ORIGINAL ARTICLE

Association of Adipokines, Insulin Resistance, Hypertension and Dyslipidemia in Patients with Psoriasis Vulgaris

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Background: Systemic inflammation in psoriasis causes insulin resistance and cardiovascular diseases. Adipokines are adipose-tissue-derived factors that are involved in metabolic processes. It is thought that these adipokines are associated with the development of psoriasis. **Objective:** The purpose of this study was to determine the changes in adipokine levels, insulin resistance, hypertension, and dyslipidemia over a 12-week period. **Methods:** The study comprised 35 psoriasis patients and 50 controls. Blood samples were obtained twice from the patients, one sample at the start and one at the end of a 12-week follow-up period. The following parameters were assessed in both groups: serum fasting glucose, fasting insulin, homeostasis model assessment-estimated insulin resistance (HOMA-IR) index, serum lipids, adiponectin, leptin, resistin, chemerin, omentin, vaspin, visfatin, retinol-binding protein 4, and high-sensitivity C-reactive protein (hs-CRP) levels; blood pressure; body mass index; and the psoriasis area severity index (PASI) scores. **Results:** The patients showed an improvement in the PASI score and a significant decrease in serum hs-CRP, omentin, and chemerin values. Moreover, at the start of the follow-up, the psoriasis patients had significantly lower levels of adiponectin and visfatin and significantly higher levels of vaspin and resistin than those of the control group. Visfatin levels correlated negatively with low-density lipoprotein (LDL) and cholesterol, while vaspin and omentin levels correlated positively with diastolic blood pressure. Decreased adiponectin levels correlated negatively with diastolic blood pressure and LDL. **Conclusion:** Plasma levels of adipokines might be useful for evaluating the disease activity of psoriasis and its comorbidities. (**Ann Dermatol 28(1) 74~79, 2016**)

INTRODUCTION

Psoriasis vulgaris is an immune-mediated chronic inflammatory disease of the skin[1]. In psoriasis, pathological findings are not confined only to the skin[2]. The pro-inflammatory molecules released during chronic inflammation may lead to the presence of one or more disorders co-occurring with psoriasis, such as atherosclerosis, atherogenesis, insulin resistance, hypertension, obesity, dyslipidemia, metabolic syndrome, and diabetes mellitus type 2[2,3]. As the psoriasis area severity index (PASI) score increases, the risk of these accompanying disorders also increases[4,5]. Obesity triggers inflammatory changes in the body. This inflammation may change the level of adipokines and cytokines. Obesity-induced inflammatory changes may trigger some immune-mediated inflammatory diseases, one of which is psoriasis[6]. In obese patients, the levels of pro-inflammatory adipokines are increased and those of anti-inflammatory adipokines are decreased[1]. There have been various studies on the changes in adipokine levels and insulin resistance in psoriasis patients, but these studies have not reported consistent results. The main purpose

of this study was to determine the effect of decreased PASI scores on adipokine levels, insulin resistance, hypertension, and dyslipidemia.

MATERIALS AND METHODS

This hospital-based, prospective cohort study included 35 psoriasis patients with no evidence of psoriatic arthritis and 50 controls. Both groups were matched in terms of age, gender, and body mass index (BMI). The study was approved by the local ethics committee (IRB No. B.30.2. PAÜ.0.20.05.08-404/056). Written consent forms were signed by the patients volunteering to participate in the study. The study was carried out according to the ethical principles of the Declaration of Helsinki.

Study population

The study consisted of a series of psoriasis patients presenting at the dermatology clinic of a medical school hospital and healthy volunteers of matching age, gender, and BMI as the control group. The criteria for exclusion from the study for both groups were previous phototherapy and/or systemic medical therapy for psoriasis of at least one month duration, age under 18 years, a diffuse skin disease, metabolic syndrome, an accompanying systemic disorder, immunodeficiency, pregnancy, or breast-feeding.

