensitivity and 94.0% specificity ($\chi^2 = 142.34$, $df = 3$, $p < 0.001$, Nagelkerke = 0.862)

the more sensitive Luminex technique used in the present study [35].

To interpret the cytokine profiles in psoriasis we have computed specific cytokine indices as explained before. First, the cytokines values were transformed or standardized into z scores, which allows comparison of variables with different units or scales [20]. Second, z unit weighted composite scores were computed based on immune phenotype patterns including macrophage type 1 (M1), Th1 and Th17 phenotypes. This procedure revealed that the Th1 (IL-2, IL-12, IFN-γ), M1 (IL-1, IL-6, TNF-α) and Th17 (IL-6, IL-17) phenotypes are all strongly activated and interconnected in psoriasis. These data extent previous knowledge indicating a prominent role of the Th1 [36] and Th17 profiles and the maintenance of the inflammatory response by M1 macrophagic cytokines including IL-1β, IL-6 and TNF-α [1, 14, 22].

A major finding of the current study is that the anti-inflammatory profile (comprising IL-4, IL-10, TGF-β, and adiponectin) is significantly elevated in psoriasis and even significantly associated with the pro-inflammatory responses, including M1, Th1 and Th17, and that the inflammatory/anti-inflammatory index is significantly increased in psoriasis. The latter may be attributed to a relative deficiency in the anti-inflammatory profile, which in turn may be explained by lowered levels of TGF-β and

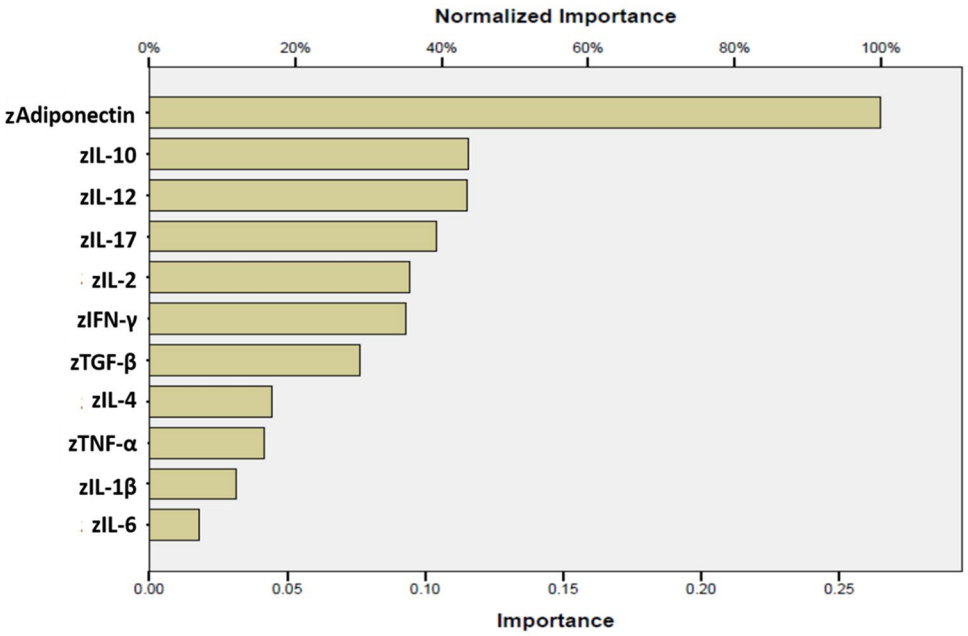


**Fig. 3** Importance and normalized importance of the 11 cytokines for psoriasis. *IL* Interleukin, *IFN-γ* interferon-gamma, *TNF-α* tumour necrosis factor-alpha, *TGF-β* transforming Growth factor-beta

adiponectin, but not IL-4 and IL-10, in psoriasis as compared with healthy controls.

The increased levels of IL-4 and IL-10 may be explained by a compensatory effect to control the primary immune-inflammatory process as part of the compensatory immune- regulatory reflex system. Importantly, the regulatory cytokine IL-4 attenuates the immune– inflammatory response and may even aggravate psoriatic lesions [5]. IL-10 is another negative immuno-regulatory cytokine [37], which may play a key role in psoriasis. For example, Asadullah et al. (1998) proposed that IL-10 may attenuate T effector cell activation by suppressing antigen- presenting cells and that IL-10 may have antipsoriatic activity since its secretion is able to change the inflammatory pattern of psoriasis [38]. This hypothesis is in agreement with other results relating diminished levels of IL-10 with the severity of psoriasis [25, 39] or that IL-10 is decreased in patients with an increased PASI [5], whilst patients with low PASI have higher IL-10 levels [40].

