

Effect of psoriasis activity on serum adiponectin and leptin levels

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Abstract

Introduction: Psoriasis is an inflammatory and chronic skin disease associated with obesity, cardiovascular diseases, diabetes and metabolic syndrome. Adipokines, as bioactive substances secreted from adipose tissue, are involved in various metabolic diseases.

Aim: To investigate the association between psoriasis severity and serum adiponectin and leptin levels in patients with psoriasis.

Material and methods: Serum fasting adiponectin and leptin levels were examined by an enzyme-linked immunosorbent assay in 49 patients with relapse of plaque-type psoriasis and 16 healthy controls. The results were correlated with the Psoriasis Area and Severity Index (PASI), body mass index (BMI), several inflammatory markers, duration of the disease and present relapse.

Results: Serum adiponectin and leptin levels were significantly decreased in psoriatic patients in comparison to the control group. There were no correlations between the above measures and PASI scores, patients' age, duration of the disease, present relapse and hospitalization, neither between white blood cells or platelets counts. Serum adiponectin levels significantly correlated with C-reactive protein (CRP) levels. Adiponectin was negatively and leptin positively correlated to BMI at statistical significance. Multivariate analysis demonstrated a significant positive correlation between adiponectin and CRP or PASI concentrations as well as between BMI and leptin concentration.

Conclusions: The data showed that serum adiponectin levels increase and serum leptin levels decrease with psoriasis severity. Leptin might be useful in assessing severity and the risk of complications of psoriasis. Moreover, these results confirmed the relationship between leptin, obesity and psoriasis.

Key words: psoriasis, adipokines, adiponectin, leptin, psoriasis severity.

Introduction

Psoriasis is a chronic inflammatory skin disease, affecting 1.5–3% of the world population. The pathogenesis of psoriasis is complex and depends on many factors, including genetic, neurogenic, hormonal or autoimmune ones [1–6]. Immunological disturbances with predominance of Th1 response and oversynthesis of proinflammatory cytokines especially in combination with genetic predisposition lead to a pathogenic vicious circle with the inception and maintenance of the chronic inflammation and abnormal epidermal proliferation [7]. In recent years clear links have been established between psoriasis and a number of diseases such as obesity, cardiovascular diseases, diabetes

and metabolic syndrome [8–10]. Psoriasis has also been recognized as an independent risk factor for myocardial infarction, especially in young patients suffering from the severe form of the disease [11, 12]. It was shown that metabolic syndrome occurs in 40% or even 65% of psoriatic patients [1, 13]. Obesity, which is also one of the diagnostic criteria of metabolic syndrome, was demonstrated as an independent risk factor for developing psoriasis and even doubling the risk [14–16]. A chronic inflammatory process observed in psoriasis is additionally aggravated by the accompanying diseases, especially obesity. It is assumed that in both these conditions, similar pathways of immune disorders occur [14, 17]. On the genetic basis, the most important susceptibility locus for psoriasis, HLA-

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CW6, is associated with obesity [12, 14]. White adipose tissue, regarded actually as the largest endocrine organ, has the ability to synthesize and secrete peptides such as adipokines which have an impact on many physiological functions. These bioactive substances play a role in regulating homeostasis, nutrition, blood pressure, carbohydrate and lipid metabolism, coagulation, insulin resistance, atherosclerosis and inflammatory or immunological processes [18, 19]. Adipokines participate in the development of certain diseases such as diabetes, obesity, metabolic syndrome, systemic sclerosis and psoriasis [12]. Adiponectin is clearly associated with obesity and metabolic syndrome, which in turn may contribute to the increased risk of psoriasis and its exacerbation [20–22]. Decreased adiponectin levels are found in obesity, insulin resistance, type 2 diabetes, dyslipidemia and coronary heart diseases (CVD) [15, 23, 24]. Hypoadiponectinemia thus may be an independent risk factor for hypertension and type 2 diabetes [14, 22]. It was shown that the gene encoding adiponectin is located in a region most likely to metabolic syndrome, type 2 diabetes and CVD [14]. These diseases strictly correlate with psoriasis. It is assumed that adiponectin may prevent the development of psoriatic lesions inter alia by inhibiting the excessive inflammatory process [25]. It is assumed that leptin acts contrary to adiponectin in numerous physiological functions. Hyperleptinemia is observed in obesity, type 2 diabetes, metabolic syndrome, chronic renal failure and atherosclerosis [15]. In patients with coronary artery disease, leptin is a new and promising predictive factor of the occurrence of cardiovascular events in the future [26]. Postulated leptin's impact on coexistence of hypertension with severe obesity may have a more negative impact on the course of psoriasis [7]. Leptin also exerts an influence on the immune system. It stimulates a Th1 immune response and inhibits Th2 response [27]. This may confirm the participation of leptin in the pathogenesis of many autoimmune inflammatory processes, such as diabetes, rheumatoid arthritis and psoriasis [27, 28]. It has been suggested that leptin may be a marker of severity of psoriasis [29]. The actual role of adipokines in the pathogenesis of psoriasis is not fully understood. Data from clinical studies are insufficient and inconsistent.