Assessments

All psoriasis patients were clinically examined, and their disease severity and PASI scores were determined. Venous blood samples were obtained twice from the patients on various therapies, once at the start and once at the end of a 12-week follow-up period, and once from the control group. The blood samples were examined for the following: fasting glucose, fasting cholesterol, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), adiponectin, leptin, resistin, chemerin, omentin, vaspin, visfatin, retinol-binding protein 4 (RBP4), and high-sensitive C-reactive protein (hs-CRP). The arterial blood pressure and BMI were determined for all members of both groups. Insulin resistance was evaluated according to the homeostasis model assessment-estimated insulin resistance (HOMA-IR) index.

Sample collection

After an 8-hour fasting period, 15 ml of venous blood were drawn from the antecubital vein of all members of both groups. After separation of the serum, levels of fasting glucose and insulin, and lipid profiles were quickly determined. The remaining serum sample was kept at -80°C until the time of use. The serum levels of adiponectin, leptin, re-

sistin, chemerin, omentin, vaspin, visfatin, RBP4, and hs-CRP were determined by enzyme-linked immunospecific assay using commercial kits. After a 12-week follow-up, a 15 ml venous blood sample was drawn only from the patients, and the levels of fasting glucose, insulin; and adipokine and lipid profiles were re-evaluated. In order to provide the validity of measurements, the mean values were calculated using computer software.

Statistical analysis

The SPSS software ver. 17.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses of data. The Student's t-test, the Mann-Whitney U test, one-sample Kolmogorov-Smirnov test, and non-parametric correlation tests were performed. A p-value of <0.05 was accepted as statistically significant. Numerical values were expressed as mean $\pm$ standard deviation.

RESULTS

In 35 patients (10 women, 25 men), the mean value of the PASI score at the beginning of the follow-up was 5.8 ± 1.78. In the 35 patients receiving systemic methotrexate therapy, after the 12-week follow-up, there was a significant decrease in the mean PASI score ($p<0.0001$).

At the beginning of the follow-up diastolic blood pressure (DBP, $p=0.032$), cholesterol ($p=0.042$), and LDL ($p=0.022$) levels were markedly higher than those of controls. However, serum HDL, systolic blood pressure, triglyceride, and glucose levels were not significantly different. Psoriasis patients were insulin resistant (HOMA-IR, 2.98 ± 3.23; normal, <2.5); although, the difference was not significant when compared to controls (Table 1).

Statistical analyses of adipokines and hs-CRP levels between both groups showed that adiponectin ($p<0.0001$) was significantly lower and hs-CRP ($p=0.01$), omentin ($p<0.0001$), resistin ($p<0.0001$), chemerin ($p=0.008$), and vaspin ($p<0.0001$) levels were higher, in the before treatment group than in the control group. Leptin, RBP4 and visfatin levels were similar before treatment, after treatment and in the control group. After treatment with methotrexate, hs-CRP levels were similar to those of control group (Table 2).

With the improvement of PASI, the patient levels of hs-CRP, leptin, omentin, and chemerin decreased significantly. In contrast, serum levels of adiponectin, leptin, RBP4, resistin, vaspin, and visfatin, did not change significantly before and after treatments ($p>0.05$) (Fig. 1, 2).

PASI values were significantly correlated with serum omentin (r=0.416, $p\leq0.01$), chemerin (r=0.614, $p\leq$ 0.01), hs-CRP (r=0.338, $p\leq0.01$), and leptin levels

**Table 1.** Demographics and laboratory findings of the patients and controls

Variable	Patient (n=35)	Control (n=50)	p-value
Age (yr)	44.43±11.59	40.48±13.47	NS
Gender (male:female)	25:10	32:18	NS
BMI (kg/m^2)	27.18±4.8	26.88±4.28	NS
DBP (mmHg)	79±12.11	74±8.3	0.032*
SBP (mmHg)	121.57±14.39	118.5±9.8	NS
Cholesterol (mg/dl)	194.43±43.65	176.44±36.22	0.042*
HDL (mg/dl)	48.48±10.81	47.92±14.1	NS
LDL (mg/dl)	119.71±34.83	102.94±30.78	0.022*
Triglyceride (mg/dl)	134.83±62.46	136.74±137.3	NS
HOMA-IR	2.98±3.23	2.32±1.43	NS
Glucose	106.11±45.37	93.64±11.77	0.06