The results on TGF-β in psoriasis are controversial. TGF-β is a growth factor necessary for the differentiation of Treg cells and, consequently, for the regulation of the immune response [41]. Our data are in agreement with a previous study that demonstrated lowered levels of TGF-β in patients with psoriasis [42]. However, other studies found no significant changes [43, 44]. TGF-β may be important in the pathogenesis of psoriasis since this cytokine is able to regulate the proliferation of keratinocytes and therefore may improve psoriasis [45]. By inference, the lowered TGF-β levels observed here may negatively affect the outcome of psoriasis. In addition, reduced levels of TGF-β may reflect lower regulation of the immune response, which contributes to the maintenance of the inflammatory state.

Previous studies showed that the secretion of adiponectin is inversely related to serum levels of pro-inflammatory cytokines including TNF-α and IL-6 [46, 47]. The decreased levels of adiponectin are often related to the development of obesity and MetS [48, 49]. Importantly, our data show that the most important marker in psoriasis is lowered adiponectin levels, independently of obesity or MetS. These results extend those of previous studies showing lower adiponectin levels in patients than in controls, independently of obesity and cardiometabolic risk factors [50]. Nevertheless, a meta-analysis did not find a significant difference in adiponectin levels between patients with psoriasis and controls [15]. These differences may be due to distinct study designs, differences in methodology used to measure adiponectin or the presence of confounding variables, such as genetic heterogeneity of individuals.

The main limitation is that this is a cross-sectional study, which does not allow make inferences on causal relationships. A second limitation is that the study sample included here shows a rather low disease activity as indicated by PASI values and, therefore, our findings may not be applicable to patients with more active disease. Further studies should be carried out in psoriasis patients with higher PASI scores in order to validate the cytokine profiles when the disease is more aggressive. A third limitation, we included patients with psoriatic arthritis ($n=10$) and guttate psoriasis ($n=3$) that had more pronounced immune profiles than plaque-type psoriasis ($n=56$). However, we performed some analyses and inspected diagrams and did not see any differences, but the number was too low to analyze the data statistically.

However, the present study also has strengths. To our knowledge, this is the first study to evaluate cytokine in patients with psoriasis using new z unit weighted composite scores reflecting cytokine profiles. Moreover, cytokines levels were evaluated with a Luminex® platform, a more sensitive technology than ELISA. Another strength is that this study combines a multivariate statistical approach, which allows controlling for many possible confounding variables including sex, age, MetS and BMI.

In conclusion, increased M1, Th1, Th2 and Th17 profiles together with lowered TGF-β and adiponectin production were strongly associated with psoriasis. We propose a model based on higher IRS and Th2 + Treg values coupled with low adiponectin values as a criterion to externally validate the diagnosis of psoriasis. The key feature of psoriasis is lowered adiponectin, which may play a role in the modulation of the chronic inflammatory response in psoriasis. Therefore, adiponectin could be a new drug target to treat psoriasis.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no competing interests.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its latter amendments or comparable ethical standards.