Aim

The aim of this study was to evaluate adiponectin and leptin serum concentrations in patients with psoriasis with respect to their association with psoriasis severity and obesity as well as inflammatory markers and clinical picture of the disease.

Material and methods

Patients

Fasting serum samples were obtained from 49 patients (15 females and 34 males) with exacerbation of

chronic plaque-type psoriasis, aged between 19 and 84 years (mean: 48.6 ± 2.4). The disease duration varied from 7 months to 55 years (mean: 17.4 ± 1.8) and duration of the present relapse from 2 weeks to 2 years (mean: 4.4 ± 0.9). Patients with other forms of psoriasis and any other chronic inflammatory or metabolic diseases were excluded from the study. Blood samples were collected before starting any treatment. Adiponectin and leptin serum concentrations were analyzed with respect to the Psoriasis Area and Severity Index (PASI) score and normal values collected from 16 age, sex and body mass index (BMI)-matched healthy controls. Informed consent was obtained from each subject before enrollment. The study was approved by the Bioethical Committee of Medical University of Białystok.

PASI score

Psoriasis area and severity index was evaluated by the same investigator (A.B.) in all patients according to rules proposed by Fredriksson and Pettersson as described previously [23, 30]. The PASI score below 10 defined psoriasis as mild, between 10 and 20 as moderate and above 20 as severe.

Samples collection

Venous blood samples were collected using vacutainer tubes and allowed to clot for 30 min before centrifugation for 15 min at 1000 g, then serum was divided for further measurements and stored at -20°C .

Measurement of adiponectin and leptin

Thawed samples were assayed in duplicate with enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions. Adiponectin and leptin serum levels were determined by Quantikine® Human Adiponectin and Leptin Immunoassays (R&D Systems, Inc. Minneapolis, USA) with sensitivity of 0.246 ng/ml and 7.8 pg/ml, respectively. Optical density was read with a microtitre plate photometer at 450 nm. The concentration was determined by interpolation from a standard curve prepared with standard samples supplied by the manufacturer. Adiponectin serum concentrations were expressed in ng/ml, whereas leptin in pg/ml.

Statistical analysis

Values were expressed as the mean and standard error (\pm SE). The statistical comparison among groups was calculated by a two-tailed Student's *t*-test. Correlations were performed using Shapiro-Wilk test, Mann-Whitney Rank Sum test and Spearman's rank-order correlation coefficient for non-parametric data. Logistic regression was used for multivariate analysis of associations. Value of $p < 0.05$ was considered as statistically significant.

Results

Of the 49 patients studied, 11 (22.5%) had mild psoriasis (PASI < 10), 23 persons (46.9%) moderate (PASI 10–20) and 15 patients (30.6%) were diagnosed with the severe form (PASI > 20). The mean concentrations of adiponectin (11648 ±1338 ng/ml) in sera of psoriatic patients were over 1.5 times lower than in healthy controls (17644 ±1659 ng/ml) and the mean values of leptin (33314 ±6937 pg/ml) was 2.4 times lower than in controls (33314 ±6937 pg/ml) and these differences were statistically significant (Table 1). For none of the investigated adipokines, a significant correlation with PASI was observed.

