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Original Article

Adipokines in Subcutaneous Adipose Tissue are Associated with Metabolic Syndrome in Psoriasis Patients

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ABSTRACT

Background: Psoriasis is associated with metabolic syndrome (MetS), and both psoriasis and MetS are associated with abnormal adipokine secretion. Much is unknown regarding the association between adipokine gene expression in subcutaneous adipose tissue (SAT) and levels of circulating adipokines in psoriasis patients with or without MetS. We examined messenger ribonucleic acid (mRNA) expression levels in SAT and circulating levels of 4 major adipokines, namely, tumor necrosis factor α (TNF-α), adiponectin, leptin, and interleukin 6 (IL-6).

Methods: Twenty-nine psoriasis patients and 25 control patients were studied; 27 of the psoriasis patients and controls did not undergo systemic therapy. One psoriasis patient was treated with TNF-α antagonist and another was treated with retinoids (etretinate). Among the 29 psoriasis patients, 24 were treated with topical therapies (topical steroids and vitamin D analogues) and 5 were not. The participants were subdivided into 4 groups based on the presence of psoriasis and MetS. Serum concentrations of adipokines were measured in all participants, and SAT samples were collected from 18 psoriasis patients and 9 controls. Topical therapies were avoided for at least 1 week before collecting biopsy specimens. Adipokine mRNA expression in SAT was measured using quantitative real-time reverse transcription polymerase chain reaction (real-time RT-PCR) amplification.

Results: Psoriasis Area and Severity Index (PASI) score, serum leptin concentration, and leptin mRNA expression in SAT were significantly higher in psoriasis patients with MetS than in those without MetS. IL-6 mRNA expression in SAT was significantly higher in controls than in psoriasis patients.

Conclusions: The association of psoriasis activity, adipokines, and MetS was confirmed. SAT from psoriasis patients was involved in increased leptin and decreased IL-6 mRNA expression. This is the first indication that SAT adipokines are involved in the pathophysiology of psoriasis.

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KEYWORDS: adipokines, psoriasis, metabolic syndrome, subcutaneous adipose tissue (SAT)

Several studies have shown that psoriasis is associated with metabolic syndrome (MetS).[1)] Psoriasis patients with MetS have higher Psoriasis Area Severity Index (PASI) scores than do those without MetS[2)]; however, the mecha-

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nisms underlying this association have not been clarified. Adipose tissue is both a reservoir for energy storage and an active endocrine tissue. It secretes a number of bioactive peptides and proteins, called adipokines.[3] Psoriasis and MetS are associated with abnormal adipokine secretion.[4] Visceral fat-type obesity induces disturbance of adipokine secretion in visceral adipose tissue (VAT). However, in persons with type 2 diabetes mellitus, expressions of tumor necrosis factor α (TNF-α), adiponectin, and leptin mRNA are significantly greater in subcutaneous adipose tissue (SAT) than in VAT,[5] which indicates that SAT, too, secretes adipokines.

No studies have examined expression of adipokine mRNA in SAT of persons with psoriasis, and the association of adipokine gene expression in SAT and circulating levels of adipokines in this population is poorly understood. In addition, it is unclear whether adipokine gene expression in SAT differs between psoriasis patients with and without MetS. Thus, we examined mRNA expression levels in SAT and circulating levels of 4 major adipokines—TNF-α, adiponectin, leptin, and interleukin (IL)-6—in psoriasis patients and control patients. In addition, we analyzed adipokine messenger ribonucleic acid (mRNA) expression levels in SAT samples from beneath lesional psoriatic skin and those from beneath apparently normal skin from the controls. We attempted to determine whether SAT has a role in the association between psoriasis and MetS.