**Informed consent** Al the participants included in this study provided written informed consent.

## References

1. Ogawa E, Sato Y, Minagawa A, Okuyama R. Pathogenesis of psoriasis and development of treatment. J Dermatol. 2018;45:264–72. https://doi.org/10.1111/1346-8138.14139.
2. Deng Y, Chang C, Lu Q. The inflammatory response in psoriasis: a comprehensive review. Clin Rev Allergy Immunol. 2016;50:377–89. https://doi.org/10.1007/s12016-016-8535-x.
3. Kagami S, Rizzo HL, Lee JJ, Koguchi Y, Blauvelt A. Circulating Th17, Th22, and Th1 cells are increased in psoriasis. J Invest Dermatol. 2010;130:1373–83. https://doi.org/10.1038/jid.2009.399.
4. Cardoso PRG, de Andrade Lima EV, de Andrade Lima MM, et al. Clinical and cytokine profile evaluation in Northeast Brazilian psoriasis plaque-type patients. Eur Cytokine Netw. 2016;27:1–5. https://doi.org/10.1684/ecn.2016.0371.
5. Roberti ML, Ricottini L, Capponi A, Sclauzero E, Vicenti P, Fiorentini E, et al. Immunomodulating treatment with low dose interleukin-4, interleukin-10 and interleukin-11 in psoriasis vulgaris. J Biol Regul Homeost Agents. 2014;28:133–9. https://doi.org/10.1111/dth.12174.
6. Onderdijk AJ, Baerveldt EM, Kurek D, Kant M, Florencia EF, Debets R, et al. IL-4 Downregulates IL-1β and IL-6 and Induces GATA3 in Psoriatic Epidermal Cells: Route of Action of a Th2 Cytokine. J Immunol. 2015;195:1744–52. https://doi.org/10.4049/jimmunol.1401740.
7. Guenova E, Skabytska Y, Hoetzenecker W, Weindl G, Sauer K, Tham M, et al. IL-4 abrogates T(H)17 cell-mediated inflammation by selective silencing of IL-23 in antigen-presenting cells. Proc Natl Acad Sci USA. 2015;112:2163–8. https://doi.org/10.1073/pnas.1416922112.
8. Takeshita J, Grewal S, Langan SM, Mehta NN, Ogdie A, Van Voorhees AS, et al. Psoriasis and comorbid diseases: Epidemiology. J Am Acad Dermatol. 2017;76:377–90. https://doi.org/10.1016/j.jaad.2016.07.064.
9. Caso F, Del Puente A, Oliviero F, Peluso R, Girolimetto N, Bottiglieri P, et al. Metabolic syndrome in psoriatic arthritis: the interplay with cutaneous involvement. Evidences from literature and a recent cross-sectional study. Clin Rheumatol. Clin Rheumatol. 2018;37:579–86. https://doi.org/10.1007/s10067-017-3975-0.
10. Fantuzzi G. Adiponectin and inflammation: consensus and controversy. J Allergy Clin Immunol. 2008;121:326–30. https://doi.org/10.1016/j.jaci.2007.10.018.
11. Versini M, Jeandel P-Y, Rosenthal E, Shoenfeld Y. Obesity in autoimmune diseases: not a passive bystander. Autoimmun Rev. Elsevier B.V. 2014;13:981–1000. https://doi.org/10.1016/j.autrev.2014.07.001.
12. Campanati A, Orciani M, Consales V, Lazzarini R, Ganzetti G, Di Benedetto G, et al. Characterization and profiling of immunomodulatory genes in resident mesenchymal stem cells reflect the Th1-Th17/Th2 imbalance of psoriasis. Arch Dermatol Res. 2014;306:915–20. https://doi.org/10.1007/s00403-014-1493-3.
13. Guimarães PM, Scavuzzi BM, Stadtlober NP, Franchi Santos LFDR, Lozovoy MAB, Iriyoda TMV, et al. Cytokines in systemic lupus erythematosus: far beyond Th1/Th2 dualism lupus: cytokine profiles. Immunol Cell Biol. 2017;95:824–31. https://doi.org/10.1038/icb.2017.53.
14. Dowlatshahi EA, van der Voort EAM, Arends LR, Nijsten T. Markers of systemic inflammation in psoriasis: a systematic review and meta-analysis. Br J Dermatol. 2013;169:266–82. https://doi.org/10.1111/bjd.12355.
15. Zhu K-J, Shi G, Zhang C, Li M, Zhu C-Y, Fan Y-M. Adiponectin levels in patients with psoriasis: a meta-analysis. J Dermatol. 2013;40:438–42. https://doi.org/10.1111/1346-8138.12121.
16. Fredriksson T, Pettersson U. Severe psoriasis–oral therapy with a new retinoid. Dermatologica. 1978;157:238–44.
17. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112:2735–52. https://doi.org/10.1161/CIRCULATIONAHA.105.169404.
18. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311:507–20. https://doi.org/10.1001/jama.2013.284427.
19. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B. 1995;57:289–300. https://doi.org/10.2307/2346101.
20. Maes M, Carvalho AF. The compensatory immune-regulatory reflex system (CIRS) in depression and bipolar disorder. Mol Neurobiol. 2018. https://doi.org/10.1007/s12035-018-1016-x.