Assessing the relationship between concentrations of adipokines and basic laboratory indices of inflammation activity, only the adiponectin serum level showed a positive correlation with the sedimentation rate (SR) and C-reactive protein (CRP) levels. Adiponectin was negatively and leptin positively correlated to BMI at statistical significance (Table 2). Multivariate analysis demonstrated a significant positive correlation between the adiponectin

Table 1. Serum adiponectin and leptin concentrations in patients with psoriasis and controls

Variable	Adiponectin [ng/ml]	Leptin [pg/ml]
Psoriasis (n = 49)	11648 ±1338	13798 ±2472
Controls (n = 16)	17644 ±1659	33314 ±6937
Value of <i>p</i>	0.004	0.002

Results presented as $\bar{x} \pm SE$.

level and CRP or PASI and negative with BMI while for leptin a significant positive correlation with BMI (Table 3).

Despite the lack of significance, serum adiponectin concentrations in patients with psoriasis increased with disease activity expressed by the PASI score (Figure 1), which was particularly evident in patients with PASI score above 20. The mean adiponectin levels in patients with PASI score < 10 (10367 ±2375 ng/ml) and in patients with PASI score between 10 and 20 (8966 ±1250 ng/ml) were significantly lower than in healthy controls (17644 ±1659 ng/ml) (Tables 4, 5).

Table 2. Mean (\pm SE) values and correlations (*R*-values) between age, duration of the disease, present relapse, basic laboratory inflammatory measures, BMI and PASI score vs. serum adiponectin and leptin concentrations

Parameter	$\bar{x} \pm SE$	Adiponectin			Leptin		
		<i>R</i>	<i>t</i>	<i>p</i>	<i>R</i>	<i>t</i>	<i>p</i>
SR [mm/h]	21.4 ±2.7	0.307	2.160	0.036*	-0.156	-1.085	0.283
CRP [mg/l]	18.9 ±7.2	0.326	2.313	0.025*	-0.064	-0.439	0.663
WBC [$\times 10^3$ /ml]	7.7 ±0.3	0.105	0.711	0.481	-0.102	-0.703	0.486
PLT [$\times 10^3$ /ml]	215.6 ±9.5	0.247	1.713	0.094	-0.161	-1.118	0.269
Age [years]	48.6 ±2.4	0.265	1.844	0.072	0.005	0.037	0.971
Length of hospitalization [days]	11.9 ±0.6	-0.042	-0.285	0.777	-0.206	-1.446	0.155
Relapse duration [months]	4.4 ±0.9	-0.033	-0.221	0.826	0.259	1.836	0.073
Disease duration [years]	17.4 ±1.8	0.111	0.746	0.459	0.117	0.811	0.422
BMI [kg/m ²]	28. ±1.2	-0.581	-4.783	< 0.001*	0.657	5.971	< 0.001*
PASI [score]	16.5 ±1.1	0.232	1.600	0.117	-0.144	-0.996	0.325

*Statistically significant correlation ($p < 0.05$).

Table 3. Summary of multivariate regression analysis of dependent variable regression (the variable regression analysis was adopted with $p < 0.15$ in univariate analysis)

Parameter	Adiponectin		Leptin	
	<i>t</i>	<i>p</i>	<i>t</i>	<i>p</i>
SR [mm/h]	-0.45	0.652	-	-
CRP [mg/l]	2.46	0.018*	-	-
PLT [$\times 10^3$ /ml]	1.89	0.068	-	-
Age [years]	1.75	0.088	-	-
PASI [score]	2.03	0.049*	-	-
Relapse duration [months]	-	-	1.85	0.071
BMI [kg/m ²]	-2.34	0.005*	3.15	0.003*

*Statistically significant correlation ($p < 0.05$).

Table 4. Comparison of serum adiponectin and leptin concentrations (*p*-values) in psoriatic patients between three groups (< 10, 10–20, > 20) depending on PASI using the Mann-Whitney test

Parameter	PASI		
	< 10 vs. 10–20	< 10 vs. > 20	10–20 vs. > 20
Adiponectin	0.755	0.357	0.133
Leptin	0.744	0.384	0.202

The mean serum leptin concentrations in patients with psoriasis decreased in accordance with disease activity demonstrated by the PASI score (Figure 2). The mean leptin levels in patients with PASI between 10 and 20 (15008 ±3258 pg/ml) and > 20 (9216 ±2701 pg/ml) were significantly lower in comparison with the controls (33314 ±6937 pg/ml) (Table 5).

