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Serum levels of chemerin and pigment epithelium-derived factor in patients with psoriasis

Ocena stężeń chemeryny i czynnika wzrostu pochodzącego z nabłonka barwnikowego w surowicy krwi u chorych na łuszczycę

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Keywords

chemerin, pigment epithelium-derived factor, psoriasis, adipokines

Słowa kluczowe

chemeryna, czynnik wzrostu pochodzący z nabłonka barwnikowego, łuszczyca, adipokiny

Summary

Introduction. Psoriasis is a multifactorial chronic inflammatory disease associated with multiple comorbidities (obesity, cardiovascular diseases, metabolic syndrome). Adipose tissue is not only an energy-storing organ but also a major source of adipokines. Affecting vascular function, adipocyte metabolism and immune regulation, adipokines are participants in the pathogenesis of various diseases. The association of the novel adipokines with psoriasis is still obscure.

Aim. The aim of this study was to investigate serum levels of adipokines in patients with chronic plaque psoriasis.

Material and methods. Serum fasting chemerin and pigment epithelium-derived factor (PEDF) levels were examined by enzyme-linked immunosorbent assay (ELISA) in 66 patients with psoriasis and 40 healthy controls. Possible correlations were searched between the serum adipokines concentrations and the Psoriasis Area and Severity Index (PASI), Body Mass Index (BMI) and inflammatory marker: C-reactive protein (CRP), erythrocyte sedimentation rate (SR).

Results. Patients with psoriasis showed considerably higher serum levels of chemerin and PEDF than healthy controls. There were no correlations between the above measures and PASI. Serum chemerin levels in psoriatic patients were significantly correlated with inflammatory markers and abnormalities of lipid profile. PEDF levels were significantly positively correlated with BMI in the overweight psoriatic patients.

Conclusions. In summary, the results of the conducted study indicate that the examined adipokines can be involved in the pathophysiology of psoriatic inflammation.

Streszczenie

Wstęp. Łuszczyca jest wieloczynnikową, przewlekłą chorobą zapalną powiązaną z wieloma współistniejącymi zaburzeniami ogólnoustrojowymi. Tkanka tłuszczowa oprócz tego, że stanowi źródło energii dla organizmu ludzkiego, spełnia także rolę aktywnego narządu wewnątrzwydzielniczego, wydzielając/uwalniając adipokiny. Adipokiny odgrywają istotną rolę w metabolizmie lipidów, modulują procesy zapalne, hemostazę, uczestnicząc w patogenezie wielu chorób zapalnych. Rola adipokin w patogenezie łuszczycy wciąż nie jest w pełni poznana.

Cel pracy. Celem pracy była ocena stężeń wybranych adipokin w surowicy krwi pacjentów z łuszczycą pospolitą oraz badanie możliwych zależności z wybranymi parametrami laboratoryjnymi i klinicznymi.

Materiał i metody. W surowicy krwi 66 pacjentów i 40 osób zdrowych oznaczono stężenia chemeryny i PEDF, stosując metodę immunoenzymatyczną ELISA. Otrzymane wyniki badano pod kątem istnienia zależności pomiędzy stężeniami wybranych adipokin a nasileniem klinicznym łuszczycy (PASI), zaburzeniami masy ciała (BMI) i parametrami stanu zapalnego: CRP, SR.

Wyniki. W grupie pacjentów z łuszczycą stwierdzono istotnie wyższe stężenia chemeryny i PEDF niż u zdrowych osób. W grupie pacjentów z łuszczycą stwierdzono istotne

Conflict of interest
Konflikt interesów

None
Brak konfliktu interesów

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statystycznie korelacje pomiędzy stężeniem chemeryny a parametrami stanu zapalnego (CRP, SR) oraz składowymi profilu lipidowego. Stwierdzono istotną statystycznie zależność pomiędzy surowiczym stężeniem PEDF a wartością wskaźnika BMI w grupie chorych na łuszczycę z nadwagą.