21. Ginhoux F, Schultze JL, Murray PJ, Ochando J, Biswas SK. New insights into the multidimensional concept of macrophage ontogeny, activation and function. Nat Immunol. 2016;17:34–40. https://doi.org/10.1038/ni.3324.
22. Campanati A, Orciani M, Lazzarini R, Ganzetti G, Consales V, Sorgentoni G, et al. TNF-α inhibitors reduce the pathological Th 1–Th 17/Th 2 imbalance in cutaneous mesenchymal stem cells of psoriasis patients. Exp Dermatol [Internet]. 2017;26:319–24. https://doi.org/10.1111/exd.13139.
23. Skendros P, Papagoras C, Lefaki I, Giatromanolaki A, Kotsianidis I, Speletas M, et al. Successful response in a case of severe pustular psoriasis after interleukin-1β inhibition. Br J Dermatol. 2017;176:212–5. https://doi.org/10.1111/bjd.14685.
24. Steinman L. A brief history of T(H)17, the first major revision in the T(H)1/T(H)2 hypothesis of T cell-mediated tissue damage. Nat Med. 2007;13:139–45. https://doi.org/10.1038/nm1551.
25. Takahashi H, Tsuji H, Hashimoto Y, Ishida-Yamamoto A, Iizuka H. Serum cytokines and growth factor levels in Japanese patients with psoriasis. Clin Exp Dermatol. 2010;35:645–9. https://doi.org/10.1111/j.1365-2230.2009.03704.x.
26. Brito-Luna MJ, Villanueva-Quintero DG, Sandoval-Talamantes AK, Fafutis-Morris M, Graciano-Machuca O, Sanchez-Hernandez PE, et al. Correlation of IL-12, IL-22, and IL-23 in patients with psoriasis and metabolic syndrome. Preliminary report. Cytokine. 2016;85:130–6. https://doi.org/10.1016/j.cyto.2016.06.020.
27. Pietrzak A, Zalewska A, Chodorowska G, Nockowski P, Michalak-Stoma A, Osemlak P, et al. Genes and structure of selected cytokines involved in pathogenesis of psoriasis. Folia Histochem Cytobiol. 2008;46:11–21. https://doi.org/10.2478/v10042-008-0002-y.
28. Bos F, Capsoni F, Molteni S, Raeli L, Diani M, Altomare A, et al. Differential expression of interleukin-2 by anti-CD3-stimulated peripheral blood mononuclear cells in patients with psoriatic arthritis and patients with cutaneous psoriasis. Clin Exp Dermatol. 2014;39:385–90. https://doi.org/10.1111/ced.12251.
29. Khandpur S, Gupta V, Das D, Sharma A. Is there a correlation of serum and tissue T helper-1 and -2 cytokine profiles with psoriasis activity and severity? A cross-sectional study. Indian J Dermatol Venereol Leprol. 2017;84:414–8. https://doi.org/10.4103/ijdvl.IJDVL_471_17.
30. Lynde CW, Poulin Y, Vender R, Bourcier M, Khalil S. Interleukin 17A: toward a new understanding of psoriasis pathogenesis. J Am Acad Dermatol. 2014;71:141–50. https://doi.org/10.1016/j.jaad.2013.12.036.
31. Coimbra S, Oliveira H, Reis F, Belo L, Rocha S, Quintanilha A, et al. Interleukin (IL)-22, IL-17, IL-23, IL-8, vascular endothelial growth factor and tumour necrosis factor-α levels in patients with psoriasis before, during and after psoralen-ultraviolet A and narrowband ultraviolet B therapy. Br J Dermatol. 2010;163:1282–90. https://doi.org/10.1111/j.1365-2133.2010.09992.x.
32. Fotiadou C, Lazaridou E, Sotiriou E, Gerou S, Kyrgidis A, Vakirlis E, et al. IL-17A, IL-22, and IL-23 as markers of psoriasis activity: a cross-sectional, hospital-based study. J Cutan Med Surg. 2015;19:555–60. https://doi.org/10.1177/1203475415584503.
33. Nakajima H, Nakajima K, Tarutani M, Sano S. Clear association between serum levels of adipokines and T-helper 17-related cytokines in patients with psoriasis. Clin Exp Dermatol. 2013;38:66–70. https://doi.org/10.1111/j.1365-2230.2012.04465.x.
34. Yilmaz SB, Cicek N, Coskun M, Yegin O, Alpsoy E. Serum and tissue levels of IL-17 in different clinical subtypes of psoriasis. Arch Dermatol Res. 2012;304:465–9. https://doi.org/10.1111/j.1365-2230.2012.04465.x.
35. Elshal MF, McCoy JP. Multiplex bead array assays: performance evaluation and comparison of sensitivity to ELISA. Methods. 2006;38:317–23. https://doi.org/10.1016/j.ymeth.2005.11.010.