Discussion

In this study, we demonstrated that measurement of adipokines can be useful for assessment of psoriasis severity and its relationships with other comorbidities. Mean serum adiponectin concentrations as reported in the literature in patients with psoriasis varied from 8374

ng/ml to 18520 ng/ml. Mean values reported in our study were located in the upper range of this interval: 11648 ±1338 ng/ml. The mean adiponectin concentrations in the control group were higher (17644 ±1659 ng/ml) compared with other studies (6122–9471 ng/ml) [29, 31–33]. These differences can be explained by high sensitivity of the assay used in our study.

Previously published data on adiponectin levels in patients with psoriasis are inconsistent. Most of the studies including our results show significantly decreased serum adiponectin concentrations in psoriasis [21, 22, 31, 34]. It is assumed that adiponectin, beyond the role in regulation of metabolic processes, has also an anti-inflammatory activity. It was shown that tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) inhibit the synthesis of adiponectin by adipose tissue. Increased levels of proinflammatory cytokines in psoriatic patients, particularly IL-6, may be one of the causes leading to decreased production of adiponectin by the subcutaneous and visceral adipose tissue [22, 31].

However, there are some studies which have not reported any difference of adiponectin levels in psoriatic patients compared to normal [20, 21, 27, 32, 33], whereas in some other recently published studies, an increase of adiponectin levels has been reported [17, 35].

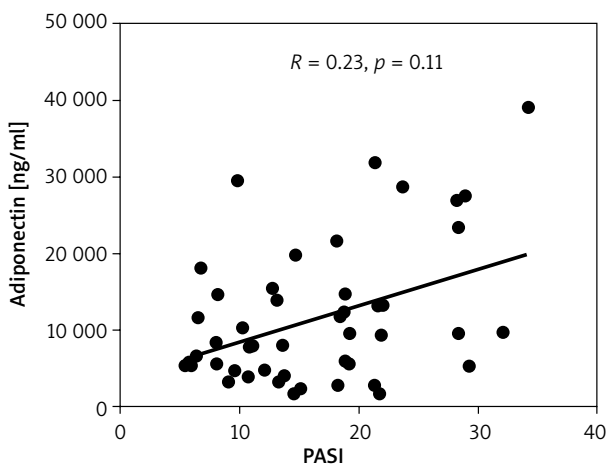


Figure 1. Correlation between serum adiponectin concentrations and PASI score

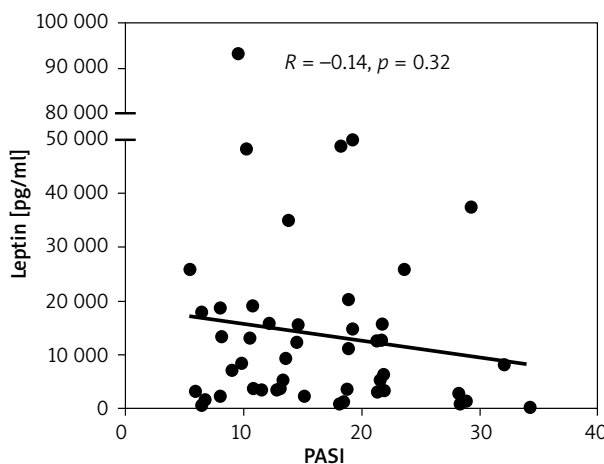


Figure 2. Correlation between serum leptin concentrations and PASI score

Table 5. Comparison of mean ±SE concentrations of serum adiponectin and leptin in controls vs. psoriatic patients depending on PASI score

Parameter	Controls	Psoriatic patients		
		< 10 (n = 11)	10–20 (n = 23)	> 20 (n = 15)
Adiponectin [ng/ml]	17644 ±1659	10367 ±2375	8966 ±1250	14713 ±2904
		0.011*	0.0003*	0.477
Leptin [pg/ml]	33314 ±6937	17516 ±7962	15008 ±3258	9216 ±2701
		0.050	0.020*	0.001*

*Statistically significant correlation (*p* < 0.05) vs. controls (Mann-Whitney test).