Wnioski. Wyniki przeprowadzonych badań wskazują na możliwy udział badanych adipokin w procesach patofizjologicznych prowadzących do rozwoju łuszczycy.

INTRODUCTION

Psoriasis is a chronic immune-mediated inflammatory skin disease affecting more than 2% of the world population (1, 2). The pathogenesis of psoriasis is complex and it has genetic, autoimmune and hormonal background (3). A number of recent studies have revealed an association between psoriasis and systemic disorders leading to the development of concomitant immune-mediated inflammatory diseases (3-5). It has been noted that systemic chronic inflammation associated with increased interaction of inflammatory mediators of various origin, including cytokines, growth factors, platelet-derived factors, adipokines, abnormal lipid profile and the activation of vascular endothelium, may be a common pathophysiological basis for psoriasis and other immune-mediated inflammatory diseases (6, 7). It appears, that the metabolic syndrome and its components, in particular, can constitute a link between cardiovascular diseases and type 2 diabetes mellitus in psoriatic patients (4, 5, 8). Understanding the importance of white adipose tissue as an endocrinologically and immunologically active organ has shed new light on the pathophysiological processes of psoriasis, especially on the possible role of bioactive mediators produced by the adipose tissue cells, namely adipokines (6, 9). Recent data indicate that adipokines are involved in the homeostasis maintenance through regulating bodily functions, such as: glucose and lipid metabolism, blood pressure, tissue sensitivity to insulin as well as immune-mediated and inflammatory processes (6, 9-11). Epidemiological surveys reveal the association of psoriasis with obesity, glucose intolerance/diabetes mellitus, hypertension and cardiovascular diseases.

Chemerin is a recently discovered 18 kDa primarily inactive protein that regulates adipocyte differentiation and stimulates chemotaxis and activation of dendritic cells and macrophages (11, 12). This adipokine has low biological activity and requires further extracellular C-terminal processing (11, 13, 14). More recent studies have shown that chemerin is elevated in tissues and fluids in inflammatory conditions and serum chemerin levels correlate with levels of the proinflammatory cytokines such as: tumor necrosis factor α (TNF-α), interleukin 6 (IL-6) and also with CRP (13, 14). In the dermis of early psoriasis leasions Albanesi et al. reported high expression of chemerin together with increased number of plasmacytoid dendritic cells (pDCs) however in the chronic plaques low chemerin expression and pDCs were found (15, 16). Nakajima et al. described elevated chemerin levels in the serum of psoriatic patients (16). Recently chemerin was reported as an adipokine regulating adipogenesis and adipocyte metabolism (11, 14, 17). In another study serum level of chemerin was highly correlated with several markers of inflammation and components of the metabolic syndrome (12). Chemerin has also been detected on dermal endothelial vessels of systemic lupus erythematosus (SLE) (15, 18). The dual role of this adipokine may be a link between chronic inflammation and obesity related disorders.

PEDF is a multifunctional glycoprotein that belongs to the superfamily of serine protease inhibitors with potent antiangiogenic and neurotrophic properties (19-21). It was first purified from the conditioned medium of human retinal pigment epithelial cells but a recent study showed that PEDF is widely distributed in variety of human tissues, including adipocytes, vascular, inflammatory cells and skin (20, 22). Recently published studies found that serum levels of PEDF are strongly associated with components of metabolic syndrome (19, 20, 22). Chen et al. recently reported that increased serum level of PEDF independently predicted the development of the metabolic syndrome in a 10 year prospective study (23). Serum PEDF correlated with several factors closely related to insulin resistance, BMI, triglycerides, systolic blood pressure. Two other studies describe a significant correlation between serum level of PEDF and obesity in humans indicating adipose tissue as the main source of PEDF (19, 21, 24). Rychli et al. suggested that PEDF can have a protective role in atherosclerosis because of its anti-oxidant, anti-inflammatory and anti-thrombotic properties in the vessel wall (25). Nakajima et al. examined PEDF levels in the serum of patients with psoriasis compered to healthy controls (22). Circulating PEDF levels were significantly higher in psoriatic patients than in control subjects. Their findings might suggest that PEDF could mediate anti-inflammatory actions in psoriasis.