Methods

Clinical evaluation of psoriasis patients and controls

All participants gave their written informed consent before being enrolled in this study. The study protocol was approved by the Institutional Review Board of Toho University (approval number: 2010-044). Twenty-eight participants with psoriasis vulgaris and 1 with psoriatic arthritis were enrolled. The clinical stage of psoriasis vulgaris is characterized by skin manifestations only, and new psoriasis skin lesions may appear. During the clinical stage of psoriatic arthritis, symptoms include skin and joint manifestations. The present control group comprised 25 persons without psoriasis. Twenty-seven psoriasis patients and controls did not undergo systemic immunosuppressant therapy, such as ultraviolet phototherapy, cyclosporin, methotrexate, retinoids, systemic glucocorticosteroids, and biological therapies (TNF-α antagonist and IL-12/23 antagonist). One psoriasis patient was treated with TNF-α antagonist and 1 psoriasis patient was treated with retinoids (etretinate). Twenty-four psoriasis patients were treated with topical therapies (topical steroids and vitamin D analogues). The most potent topical steroid used was betamethasone butyrate propionate ointment. The dosage of topical steroids was less than 17.5 g/week. Five psoriasis patients were not treated with topical therapies. Among controls, the diagnoses were chronic eczema (n = 2), herpes zoster (n = 1), tinea unguium (n = 1), and patients who underwent skin surgery for acanthosis nigricans (n = 1), basal cell carcinoma (n = 2), Bowen's disease (n = 5), epidermal cyst (n = 2), extramammary Paget's disease (n = 1), lipoma (n = 5), mastocytoma (n = 1), sebaceous carcinoma (n = 1), seborrheic keratosis (n = 1), soft fibroma (n = 1), and squamous cell carcinoma (n = 1). Psoriasis patients and controls were subdivided into 4 groups based on the presence of psoriasis and MetS. We measured weight, height, waist circumference, systolic blood pressure (BP), and diastolic BP of all participants. Body mass index (BMI) was calculated as weight divided by the square of the height (kg/m^2). In all psoriasis patients, disease severity was assessed by means of PASI score by the same physician.

Metabolic syndrome

The Japan Society for the Study of Obesity (JASSO) has defined the Japanese diagnostic criteria for MetS, which are similar to those used by the International Diabetes Federation (IDF).[6] We used the JASSO diagnostic criteria for MetS in this study.

Biochemical and hormonal assays

Serum samples were collected from psoriasis patients and controls at random time points during the day. Random plasma glucose, glycated hemoglobin (HbA1c), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride concentrations were measured using routine methods at the clinical laboratory of our hospital. HbA1c was measured using the Japan Diabetes Society (JDS) method, which yields values 0.4% lower than National Glycohemoglobin Standardization Program (NGSP) values.[7] Serum concentrations of TNF-α and IL-6 were measured using enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions (R&D Systems, Inc., Minneapolis, MN, USA). Serum adiponectin concentrations were measured using latex immune-nephelometry measurement kits (Mitsubishi Chemical Medience, Corp., Tokyo, Japan), and serum leptin concentrations were measured

using radioimmunoassay kits (Millipore, Corp., St. Charles, MO, USA).

Collection of SAT

During skin biopsies, 18 SAT samples were collected from beneath lesional psoriatic skin of 18 patients with psoriasis vulgaris; 16 psoriasis patients did not undergo systemic therapy. One psoriasis patient was treated with a TNF-α antagonist, and 1 psoriasis patient was treated with retinoids (etretinate). Fourteen psoriasis patients were treated with topical therapies (topical steroids and vitamin D analogues). Among these 14 psoriasis patients, topical therapies for psoriatic skin lesions at the biopsy site were avoided for at least 1 week before biopsy. Topical therapies for psoriatic skin lesions at non-biopsy sites were continued. Four psoriasis patients were not treated with topical therapies. During skin tumor resection surgery or skin grafting surgery, 9 control SAT samples were taken from 9 patients without psoriasis. The SAT of controls was carefully collected from beneath apparently normal skin near tumors or skin graft donor sites. The fresh SAT samples were immediately incubated in RNA*later*™ RNA Stabilization Reagent (Qiagen GmbH, Hilden, Germany) for 24 hours. After incubation, tissue samples were frozen and stored at −80℃ until RNA isolation. The skin and SAT samples collected for pathologic investigation were fixed immediately with 10% formalin, to avoid secondary degeneration. Formalin-fixed paraffin embedded sections were stained with hematoxylin-eosin (HE).