Our study demonstrated a significant negative correlation between BMI and adiponectin levels, what was consistent with the results of others [17, 21, 31, 33]. Thus, data indicate the need to consider the nutritional state of patients with psoriasis when assessing clinical studies on adipokines. Decreased levels of adiponectin in patients with obesity may be due to its higher risk of development of numerous chronic diseases accompanied by inflammation. Kaur *et al.* [20] confirmed the aggravation of generalized inflammation and oxidative stress, denoted by the glutathione redox ratio (GSH) in obese psoriatic patients in comparison to patients with normal body weight. Carrascosa *et al.* [36] indicate that obesity increases the risk of adverse effects of systemic treatment of psoriasis and may lead to augmentation of biological agents' dosages in order to avoid a decrease in efficacy of these drugs.

We were not able to show any statistically significant correlation between serum adiponectin levels and PASI score, which is consistent with the results of other authors [17, 21, 37].

Our data showed that serum adiponectin levels increase with psoriasis severity defined as the PASI score. However, the significant correlation with PASI, CRP and BMI (negative) in multivariate analysis was confirmed. Therefore, it must be assumed that serum adiponectin levels in psoriatic patients are dependent not only on the disease activity, but also on several systemic immune and inflammatory processes, which undoubtedly affect the body's metabolic state associated mainly with the body weight. In our study, we found overweight in 36.7% and obesity in 32.6% of patients with psoriasis. These results are consistent with the data from the literature and confirm a positive correlation between psoriasis and obesity and its possible impact on the reduction of adiponectin levels [15, 20, 31].

In the present study, there were no correlations between adiponectin levels and patients' age, duration of the disease, present relapse and hospitalization. We could not find in the literature data such associations beside one positive correlation between adiponectinemia and age of the psoriatic patients, what highlights a unique value of our study [21].

There are only few investigations evaluating the association between adiponectin and inflammatory markers [21, 38]. In the presented study, the adiponectin serum level showed a positive correlation with SR and CRP levels. Associations between adiponectinemia and basic laboratory measures of inflammatory activity indicate possible importance in the course of psoriasis, but knowledge in this field is still insufficient.

Mean serum leptin levels in psoriatic patients as reported in the literature varied from 14250 ng/ml to 26390 ng/ml. The mean leptin concentration in our study was slightly lower (13798 ± 2472 pg/ml), but similar. Data from other papers on leptin levels in psoriatic patients are more uniform and consistent in comparison to adiponec-

tin, but also few and contradictory with our results. Only two studies have not reported any difference in leptin levels in psoriatic patients [17, 27]. The majority of authors have demonstrated a significant increase in leptin levels in psoriasis [33–35, 39–41].

In this study the mean serum leptin concentration in patients with psoriasis was significantly lower than in the controls. The divergent behavior of leptin levels in comparison to few other studies may be due to genetic and nutritional differences affecting the development of obesity. As demonstrated in our study there is a clear significant correlation between leptin and BMI, confirmed by both univariate and multivariate analysis. This corroborates the link between leptin, psoriasis and obesity, expressed as BMI found in other papers [12, 17, 21, 27, 31, 41, 42]. The divergence of various investigations indicates existence of other unknown aspects related to the role of leptin in the pathogenesis of psoriasis. We should also take into consideration some possible methodological variations or differences in leptin levels between different populations [29].

In discussed studies, serum leptin levels decreased with psoriasis severity, expressed as PASI score but without statistical significance. However, data concerning this relationship are very limited [17, 29, 40, 43]. The association between serum leptin levels and inflammatory markers (CRP, IL-6) was assessed probably once by Kaur *et al.* [21]. Our study also showed no significant association with white blood cell count (WBC), platelet count (PLT), sedimentation rate (SR) and CRP. These results seem to contradict previous assumptions that leptin itself may be an acute phase protein derived from adipose tissue [44].

We were not able to present any significant correlations between serum leptin levels and patients' age, duration of the disease, present relapse and hospitalization. In the literature there are few and inconsistent data on these issues [12, 29, 40, 41].

Conclusions

Results of our study demonstrated an increase in adiponectin and decrease in leptin serum levels with psoriasis severity. Serum leptin measurement might be useful in assessing the severity and risk of complications of psoriasis. Additionally presented data confirmed the relationship between leptin, obesity and psoriasis.

Conflict of interest

The authors declare no conflict of interest.

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