Original paper

Analysis of serum chemerin concentrations in psoriatic patients in relation to metabolic abnormalities

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Abstract

Introduction: Recent data depict psoriasis as a systemic disease with many comorbidities, especially metabolic syndrome and cardiovascular diseases. Chemerin, an adipokine secreted by adipose tissue cells, may prove to be an important link between psoriasis and its comorbidities.

Aim: Assessment of serum concentrations of chemerin in patients with psoriasis and the healthy control group as well as evaluation of a possible correlation between adipokine concentrations and selected psoriasis severity indices and metabolic syndrome components.

Material and methods: One hundred and two patients with diagnosed psoriasis and 40 healthy volunteers were enrolled in the study. In all subjects, serum chemerin concentrations and selected metabolic syndrome components including lipid and glucose levels were determined. Psoriasis severity was assessed using the PASI and BSA indices.

Results: A higher concentration of chemerin was demonstrated in the group of psoriasis patients compared to the control group ($p < 0.05$). A positive correlation between chemerin concentration and C-reactive protein concentration ($p = 0.001$), body mass index ($p = 0.031$) and triglyceride concentration ($p = 0.043$) was found. An inverse correlation with high-density lipoprotein cholesterol concentrations ($p = 0.015$) was also noted. Significantly higher concentrations of chemerin were observed in psoriatic patients with elevated low-density lipoptotein (LDL) cholesterol levels in comparison with patients with normal LDL values ($p = 0.032$). Chemerin concentrations were also significantly higher in patients with both psoriasis and elevated glucose levels compared to patients with normal blood glucose values ($p = 0.043$).

Conclusions: The results obtained suggest a possible role of chemerin as an adipokine linking psoriasis with metabolic syndrome.

Key words: chemerin, adipokines, metabolic syndrome, psoriasis.

Introduction

Psoriasis is a common, chronic, inflammatory skin disease affecting 2–3% of the world population [1–7]. Pathophysiological processes involved in the development of psoriasis have not been fully explained. However, genetic predispositions, immunological abnormalities and environmental triggering factors are taken into consideration in its etiopathogenesis. The role of psychosomatic, vascular and inflammatory disturbances is also emphasized [5, 6]. A growing body of literature indicates that psoriasis is a systemic disease, often coexisting with metabolic syndrome, cardiovascular diseases and obesity. It is suggested that adipokines, molecules secreted by adipose tissue cells, may prove to be an important link between psoriasis and its comorbidities.

Chemerin is an adipokine composed of 163 amino acids, with a molecular weight of 18 kDa. It is produced from biologically inactive prochemerin in visceral adipose tissue and in the liver [8, 9]. Chemerin displays a chimeric nature: depending on the active promoter and the length of the cleaved amino acid chain, biologically active and inactive forms with either pro- or anti-inflammatory properties may arise [8–11]. Chemerin exerts its pro-inflammatory effect via stimulation of dendritic cells,

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macrophages, NK cells and probably also neutrophil migration [8, 9, 12, 13]. It was demonstrated that chemerin increases synthesis of pro-inflammatory factors such as interleukin (IL)-6, IL-8, tumor necrosis factor α (TNF-α) and IL-1β [11, 14, 15]. Interestingly, cytokines released in the inflammatory environment further increase the expression of chemerin in endothelial cells, which leads to endothelial dysfunction and the formation of new vessels [8]. Chemerin is also involved in the last phase of the inflammatory reaction. It increases the recruitment of NK cells, stimulates the clearance of leukocytes and enhances the phagocytosis of apoptotic cells and bacteria by macrophages [8, 12]. Apart from its pro-inflammatory effect, this adipokine can also decrease the adhesion and migration of monocytes to tissues, and increases the concentration of anti-inflammatory adiponectin [11, 16].

Chemerin is also involved in the regulation of metabolic processes by acting both in an autocrine manner, by regulating the differentiation of preadipocytes to adipocytes, increasing blood supply and adipose tissue mass, and in a paracrine manner by intensifying chemotaxis of inflammatory cells and increasing the secretion of pro-inflammatory cytokines. Thus, it is one of the factors responsible for the occurrence of adipose tissue infiltration and secondary insulin resistance in obese individuals [12, 17]. Chemerin may also lead to an increase in adipose tissue mass by increasing appetite [9, 18]. The results of some studies indicate an increased concentration of chemerin in the peripheral blood and in psoriatic plaques in patients with psoriasis vulgaris [17, 19].

Aim

The aim of the study was assessment of serum concentrations of chemerin in patients with psoriasis and the healthy control group, as well as evaluation of a possible correlation between adipokine concentrations and selected psoriasis severity indices and metabolic syndrome components.