RNA isolation and cDNA synthesis

Total RNA was isolated from SAT samples using the RNeasy® Lipid Tissue Mini Kit (Qiagen) according to the manufacturer's instructions. Isolated RNA was quantified by measuring absorbance at 230, 260, and 280 nm. RNA samples were stored at −80℃ until they were used for cDNA synthesis. Reverse transcription of RNA was carried out using the High-Capacity RNA-to-cDNA™ Kit (Applied Biosystems Life Technologies, Corp., Carlsbad, CA, USA) and the GeneAmp® PCR System 9700 (Applied Biosystems Life Technologies). The cDNA samples were stored at −80℃ until gene expression was measured.

Real-time RT-PCR protocol

cDNA was used as a template for quantitative real-time reverse transcription polymerase chain reaction (real time RT-PCR) amplification. Expression of mRNA for TNF-α, adiponectin, leptin, and IL-6 was measured using real time RT-PCR, with 18S ribosomal RNA (18S rRNA) as an endogenous control, using TaqMan® Fast Advanced Master Mix (Applied Biosystems Life Technologies) on a StepOnePlus™ Real-Time PCR System (Applied Biosystems Life Technologies) according to the manufacturer's instructions. The TaqMan® PCR primers were obtained from Qiagen. The cDNA of adipokines and 18S rRNA were amplified in different wells and in duplicate. The increase in fluorescence was measured in real time. Data were obtained as threshold cycle (Ct) values, and the mean Ct of duplicates for each sample was calculated. The expression levels of adipokine mRNA were normalized to the 18S rRNA. The data were analyzed by relative quantitation using the comparative Ct method.

Statistical analysis

All numerical data are expressed as mean ± standard deviation (SD). The statistical significance of differences in group means was analyzed using the unpaired Student *t* test for parametric variables and the Mann-Whitney *U* test for nonparametric variables. The means of the 4 groups were compared using the Kruskal-Wallis test followed by the Steel-Dwass post-hoc test, because the relatively small sample size undermined the normal distributional assumptions of a parametric test like one-way analysis of variance (ANOVA) followed by the Tukey-Kramer post-hoc method. Multivariable analysis was used to evaluate sex differences in clinical characteristics in multiple logistic regression analysis including all clinical characteristics, such as sex, age, weight, BMI, waist circumference, random plasma glucose, HbA1c, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, systolic BP, and diastolic BP, as covariates. A p-value of less than 0.05 was considered statistically significant.

Results

Table 1 shows the clinical characteristics of psoriasis patients and controls in the 4 subgroups. There were significant differences between groups in age and sex ratio. Weight, BMI, waist circumference, and triglycerides were significantly higher in psoriasis patients with MetS and in controls with MetS than in controls without MetS. HDL cholesterol was significantly lower in psoriasis patients with MetS and in controls with MetS than in controls without MetS. HbA1c was significantly higher in controls with MetS than in controls without MetS. Total cholesterol, triglyceride, systolic BP, and diastolic BP were significantly higher in psoriasis patients with MetS than in those without MetS. Diastolic BP was significantly higher in psoriasis patients with MetS than in controls without MetS. PASI