AIM

Taking into consideration, that the results of previous studies are often inconclusive, the own study has been undertaken to evaluate the selected adipokines in the psoriatic patients and to investigate the potential role of adipokines in systemic abnormalities as part of the metabolic syndrome. In particular, the present study focuses on:

1. The assessment of the serum levels of selected adipokines – chemerin and PEDF in patients suffering from psoriasis as compared with healthy controls.

2. The assessment of the possible relationship between the disease severity and the serum levels of selected adipokines in patients with psoriasis.
3. The assessment of the possible correlations between the serum levels of selected adipokines and selected laboratory indicators of inflammation, lipid profile and the components of the metabolic syndrome.

MATERIAL AND METHODS

Patients

The study was carried out on 66 adult male patients diagnosed with the plaque-type psoriasis and treated at the Department of Dermatology, Venereology and Paediatric Dermatology of the Medical University of Lublin. The control group consisted of 40 healthy volunteers whose sex and age matched the study group. The complete medical histories of patients with psoriasis were reviewed, their general health condition was assessed. The used protocol was approved by the Committee on Ethics of the Medical University of Lublin and all the psoriatic patients gave informed consent to participate in the study.

Psoriasis severity was evaluated by the PASI score. The PASI score below 10 defined psoriasis as mild, a score >10 was considered as moderate to severe. The weight and height of all patients and volunteers from the control group were measured.

BMI was calculated as the weight in kilograms divided by square of height in metres and participants were classified as being of normal weight (≥ 18.5 and < 25), overweight (≥ 25 and < 30), or obese (≥ 30).

Assays

Venous blood samples were collected from both psoriatic patients and healthy individuals. The laboratory tests included: lipid profile parameters (total cholesterol, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), triglycerides), CRP concentration and SR. The serum concentrations of chemerin and PEDF were measured by enzyme-linked immunosorbent assay (ELISA) using commercially available kits according to the manufacturer's instructions (Biovendor Human Chemerin ELISA; Biovendor GmbH Heidelberg, Germany, PEDF ELISA Kit; Wuhan EIAAB Science CO Wuhan, China).

Statistical analysis

Statistical analyses were performed using Statistica ver. 10.0 PL. Results are presented as mean, standard deviation (SD) or median with interquartile as appropriate. The statistical comparison among groups was calculated by the Mann-Whitney test. The correlation analysis was performed by calculating the Spearman coefficient correlation. A p value < 0.05 was considered as statistically significant.

RESULTS

In our study no statistically significant differences were found between patients and controls ($p > 0.05$) regarding age, sex. The mean PASI was 21.09 (tab. 1).

Tab. 1. Assessment of psoriasis severity using the PASI score

	N	Mean	SD	Median	Min-max
PASI	66	21.09	11.85	20.5	3-50

Patients, compared to controls, presented a statistically significant higher BMI ($p = 0.014$) (tab. 2).

Serum total cholesterol, triglycerides, LDL cholesterol and HDL cholesterol levels did not show any significantly difference between the patients with psoriasis and healthy controls ($p > 0.05$) (tab. 2). Statistically significant higher serum levels of CRP and SR were observed in the psoriatic patients in comparison with the healthy control ($p < 0.0001$ and $p = 0.01$, respectively) (tab. 2). Serum chemerin concentration in patients with psoriasis was significantly higher than that of the controls ($p = 0.0003$) (tab. 2). There were no statistically significant differences between normal weight, overweight and obese patients regarding serum chemerin level ($p > 0.05$). Statistically significant higher serum level of PEDF was observed in the psoriatic patients in comparison with the healthy controls ($p = 0.000001$) (tab. 2).