Values are presented as mean±standard deviation and number. BMI: body mass index, NS: not significant, DBP: diastolic blood pressure, SBP: systolic blood pressure, HDL: high density lipoprotein, LDL: low density lipoprotein, HOMA-IR: homeostasis model assessment-estimated insulin resistance. *$p \leq 0.05$.

Table 2. The comparisons of adipokines among before and after methotrexate treatment and control groups

	Before treatment	After treatment	Control	P1	P2	P3
Adiponectin (ng/ml)	8.53±6.68	8.51±9.4	15.8±8.58	NS	<0.0001*	<0.0001*
hs-CRP (pg/ml)	2.64±1.59	1.99±0.96	1.8±1.32	0.04*	0.01*	NS
Leptin (ng/ml)	2.79±1.79	2.2±1.5	2.82±1.57	NS	NS	NS
Omentin (ng/ml)	55.99±18.62	39.68±19.93	24.52±11.32	0.001*	<0.0001*	<0.0001*
RBP4 (ng/ml)	61.01±6.11	64.56±8.83	61.37±6.9	NS	NS	NS
Resistin (ng/ml)	4.11±1.19	4.25±1.21	3.22±0.88	NS	<0.0001*	<0.0001*
Chemerin (ng/ml)	125.28±39.85	3.7±0.75	100.04±36.86	<0.0001*	0.008*	<0.0001*
Vaspin (pg/ml)	463.53±28.81	456.7±71.16	85.27±37.76	NS	<0.0001*	<0.0001*
Visfatin (ng/ml)	8.37±1.41	9.45±15.3	12.89±27.26	NS	0.054	NS
PASI	5.85±1.78	1.83±2.26	-	<0.0001*	NS	NS

Values are presented as mean±standard deviation. P1: pretreatment and posttreatment comparison, P2: pretreatment and control comparison, P3: posttreatment and control comparison, NS: not significant, hs-CRP: high sensitive C reactive protein, RBP4: retinol binding protein 4, PASI: psoriasis area severity index. *$p \leq 0.05$.
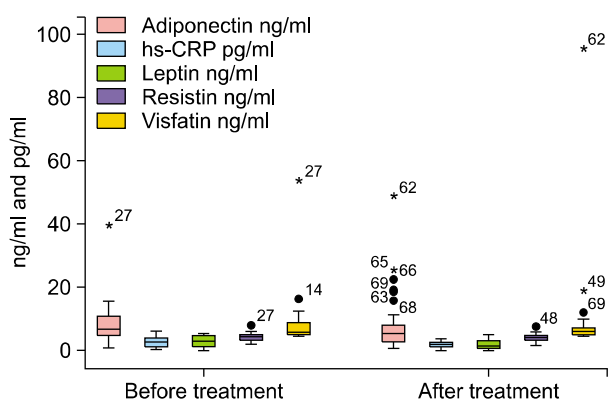
Fig. 1. Follow-up, adiponectin, hs-CRP, leptin, resistin, visfatin levels of psoriasis patients before and after systemic methotrexate treatment. hs-CRP: high-sensitivity C-reactive protein.
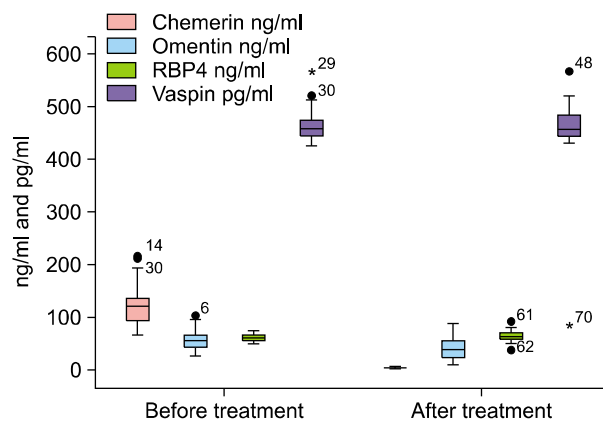
Fig. 2. Follow-up, chemerin, omentin, RBP4, vaspin levels of psoriasis patients before and after systemic methotrexate treatment. RBP4: retinol-binding protein 4.