36. Quaglino P, Bergallo M, Ponti R, Barberio E, Cicchelli S, Buffa E, et al. Th1, Th2, Th17 and regulatory T cell pattern in psoriatic patients: modulation of cytokines and gene targets induced by etanercept treatment and correlation with clinical response. Dermatology. 2011;223:57–67. https://doi.org/10.1159/000330330.
37. Mavropoulos A, Varna A, Zafiriou E, Liaskos C, Alexiou I, Roussaki-Schulze A, et al. IL-10 producing Bregs are impaired in psoriatic arthritis and psoriasis and inversely correlate with IL-17- and IFNγ-producing T cells. Clin Immunol. 2017;184:33–41. https://doi.org/10.1016/j.clim.2017.04.010.
38. Asadullah K, Sterry W, Stephanek K, Jasulaitis D, Leupold M, Audring H, et al. IL-10 is a key cytokine in psoriasis. Proof of principle by IL-10 therapy: a new therapeutic approach. J Clin Invest. 1998;101:783–94. https://doi.org/10.1016/j.clim.2017.04.010.
39. Jin S-P, Koh S-J, Yu D-A, Kim M-W, Yun HT, Lee DH, et al. Imiquimod-applied Interleukin-10 deficient mice better reflects severe and persistent psoriasis with systemic inflammatory state. Exp Dermatol. 2018;27:43–9. https://doi.org/10.1111/exd.13403.
40. Antiga E, Volpi W, Cardilicchia E, Maggi L, Filì L, Manuelli C, et al. Etanercept downregulates the Th17 pathway and decreases the IL-17 +/IL-10 + cell ratio in patients with psoriasis vulgaris. J Clin Immunol. 2012;32:1221–32. https://doi.org/10.1007/s10875-012-9716-x.
41. Han G, Williams CA, Salter K, Garl PJ, Li AG, Wang X-J. A role for TGFbeta signaling in the pathogenesis of psoriasis. J Invest Dermatol. 2010;130:371–7. https://doi.org/10.1038/jid.2009.252.
42. Doi H, Shibata M-A, Kiyokane K, Otsuki Y. Downregulation of TGFbeta isoforms and their receptors contributes to keratinocyte hyperproliferation in psoriasis vulgaris. J Dermatol Sci. 2003;33:7–16. https://doi.org/10.1016/S0923-1811(03)00107-5.
43. Flisiak I, Chodynicka B, Porebski P, Flisiak R. Association between psoriasis severity and transforming growth factor beta(1) and beta (2) in plasma and scales from psoriatic lesions. Cytokine. 2002;19:121–5. https://doi.org/10.1006/cyto.2002.1953.
44. Zaher H, Shaker OG, EL-Komy MHM, El-Tawdi A, Fawzi M, Kadry D. Serum and tissue expression of transforming growth factor beta 1 in psoriasis. J Eur Acad Dermatol Venereol. 2009;23:406–9. https://doi.org/10.1111/j.1468-3083.2008.03064.x.
45. Di Fusco D, Laudisi F, Dinallo V, Monteleone I, Di Grazia A, Marafini I, et al. Smad7 positively regulates keratinocyte proliferation in psoriasis. Br J Dermatol. 2017;177:1633–43. https://doi.org/10.1111/bjd.15703.
46. Sereflican B, Goksugur N, Bugdayci G, Polat M, Haydar Parlak A. Serum visfatin, adiponectin, and tumor necrosis factor alpha (TNF-α) levels in patients with psoriasis and their correlation with disease severity. Acta Dermatovenerol Croat. 2016;24:13–9.
47. Gerdes S, Rostami-Yazdi M, Mrowietz U. Adipokines and psoriasis. Exp Dermatol. 2011;20:81–7. https://doi.org/10.1111/j.1600-0625.2010.01210.x.
48. Baran A, Flisiak I, Jaroszewicz J, Świderska M. Effect of psoriasis activity on serum adiponectin and leptin levels. Adv Dermatology Allergol. 2015;2:101–6. https://doi.org/10.5114/pdia.2014.40960.
49. Eder L, Jayakar J, Pollock R, Pellett F, Thavaneswaran A, Chandran V, et al. Serum adipokines in patients with psoriatic arthritis and psoriasis alone and their correlation with disease activity. Ann Rheum Dis. 2013;72:1956–61. https://doi.org/10.1136/annrheumdis-2012-202325.
50. Li RC, Krishnamoorthy P, DerOhannessian S, Doveikis J, Wilcox M, Thomas P, et al. Psoriasis is associated with decreased plasma adiponectin levels independently of cardiometabolic risk factors. Clin Exp Dermatol. 2014;39:19–24. https://doi.org/10.1111/ced.12250.