Tab. 2. Characteristics of psoriatic patients and controls

	Patients (N = 66)			Controls (N = 40)			p-value
	mean	SD	min-max	mean	SD	min-max	
BMI	28.3	4.73	20.7-48.2	25.9	3.57	19.0-33.2	0.014
Total cholesterol (mg/dL)	193.57	33.26	108.9-289.30	189.89	48.94	99.90-341.10	0.3
LDL (mg/dL)	124.62	47.99	53.0-300	121.03	55.86	50.0-300	0.35
HDL (mg/dL)	49.14	15.21	27.4-102.8	51.21	11.81	30.6-80.1	0.22
Triglycerides (mg/dL)	140.63	99.88	41.00-698	123.95	68.63	52.00-327	0.19
CRP (mg/L)	4.57	9.43	0.3-70.1	1.54	2.72	0.1-17.6	< 0.0001
SR (mm/h)	12.2	12.2	1-68	6.65	5.7	2-36	0.01
Chemerin (ng/mL)	206.93	56.39	105-452	174.54	71.07	96-532	0.0003
PEDF (ng/mL)	0.19	0.26	0.02-2.17	0.09	0.12	0.01-0.71	0.000001

BMI – Body Mass Index; LDL – low density lipoprotein cholesterol; HDL – high density lipoprotein cholesterol; CRP – C-reactive protein; SR – erythrocyte sedimentation rate; PEDF – pigment epithelium-derived factor

Correlation analyses between serum levels of adipokines and lipid profile parameters showed a statistically significant positive correlation between triglycerides concentration and the serum levels of chemerin in the psoriatic patients ($p = 0.02$) (fig. 1) and statistically significant negative correlation between HDL cholesterol level and the serum of chemerin in patients with psoriasis ($p = 0.003$) (fig. 2). There were no correlation between PEDF concentration and lipid profile parameters ($p > 0.05$).

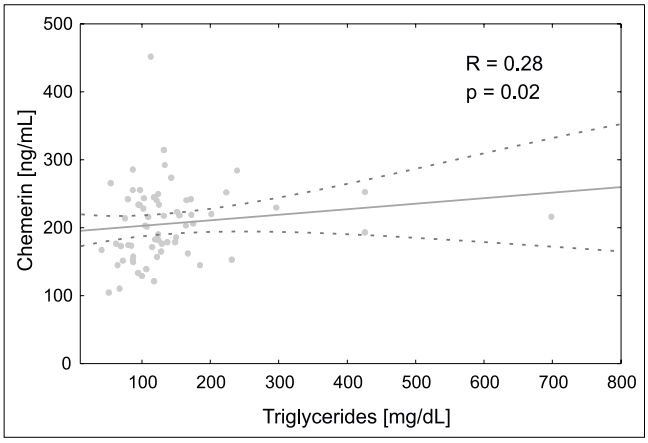

Fig. 1. Correlation between serum levels of chemerin and triglycerides in psoriatic patients

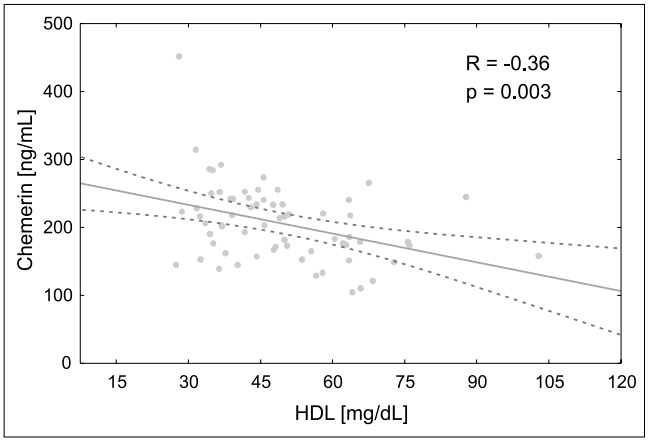

Fig. 2. Correlation between serum levels of chemerin and HDL cholesterol in psoriatic patients
HDL – high density lipoprotein cholesterol

Assessing the relationship between concentrations of adipokines and basic laboratory indices of inflammation activity, only serum level of chemerin showed a positive correlation with CRP ($p = 0.0016$) (fig. 3) and SR ($p = 0.0002$) levels (fig. 4).