Material and methods

The study included 102 male patients with psoriasis hospitalized in the Department of Dermatology and 40 healthy age-matched male volunteers as a control group. A detailed medical history allowed to determine the presence of previously diagnosed diseases that are components of the metabolic syndrome, such as diabetes, hypertension, hypercholesterolemia and also medicines taken for this reason. At the time of the examination patients received local treatment for psoriasis. The following inclusion criteria were applied: mild, moderate, severe psoriasis, exacerbation of the disease 2–4 weeks before enrolment, age of 18–78 years, and male gender. The male patients were chosen due to the idea of unifying the study and control groups and eliminating the influence of hormonal factors. The exclusion criteria included: pustular and exudative psoriasis, biologic treatment within one year prior to the examination, systemic connective tissue diseases, neoplastic diseases and active infectious diseases. In all subjects, body mass index (BMI), waist-hip ratio (WHR) and blood pressure were assessed. In the study group, psoriasis severity was evaluated using the Psoriasis Area and Severity Index (PASI) score and body surface area (BSA) index. In both groups, serum concentrations of chemerin, C-reactive protein (CRP), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides (TG) and fasting blood glucose were determined. The serum chemerin concentration was quantified using the immunoenzymatic assay (ELISA), according to the procedure recommended by the manufacturers, using ready-made reagent and platelet sets: BioVendor Human Chemerin ELISA, test sensitivity: 0.1 ng/ml, absorbance reading at 450 nm. The study protocol was approved by the Local Ethics Committee.

The following standards were adopted for the determined parameters: normal TG values in the range from 40 to 150 mg/dl, total cholesterol from 115 to 190 mg/dl, LDL cholesterol from 70 to 115 mg/dl, HDL cholesterol from 45 to 60 mg/dl, glucose < 100 mg/dl, and CRP < 5 mg/l. A PASI index above 10 indicated moderate psoriasis, whereas > 18 showed severe psoriasis. Patients with a BMI exceeding 30 points were considered obese, WHR > 1 indicated an android fat distribution.

Statistical analysis

Statistical analysis was computed using the IBM SPSS Statistics program. In all statistical analyses performed, p-values < 0.05 were considered significant.

Results

The results of laboratory tests and examined clinical parameters are presented in Tables 1 and 2, respectively. Significantly higher chemerin values were found in the group of psoriatic patients compared to the control group ($p < 0.05$) (Table 1). In the study group, no correlation between serum chemerin concentrations and PASI index ($p = 0.399$), BSA ($p = 0.710$) and the duration of disease ($p = 0.974$) was found, while there was a positive correlation between chemerin concentration and CRP concentration ($p = 0.001$) (Table 3). There was a positive correlation between chemerin concentration and BMI ($p = 0.031$), while no correlation was found between chemerin levels and WHR index ($p = 0.424$) (Table 3).

In the study group, a positive correlation between adipokine concentration and TG concentrations ($p = 0.043$), and an inverse correlation with HDL cholesterol concentrations ($p = 0.015$) were observed (Table 3); however, there was no correlation between chemerin and total cholesterol levels ($p = 0.244$) and LDL cholesterol

Table 1. Values of chemerin and selected laboratory parameters in the study group and control groups

Parameter	The study and control group	Mean	Median	Minimum	Maximum	Lower quartile	Upper quartile	Standard deviation	*P*-value
Chemerin [pg/ml]	102	366.80	383.51	92.16	489.57	309.64	429.85	83.59	< 0.05
	40	0.93	0.78	0.15	2.67	0.40	1.38	0.62	
CRP [mg/l]	102	4.06	1.75	0.80	57.30	1.00	3.20	7.59	0.008
	40	2.25	1.60	1.00	4.80	1.20	3.05	1.25	
Total cholesterol [mg/dl]	102	183.28	184.00	89.60	282.50	153.70	213.40	38.75	< 0.001
	40	158.53	158.50	112.00	214.00	127.00	183.50	28.97	
LDL cholesterol [mg/dl]	102	110.95	99.50	27.00	300.00	82.00	130.00	55.66	0.676
	40	98.45	105.00	55.00	118.00	92.50	107.00	16.05	
HDL cholesterol [mg/dl]	102	54.00	49.80	27.40	131.70	40.00	60.50	20.45	0.374
	40	54.00	51.50	35.00	89.00	45.00	59.00	13.27	
Triglycerides [mg/dl]	102	135.41	118.00	47.00	449.00	88.00	171.00	67.84	0.079
	40	110.60	108.00	34.00	201.00	77.00	141.50	43.52	
Glucose [mg/dl]	102	90.16	86.80	61.20	165.25	81.50	93.80	16.70	0.681
	40	88.58	87.00	74.00	116.00	83.50	92.00	8.37	