Table 3. The correlations between adipokines and clinical parameters (r)

	PASI	HOMA-IR	DBP	BMI	LDL	Cholesterol
Omentin	0.416**	−0.117	0.24**	0.49	0.162	0.147
Adiponectin	−0.04	0.113	−0.25**	−0.11	−0.207*	−0.176
Leptin	0.251*	0.097	0.013	0.424**	0.009	0.026
RBP4	−0.018	0.132	0.117	−0.086	−0.024	0.012
Resistin	0.087	−0.044	0.141	0.205*	0.021	0.081
Chemerin	0.614**	0.027	−0.018	0.013	0.110	0.182*
Vaspin	−0.041	0.052	0.221*	−0.047	0.171	0.141
Visfatin	0.168	0.015	−0.026	−0.024	−0.215**	−0.264**
hs-CRP	0.338**	0.05	0.129	0.444**	0.20*	0.207*

PASI: psoriasis area severity index, HOMA-IR: homeostasis model assessment-estimated insulin resistance, DBP: diastolic blood pressure, BMI: body mass index, LDL: low-density lipoprotein, RBP4: retinol binding protein 4, hs-CRP: high sensitive C reactive protein. *$p \leq 0.05$, **$p \leq 0.01$.

(r=0.251, $p \leq 0.05$). Also, the BMI was significantly correlated with serum leptin (r=0.424, $p \leq 0.01$), hs-CRP (r=0.444, $p \leq 0.01$), and resistin (r=0.205, $p \leq 0.05$) levels. A significant positive correlation was observed between DBP and omentin (r=0.24, $p \leq 0.01$), vaspin (r=0.221, $p \leq 0.05$). There was a negative correlation between DBP and adiponectin (r=0.25, $p \leq 0.01$). A significant negative correlation was observed between LDL levels and adiponectin (r=0.207, $p \leq 0.05$) and visfatin (r=0.215, $p \leq 0.01$). There was a negative correlation between LDL and hs-CRP (r=0.20, $p \leq 0.05$) Cholesterol levels were negatively correlated with serum visfatin (r=0.416, $p \leq 0.01$), adiponectin (r=0.614, $p \leq 0.01$). A negative correlation between cholesterol and serum visfatin levels was observed (r=0.264, $p \leq 0.01$). The correlations between adipokines and clinical parameters are presented in Table 3.

DISCUSSION

Psoriasis is a disease accompanied by systemic inflammation[7]. Chronic inflammation predisposes to atherosclerosis and may subsequently lead to cardiovascular disease[8,9]. In the pro-inflammatory setting, insulin resistance may occur, which also causes atherosclerosis[7,10]. Insulin resistance is associated with pro-inflammatory cytokines and adipokines produced by the truncal adipose tissue. It has been observed that adipokine levels in psoriasis patients are similar to those observed in prediabetic individuals[1].

Adipokines, some of which are anti-inflammatory and others pro-inflammatory, have various roles in the systemic inflammation observed in psoriasis patients. There have been numerous studies on the effect of changes in the PASI associated with changes in adipokine levels[6], but the findings in these studies are inconsistent.

High or low levels of adiponectin, an anti-inflammatory protein, have been observed in different inflammatory disorders; and low levels of adiponectin have been found to have a different impact on the course of psoriasis[11]. It has been reported that a decrease in the PASI accompanies decreased levels of leptin. The values of these two parameters in controls have been found to be either higher or lower than those found in psoriasis patients[12,13].