For none of the investigated adipokines, a significant correlation with the PASI score was observed.

Analysing the results of adipokines concentrations in relation with the body mass, we have found a statistically significant positive correlation between the serum levels of PEDF and BMI in the overweight psoriatic patients ($p = 0.001$) (fig. 5). There were no correlations between the serum levels of chemerin and BMI in the groups of normal-weight, overweight and obese patients ($p > 0.05$).

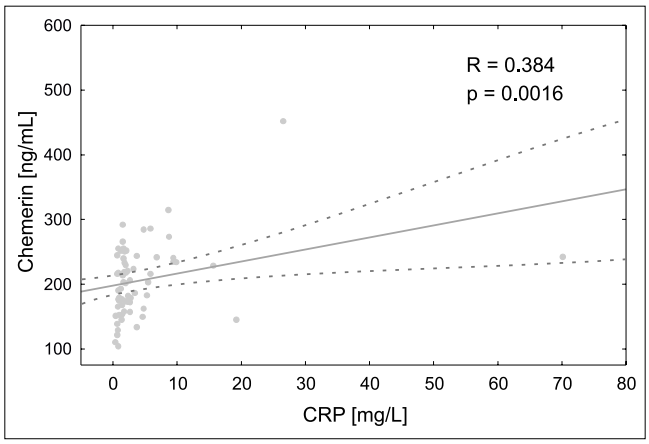

Fig. 3. Correlation between serum levels of chemerin and CRP in psoriatic patients
CRP – C-reactive protein

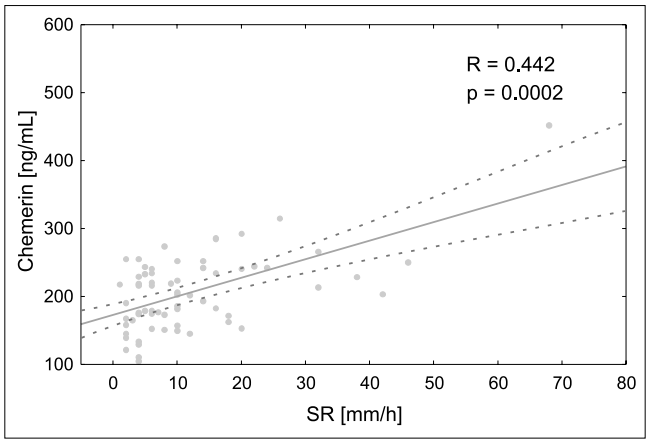

Fig. 4. Correlation between serum levels of chemerin and SR in psoriatic patients
SR – erythrocyte sedimentation rate

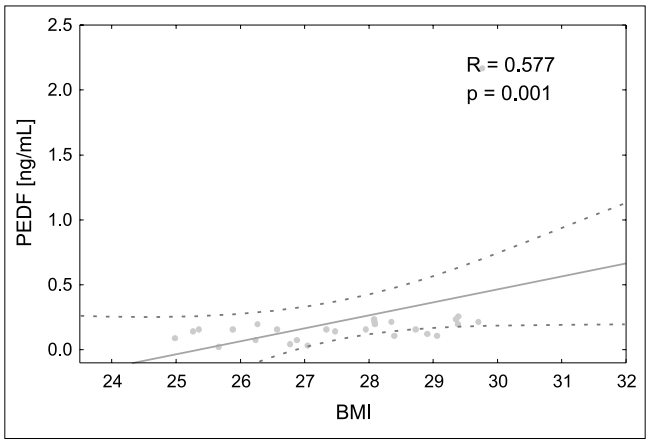

Fig. 5. Correlation between serum levels of PEDF and BMI in overweight psoriatic patients
PEDF – pigment epithelium-derived factor, BMI – Body Mass Index