Table 2. Clinical indices of obesity and adipose tissue distribution, the severity of psoriasis and the duration of the disease

Parameter	*N*	Mean	Median	Minimum	Maximum	Lower quartile	Upper quartile	Standard deviation	*P*-value
BMI	102	28.00	27.05	14.80	42.00	24.50	30.30	5.21	< 0.001
	40	23.25	22.95	20.07	31.31	21.73	24.43	2.22	
WHR	102	0.97	0.96	0.63	1.40	0.93	1.03	0.10	< 0.001
	40	0.89	0.92	0.63	0.98	0.86	0.94	0.07	
PASI	102	15.16	12.65	3.30	45.00	8.00	19.00	9.21	
BSA (%)	102	0.33	0.25	0.05	0.90	0.12	0.45	2.24	
DLQI	102	13.08	14.00	1.00	29.00	8.00	18.00	6.55	
Duration	102	18.91	20.00	0.20	46.00	8.00	30.00	11.69	

(p = 0.051) (Table 3). Significantly higher concentrations of chemerin were observed in patients with psoriasis and elevated LDL-cholesterol levels compared to patients with normal LDL values (p = 0.032). Significantly higher chemerin levels were found in patients with psoriasis and elevated glucose levels compared with normoglycemic patients (p = 0.043). There was no statistically significant difference between chemerin concentrations in the group of psoriatic patients with arterial hypertension (p = 0.944) and diabetes (p = 0.165) compared to psoriatic patients without these comorbidities.

Discussion

Recent studies showed that chemerin might be involved in pathophysiological processes present in obesity and metabolic syndrome, as well as inflammatory diseases such as inflammatory intestinal or joint diseases and psoriasis. Moreover, this protein may be a link between them. However, literature data regarding the relationship between serum chemerin and obesity indices, lipid and glucose metabolism disturbances, markers of inflammation, as well as psoriasis severity are inconclusive.

It is suggested that chemerin might be involved in the pathophysiological processes in psoriasis. An increased chemerin expression was found in skin biopsies in psoriatic patients [20, 21]. In the early stages of psoriasis, the increased concentration of this protein in dermal fibroblasts, mast cells and endothelial cells might be responsible for the increased recruitment of dendritic cells and NK cells to the inflammation site [20]. An additional factor involved in the development of psoriatic inflammation may be the promotion of angiogenesis [22]. The finding that chemerin promotes formation of new vessels may suggest a possible role of this adipokine in psoriasis [8].

Table 3. Correlations between chemerin and PASI, BSA, DLQI, duration of psoriasis, CRP, total cholesterol, LDL, HDL, triglycerides, glucose, WHR and BMI

Parameter	Chemerin	
	rho	*P*-value
PASI	0.085	0.399
BSA %	0.038	0.710
Duration of disease	–0.003	0.974
CRP [mg/l]	0.338	0.001
Total cholesterol [mg/dl]	0.117	0.244
LDL [mg/dl]	0.196	0.051
HDL [mg/dl]	–0.244	0.015*
Triglycerides [mg/dl]	0.203	0.043*
Glucose [mg/dl]	0.138	0.172
WHR	–0.081	0.424
BMI	0.216	0.031*

It is worth noting that within long-lasting lesions, chemerin might display/show anti-inflammatory activity by inducing the clearance of leukocytes from the area affected by inflammation, restoring homeostatic balance in the psoriatic skin [20].

In the present study, a significantly higher serum chemerin concentration was found in patients with psoriasis compared to the control group ($p < 0.05$). However, there was no significant correlation between chemerin levels and clinical severity of psoriasis assessed using the PASI score ($p = 0.399$), BSA index ($p = 0.710$) and disease duration ($p = 0.974$). Significantly higher serum chemerin levels in psoriatic patients compared to the control group were also observed by other authors [23, 24]. In line with our results, Gisondi *et al.* [24] did not observe a linear relationship between the level of chemerin and PASI or BSA, whereas Coban *et al.* [23] reported a strong positive correlation between these parameters. Moreover, Nakajima *et al.* [25] demonstrated that patients with psoriasis vulgaris had higher serum chemerin concentrations than patients with other chronic skin diseases and healthy volunteers. As in our study, there was no correlation between the serum adipokine concentration and PASI score or duration of the disease.