Table 1 Clinical characteristics of psoriasis patients and controls

Characteristic	Controls without MetS (n = 16)	Controls with MetS (n = 9)	Psoriasis patients without MetS (n = 12)	Psoriasis patients with MetS (n = 17)	P value (Kruskal-Wallis test)
Sex (men/women)[a]	3/13	7/2	11/1	13/4	0.0283
Age (years)	73 ± 16[b]	64 ± 14	60 ± 17	54 ± 15[b]	0.0027
Weight (kg)	53.8 ± 7.6[b, c]	73.1 ± 9.2[b]	64.9 ± 16.9	79.4 ± 23.9[c]	0.0000
BMI (kg/m^2)	23.2 ± 3.4[b, c]	27.7 ± 2.7[b]	23.7 ± 4.7	29.0 ± 7.5[c]	0.0038
Waist circumference (cm)	84.0 ± 9.9[b, c, e]	97.3 ± 5.9[b, f]	86.9 ± 11.9	101.7 ± 16.7[c]	0.0012
Random plasma glucose (mg/dl)	103.3 ± 21.1	145.8 ± 53.5	108.3 ± 26.0	118.7 ± 44.5	0.0918
HbA1c (%)	5.38 ± 0.46[b]	7.10 ± 1.35[b]	5.60 ± 0.91	5.98 ± 1.25	0.0042
Total cholesterol (mg/dl)	192.2 ± 33.8	204.9 ± 54.2	185.4 ± 25.3[b]	219.6 ± 26.9[b]	0.0248
HDL cholesterol (mg/dl)	59.6 ± 19.8[b, c]	42.7 ± 9.4[b]	47.5 ± 11.4	45.6 ± 12.1[c]	0.0188
LDL cholesterol (mg/dl)	108.9 ± 26.2	122.6 ± 38.1	114.5 ± 22.8	132.9 ± 36.4	0.1406
Triglycerides (mg/dl)	93.0 ± 57.1[b, c]	262.3 ± 181.4[b]	111.1 ± 29.1[d]	280.7 ± 146.1[c, d]	0.0000
Systolic BP (mmHg)	130.9 ± 14.2[g]	131.7 ± 20.1	119.6 ± 11.6[b]	146.1 ± 14.2[b]	0.0011
Diastolic BP (mmHg)	68.1 ± 9.9[b, g]	77.9 ± 17.1	70.7 ± 10.1[c]	88.0 ± 8.4[b, c]	0.0001
PASI score	—	—	8.5 ± 3.3[e]	15.2 ± 10.3[e]	0.0208

Values are expressed as mean ± standard deviation (SD).
[a]Significant difference on multiple logistic regression analysis
[b, c, d]Different letters indicate statistical difference in analysis by the Kruskal-Wallis test followed by the Steel-Dwass post-hoc test.
[e]Significant difference between groups on Student *t* test
[e]n = 12
[f]n = 8
[g]n = 8
BMI: body mass index, BP: blood pressure, HbA1c: hemoglobin A1c, HDL: high-density lipoprotein, LDL: low-density lipoprotein, MetS: metabolic syndrome, PASI: Psoriasis Area and Severity Index

Table 2 Serum concentrations of adipokines in psoriasis patients and controls

	Controls without MetS (n = 16)	Controls with MetS (n = 9)	Psoriasis patients without MetS (n = 12)	Psoriasis patients with MetS (n = 17)	P value (Kruskal-Wallis test)
TNF-α (pg/ml)	0.43 ± 0.54[a, b]	0.77 ± 0.68	1.45 ± 1.21[a]	12.55 ± 36.87[b]	0.0051
Adiponectin (μg/ml)	14.05 ± 8.22[a, b]	5.84 ± 3.83[a]	9.80 ± 5.49	7.05 ± 4.40[b]	0.0013
Leptin (ng/ml)	9.56 ± 6.34	11.48 ± 7.75	5.73 ± 3.10[a]	13.93 ± 8.38[a]	0.0246
IL-6 (pg/ml)	4.06 ± 4.17	3.52 ± 5.71	4.92 ± 4.87	1.92 ± 1.30	0.4397

Values are expressed as mean ± standard deviation (SD).
[a, b]Different letters indicate statistical difference in analysis by the Kruskal-Wallis test followed by the Steel-Dwass post-hoc test.
IL-6: interleukin 6, MetS: metabolic syndrome, TNF-α: tumor necrosis factor α

score was significantly higher in psoriasis patients with MetS than in those without MetS (Table 1).

Serum TNF-α concentration was significantly higher in psoriasis patients with MetS and in those without MetS than in controls without MetS (Table 2). Serum adiponectin concentration was significantly lower in psoriasis patients with MetS and in controls with MetS than in controls without MetS (Table 2). Serum leptin concentration was significantly higher in psoriasis patients with MetS than in those without MetS (Table 2).

Leptin mRNA expression in SAT was significantly higher in psoriasis patients with MetS than in those without MetS (Table 3). Expression of IL-6 mRNA in SAT was significantly higher in controls overall than in psoriasis patients overall (Table 4). However, serum IL-6 concentration did not significantly differ between controls overall and psoriasis patients overall (Table 5).