Romani et al.[14] have reported that a decrease in the PASI score is accompanied by an increase in omentin levels. Takahashi et al.[15] have observed higher levels of ometin in controls than in patients and a negative correlation between the PASI and omentin. In our study, serum omentin levels correlated inversely with PASI but serum omentin levels in our patients were higher than in controls. This result may point to the close relationship between ometin and BMI. Of note, our patients had a lower BMI than those in the Takahashi et al.[15] study. A study including patients with psoriatic arthritis[16] has reported significantly higher levels of omentin in patients than in controls.

The decrease in the PASI score may be accompanied by a decrease predominantly in RPB4 and resistin levels, but there are also some studies reporting an elevation in resistin levels[12-15]. One study has determined a positive correlation between RBP4 and PASI values[14]. However, our study showed that resistin levels of patients were higher than controls, but RBP4 levels did not differ significantly between patients and controls. These results may be related to the patient's inflammatory profile, or on lifestyle and genetic factors.

Gisondi et al.[17] found a significant decrease in the PASI score and serum chemerin levels, but no correlation was identified between these two parameters. We observed higher levels of chemerin in patients than in controls and a strongly positive correlation between the PASI score and

chemerin.

A cross-sectional study[18] has reported higher levels of vaspin in psoriasis patients. To the best of our knowledge, there is no prospective study evaluating vaspin levels in the literature. We found that higher levels of vaspin in patients than in controls.

It has been reported that psoriasis patients show significantly higher levels of visfatin than controls[17,19,20]. In our study, we did not find any significant differences in plasma visfatin levels between patients and controls.

Studies on hs-CRP levels have described higher levels of hs-CRP in psoriasis patients compared to controls, with a significant fall in hs-CRP as the PASI score decreases[21-23]. Kanelleas et al.[22] have reported a positive correlation between hs-CRP and psoriasis, but in other studies, no correlation has been found[21,24]. In our study, we found higher levels of hs-CRP in psoriasis patients compared to controls and a strongly positive correlation between the PASI score and hs-CRP levels.

In particular, HOMA-IR values have been found to be higher in patients than in controls[13,25,26]. One study[13] has reported that the decrease in the PASI is accompanied by a significant decrease in HOMA-IR values. In the present study, we found psoriasis patients were insulin resistant. Unfortunately, given our relatively small sample size, the difference was not significant when compared to controls. There are studies reporting the presence or absence of an association between the severity of psoriasis and blood pressure, with inconsistent results[25,26].

The purpose of this study was to assess the effect of decreased PASI on hs-CRP, adipokine levels, hypertension, dyslipidemia, and insulin resistance in psoriasis patients. We found a significant decrease in PASI scores. We observed that in psoriasis patients, the values of adiponectin and visfatin were lower, and values of omentin, resistin, chemerin, vaspin, and hs-CRP were higher than those in controls. Moreover, we found that the PASI score positively correlated with hs-CRP, omentin, and chemerin values. DBP, glucose, LDL, cholesterol were significantly higher in patients than in the controls.

The concurrent decrease in pro-inflammatory hs-CRP and PASI supports the hypothesis that the inflammatory response decreases as the PASI score improves. Moreover, we observed that hs-CRP showed a positive correlation with dyslipidemia, and obesity.

The limitations of our study are the relatively small samples and the short duration of follow-up. The results of our study may be validated by further studies including more patients followed-up for a longer time.

According to the results of our study, hs-CRP, omentin and chemerin may be used as positive markers in the clinical follow-up of psoriasis patients. Determination of these adipokine levels may help the clinician in the clinical follow-up of psoriasis patients. Our data strongly suggest that hs-CRP levels, in particular, will be of considerable help in the clinical follow-up of psoriasis patients. We also believe that the determination of HOMA-IR values, glucose, LDL, and cholesterol levels, as well as blood pressure control will also be of assistance in preventing the onset of psoriasis comorbidities.

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