Since both pro-inflammatory and anti-inflammatory effects of chemerin have been reported, a positive correlation between serum chemerin and CRP concentration ($p = 0.001$) found in the present study is of special interest. In a large population study, Zylla *et al.* [26] confirmed the correlation between serum chemerin concentration and pro-inflammatory proteins: CRP and fibrinogen, which is in line with our results. Increased chemerin values were accompanied by an increased serum concentration of both proteins, observed even after considering the waist circumference, which indicates a pro-inflammatory role of this adipokine, independent of obesity.

Interestingly, Lora *et al.* [27] also observed increased levels of chemerin and CRP in psoriatic patients when compared to the healthy control group. After 2 and 12 months of treatment with infliximab, a significant decline in these parameters was found along with a decrease in PASI scores. Therefore, it has been suggested that chemerin exerts pro-inflammatory rather than anti-inflammatory activity in psoriasis. A positive linear correlation between the concentration of chemerin and the serum concentration of CRP in patients with psoriasis was also reported by Gisondi *et al.* [24]. As in the previously cited study, the concentrations of both proteins decreased after 2 and 12 months of treatment with infliximab. Of interest is the study conducted by Lachine *et al.* [28] who presented a positive correlation between the concentration of chemerin, the level of C-reactive protein and the intima media thickness of the carotid artery. The authors suggested that the concentrations of hs-CRP along with serum chemerin concentration might serve as a marker for early atherosclerotic lesions in patients suffering from type 2 diabetes. This is of special interest since both diseases are common psoriasis comorbidities. Therefore, further studies are required to evaluate the potential role of chemerin as a marker of early atherosclerosis in psoriasis.

Chemerin has been described as a pro-inflammatory cytokine affecting the pathophysiological processes occurring in adipose tissue. This protein, mainly produced within the adipose tissue surrounding the internal organs, induces differentiation, hypertrophy, angiogenesis and inflammation in this tissue. It has been suggested that, due to its dual role in metabolism and inflammation, chemerin could be a link between chronic inflammation, obesity and type 2 diabetes [17, 29].

Bozaoglu *et al.* [30] assessed chemerin levels and metabolic syndrome parameters in the Mexican-American population. After comparing chemerin concentrations in patients with and without diabetes, they came to the conclusion that the concentration of chemerin is significantly higher in non-diabetic but obese patients with BMI > 30 kg/m^2, when compared to patients with BMI < 25 kg/m^2. The authors also reported a positive correlation between serum chemerin levels and BMI.

Similarly, Weigert *et al.* [31] also demonstrated the presence of a positive correlation between the serum chemerin concentration and BMI as well as the WHR index. Moreover, obese patients had higher levels of serum chemerin when compared to the control subjects. The correlation between chemerin and obesity indices has also been confirmed by other research groups [32–34].

Significantly, in patients who underwent bariatric surgery, weight loss was accompanied by a reduced concentration of circulating chemerin. Moreover, a significant improvement in metabolic parameters along with a de-

crease in chemerin concentration obtained after bariatric surgeries was observed [35].

Similar conclusions were presented by Cheon *et al.* [36], showing a positive correlation between chemerin concentration and BMI indices, waist circumference and the thickness of visceral adipose tissue measured by ultrasonography in patients with type 2 diabetes.

In our study, a significant correlation between chemerin concentration and BMI ($p = 0.031$) was found in the group of psoriatic patients. An increased BMI was accompanied by an increased concentration of chemerin. However, there was no correlation between the concentration of circulating serum chemerin and the WHR index ($p = 0.424$). A tendency towards higher chemerin levels in obese patients with psoriasis has been reported by other authors [24]. Nevertheless, Nakajima *et al.* [25] published opposite results. The authors did not observe any correlation between the increased concentration of chemerin and the BMI index in patients with psoriasis.

It is suggested that chemerin plays a role not only in obesity but also in its metabolic complications. Therefore, the present study assessed the possible correlation between chemerin and individual components of the lipid profile. There was a positive correlation between serum chemerin concentration and TG ($p = 0.043$) and a negative correlation between chemerin concentration and HDL cholesterol values ($p = 0.015$). However, no correlations between the concentration of chemerin and the values of total cholesterol and LDL cholesterol ($p = 0.244$ and $p = 0.051$, respectively) were observed. After dividing the study group into categories: individuals with an elevated (> 115 mg/dl) and normal (< 115 mg/dl) LDL cholesterol level, significantly higher levels of chemerin were found in psoriatic patients with elevated LDL cholesterol values compared to those with psoriasis and normal LDL cholesterol levels ($p = 0.032$). Similar results were obtained by other authors [26, 37, 38]. The higher chemerin levels observed in patients with hypertriglyceridemia accompanied by low HDL cholesterol or high LDL cholesterol are of special interest. According to some authors, the presence of such lipid abnormalities is associated with cardiovascular disease [38].