In all psoriasis cases, histopathologic findings of psoria-

Table 3 Expression of adipokine mRNA in subcutaneous adipose tissue of psoriasis patients and controls

	Controls without MetS (n = 6)	Controls with MetS (n = 3)	Psoriasis patients without MetS (n = 9)	Psoriasis patients with MetS (n = 9)	P value (Kruskal-Wallis test)
TNF-α	1.50 ± 0.65	1.72 ± 1.22	1.68 ± 0.84	2.18 ± 0.92	0.3722
Adiponectin	2.95 ± 0.95	2.67 ± 0.52	2.38 ± 1.15	3.19 ± 2.00	0.6597
Leptin	1.94 ± 1.17	3.00 ± 2.37	1.53 ± 0.55 *	3.65 ± 1.73 *	0.0393
IL-6	14.45 ± 24.82	41.20 ± 22.84	3.02 ± 5.24	5.94 ± 7.14	0.0137

Values are expressed as mean ± standard deviation (SD) in arbitrary units of the ratio of adipokines to 18S rRNA.
*Significant difference between groups in analysis by the Kruskal-Wallis test followed by the Steel-Dwass post hoc test.
IL-6: interleukin-6, MetS: metabolic syndrome, mRNA: messenger ribonucleic acid, rRNA: ribosomal ribonucleic acid, TNF-α: tumor necrosis factor α

Table 4 Expression of interleukin 6 (IL-6) mRNA in subcutaneous adipose tissue of psoriasis patients and controls

	Controls (n = 9)	Psoriasis patients (n = 18)	P value (Mann-Whitney *U* test)
IL-6	23.37 ± 26.35	4.48 ± 6.26	0.0236

Values are expressed as mean ± standard deviation (SD) in arbitrary units of the ratio of IL-6 to 18S rRNA.
mRNA: messenger ribonucleic acid, rRNA: ribosomal ribonucleic acid

Table 5 Serum concentrations of interleukin 6 (IL-6) in psoriasis patients and controls

	Controls (n = 25)	Psoriasis patients (n = 29)	P value (Mann-Whitney *U* test)
IL-6 (pg/ml)	3.87 ± 4.67	3.16 ± 3.54	0.9654

Values are expressed as mean ± standard deviation (SD).

sis, such as hyperkeratosis, parakeratosis, acanthosis, and perivascular lymphocytic infiltration in superficial dermis, were seen to various degrees. In contrast, no histologic changes, including inflammatory cell infiltration, were detected in SAT from psoriasis patients or controls. The histopathologic findings of SAT inflammation were not found in all cases.

Discussion

To our knowledge, this is the first report of adipokine mRNA expression levels in SAT from psoriasis patients with and without MetS. The first major finding is that serum leptin concentration, leptin mRNA expression in SAT, and PASI score were significantly higher in psoriasis patients with MetS than in those without MetS (Table 1-3).

Obese persons have higher serum leptin concentrations because of leptin resistance caused by obesity.[4,8] Serum leptin concentrations are higher in psoriasis patients than in healthy controls.[9] Serum leptin concentration was positively correlated with BMI,[8] body fat percentage,[10] and PASI score in psoriasis patients.[9] Leptin mRNA expression is significantly higher in SAT than in VAT in lean and obese adults.[11] Leptin mRNA expression in SAT is positively correlated with BMI and waist circumference.[12] Past and present evidence suggests that leptin production by SAT is higher in psoriasis patients with MetS and that leptin produced by SAT is a source of serum leptin.

The main biological effect of leptin is to regulate food consumption and energy expenditure, through the hypothalamus, by reducing appetite. Leptin is also associated with inflammation, immune response, obesity, insulin resistance, and atherosclerosis. It is also a pro-inflammatory cytokine. Leptin expression and the number of leptin receptors in psoriatic skin tissue are higher in patients with se-

vere psoriasis than in those with mild or moderate psoriasis, those with other diseases, or healthy controls.[9] Leptin increases secretion of TNF-α, IL-6, IL-17, IL-22, and interferon-gamma (IFN-γ) by T lymphocytes and keratinocytes.[13] Moreover, leptin induces proliferation of keratinocytes through both autocrine and paracrine effects.[13, 14] These findings suggest that leptin is involved in the pathogenesis of psoriasis. Our findings indicate that increased leptin expression in the SAT of psoriasis patients with MetS may lead to a worsening of psoriasis severity.

Our second major finding is that IL-6 mRNA expression in SAT was significantly lower in psoriasis patients overall than in the controls overall (Table 4). IL-6 is a major inflammatory mediator and has pro- and anti-inflammatory effects.[4, 15] IL-6 is a pleiotropic cytokine in immune regulation, hematopoiesis, inflammation, and oncogenesis,[16] is highly expressed in psoriatic skin,[4, 17] and stimulates keratinocyte proliferation.[17] Serum IL-6 concentration is significantly correlated with BMI and fasting plasma insulin level.[18] However, findings from studies of serum IL-6 levels in psoriasis patients are contradictory. Some found that serum IL-6 level is elevated in psoriasis patients[17]; others reported that serum IL-6 levels in psoriasis patients do not differ from those in healthy control patients.[19] Thus, no associations have been established between IL-6, SAT, and psoriasis.

We found no significant difference in serum IL-6 concentration. IL-6 mRNA expression in SAT was lower in psoriasis patients, but the difference was not significant (Table 2, 3), probably because of the low sample size of the groups. In analysis comparing all controls with all psoriasis patients (*i.e.*, MetS status was disregarded). As expected, IL-6 mRNA expression in SAT significantly differed between psoriasis patients and controls (Table 4). The difference in serum IL-6 concentration remained nonsignificant (Table 5).

Tocilizumab (TCZ) is a humanized monoclonal antibody against IL-6, and its efficacy against inflammatory diseases such as rheumatoid arthritis[20, 21] has been established. However, TCZ was reported to be ineffective in treating psoriasis.[20] Psoriasis developed or exacerbated during TCZ treatment of rheumatoid arthritis, adult-onset Still disease, and psoriatic arthritis.[20–22] These reports suggest that increased IL-6 production is not necessarily associated with psoriasis exacerbation. Our finding of decreased IL-6 production in SAT beneath lesional psoriatic skin may reflect psoriasis activity. Low IL-6 production in SAT might be compensated for by other sources, such as VAT.

In our study, the control and psoriasis groups were not matched for age or sex. Previous studies showed that circulating adiponectin and leptin levels are higher in women than in men[23] and that serum leptin levels progressively increase after puberty in girls but decrease after puberty in boys.[24] However, we believe this limitation can be overcome by using multiple logistic regression analysis.

Another limitation of our study is that topical therapies were continued for psoriatic skin lesions at non-biopsy sites in 24 psoriasis patients. It is probable but not certain that the effects of topical steroid on SAT at biopsy sites completely disappear within 7 days of treatment cessation. Prolonged corticosteroid use can suppress the hypothalamic-pituitary (HPA) axis and cause adrenal insufficiency. Weston et al. studied the effect of topical steroids on the HPA axis in psoriasis patients at different time points.[25] They treated 18 men with psoriasis with 49 g/week of steroid ointment. Plasma cortisol was suppressed in 17% of patients and was normal at 7 days after treatment cessation. Their findings suggest that it is unlikely that the topical therapies used in our study affected systemic inflammation or the kinetics of adipokine secretion, as the topical steroid dosage was less than 17.5 g/week.

Conclusion

PASI score was significantly higher in psoriasis patients with MetS than in those without MetS. Despite the limitations of this study, we have shown that serum TNF-α concentration was higher in psoriasis patients, especially those with MetS, and that serum adiponectin level was lower in participants with psoriasis and MetS. These results confirm those of previous reports. Our finding that expressions of TNF-α and adiponectin mRNA in SAT were similar indicates that SAT from psoriasis patients is not involved in TNF-α and adiponectin production. In contrast, IL-6 mRNA expression in SAT was significantly lower in psoriasis patients, even though there was no difference in serum IL-6 level between psoriasis patients and controls. Future studies should investigate how a lower IL-6 mRNA level in SAT relates to psoriasis skin lesions. The present findings are the first indication of SAT adipokine involvement in the pathophysiology of psoriasis.

Conflict of interest statement: The authors have no conflicts of interest to declare.

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