Contrary to the above reports, Weigert *et al.* [31] did not show any relationship between chemerin concentration and lipid profile parameters including total cholesterol, LDL cholesterol and TG levels in patients with obesity and type 2 diabetes. As in our study, the authors reported a decrease in HDL cholesterol levels, which was associated with an increase in chemerin concentration [31].

Although the link between chemerin and disorders of glucose metabolism is known, studies performed so far have not clarified whether this adipokine leads to an increased or reduced glucose uptake by the tissues [17, 19, 39–41]. It cannot be excluded that the potential impact of chemerin on glucose metabolism may depend on its concentration, treatment duration and local conditions [17]. The results of studies regarding the role of chemerin in disorders of glucose metabolism are inconclusive.

In the present study, there was no correlation between chemerin values and fasting glucose concentrations in patients with psoriasis vulgaris ($p = 0.172$). However, after dividing the study group into two subgroups: one having normal serum glucose levels (< 100 mg/dl) and another with increased levels (> 100 mg/dl), a significantly higher chemerin concentration was found in psoriatic patients with hyperglycaemia compared to patients with psoriasis and normal glycemia levels ($p = 0.043$). Nevertheless, no statistically significant difference between the chemerin values in the group of psoriatic patients with diabetes and non-diabetic psoriatic patients was observed ($p = 0.165$).

Lachine *et al.* [28] showed a significantly higher level of chemerin in patients with type 2 diabetes compared to the control group. The concentration of chemerin was also positively correlated with HOMA-IR, the insulin resistance index, whereas, as in our study, they observed no correlation with fasting glucose. Moreover, in line with our study results, other authors [26, 42] showed that there was no correlation between serum adipokine concentration and fasting glucose levels.

Furthermore, Habib *et al.* [33] found elevated chemerin levels in the peripheral blood in diabetic patients as compared to the healthy control group. Chemerin was positively correlated with serum insulin levels and the HOMA-R index, and inversely correlated with the QUICKI index. Moreover, the fasting insulin level proved to be an independent predicting factor of an increased concentration of chemerin.

In addition to its immunomodulatory effects, chemerin has been linked to multiple components of metabolic syndrome, including hypertension [43].

When a possible correlation between chemerin and hypertension was examined, there was no significant difference between chemerin concentrations in the group of patients with psoriasis with coexisting hypertension, and in the group of patients with psoriasis without hypertension ($p = 0.944$). Studies conducted by other authors provide inconsistent results. There are studies that indicate both presence [42, 44, 45] and a lack of correlation between hypertension and serum chemerin levels [28, 30, 36].

Aydin *et al.* [42] found a positive correlation between serum chemerin concentrations and systolic and diastolic blood pressure values in the group of diabetic patients and a lack of such correlation in the group with impaired glucose tolerance and in healthy subjects.

Shin *et al.* [34] also showed a positive correlation between serum chemerin concentrations and systolic and diastolic blood pressure values. Mean arterial pressure values in addition to total cholesterol and visceral adipose tissue mass were considered independent factors affecting the concentration of chemerin in the peripheral blood.

The limitation of our study was the homogeneity in terms of sex of the study and control groups. However considering the hormonal impact on the pathogenic processes occurring in the course of psoriasis, we have decided to perform the study among men to eliminate the possible confounding effect of gender diversity [46, 47].

Conclusions

The chimeric properties of chemerin have not been sufficiently studied so far. This adipokine affects the differentiation and increase in adipose tissue mass, glucose metabolism, and is involved in angiogenesis. It may also prove to be an important prognostic tool for metabolic syndrome and inflammatory diseases, and, like CRP, indicates inflammatory processes in the body. Significantly higher chemerin concentrations in patients with psoriasis as well as a positive correlation between adipokine and CRP concentrations reported in this study suggest this protein's involvement in the pathophysiological processes and systemic inflammation present in psoriasis. In addition, the observed correlations with BMI and lipid profile components as well as significantly higher chemerin concentrations in patients with hyperglycaemia compared to psoriatic patients who have normal glucose levels indicate that chemerin levels might reflect metabolic disorders in this group of patients. However, further research is needed to fully understand the role of chemerin in metabolic disorders in patients with psoriasis.

Conflict of interest

The authors declare no conflict of interest.

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