DISCUSSION

In the present study we demonstrated that patients with psoriasis showed a high incidence of overweight/obesity as 71.2% of them presented a BMI greater than or equal to 25 which is in accordance with Gisondi et al. results (26). Herron et al. found that obesity is almost twice as prevalent in psoriasis patients than in

healthy controls (27). Similarly, Neimann et al. found that the risk of obesity was significantly increased in patients with psoriasis when compared to controls (28). Naldi et al. in a case-control study found that psoriasis prevalence was linked with increasing BMI values (29). Significant higher values of BMI, compared to controls, observed in our psoriatic patients indicate that psoriasis is associated with metabolic abnormalities.

In addition to obesity there is evidence to suggest a link between psoriasis and lipid abnormalities. Several reports suggest that patients with psoriasis have a proatherogenic lipoprotein profile including hypertriglyceridemia, raised plasma concentrations of total cholesterol, LDL cholesterol and lowered HDL cholesterol concentration (30-32). Among many studies on serum lipid values in psoriasis conflicting results have been reported. It is still controversial whether changes in lipid profile are primary events or secondary to psoriasis or due to medications such as retinoids or cyclosporin (32-34).

In our study we did not find any significant difference in serum levels of the lipid parameters between patients with psoriasis and control group ($p > 0.05$). Similar to the results of our study Farshchian et al. in a study on Iranian patients with psoriasis and control subjects reported that serum lipid concentration between both groups did not differ significantly (35). The results of our study are very similar to those obtained by Seishima et al. and Seckin et al.; there were no significant differences in serum levels of total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride (32, 34). In contrast Akhyani et al. reported significantly higher levels of serum total cholesterol, triglyceride and LDL cholesterol in patients with psoriasis compared to healthy controls (33). HDL cholesterol levels did not show any significant difference between the two groups. In another assay total cholesterol and LDL cholesterol levels were found to be significantly higher in patients with psoriasis than those of controls, but no significant differences were found in the triglycerides and HDL cholesterol levels (31). The reasons for the changes in lipid profile in psoriasis have not been sufficiently explained in the literature.

A recent studies showed that PEDF is a novel adipokine secreted mainly by adipocytes (21, 22, 36). Japanese scientists demonstrated that circulating levels of PEDF were significantly elevated in the sera of psoriasis patients compared to normal controls (22). There were no correlation between PEDF levels and PASI in psoriasis patients, as well as PEDF levels and inflammatory markers. However their study demonstrated a significant positive correlation between PEDF levels and BMI in overweight psoriasis patients. Similarly Jenkins et al. and Yamagishi et al. found a significant correlation between serum levels of PEDF and BMI in overweight/obese people, indicating that adipose tissue is the main source of this adipokine in human body (19, 24). Our results are in accordance with aforementioned literature data. Our study demonstrated significantly elevated levels of PEDF in patients with psoriasis compared to healthy controls. We were not able to show any statistically significant correlation between serum PEDF levels and PASI as well as inflammatory markers (CRP and SR). Our data showed statistically significant positive correlation between circulating levels of PEDF and BMI in overweight psoriatic patients, which is consistent with the results of other authors (19, 22, 24). The observed significant positive correlation between PEDF and BMI in the overweight psoriatic patients may indicate that this adipokine accurately reflect the body mass disorders in overweight psoriatic patients.

Chemerin has been associated with inflammation, adipogenesis and with glucose and lipid metabolism (7, 11, 37). Taking into consideration data from the literature pointing to the possible role of chemerin in inflammatory processes, the own study has been undertaken to evaluate chemerin serum concentration in psoriasis patients and to investigate the association between this adipokine and inflammatory markers as well as disorders of lipid profile. Most of the studies including our results show significantly increased serum chemerin levels in patients with psoriasis compared to control group (16, 38-40). Our study demonstrated a significant negative correlation between this adipokine and HDL cholesterol as well as statistically significant positive correlation between chemerin and triglycerides in the patients with psoriasis, which was consistent with the results of others (16, 37). These results indicate that chemerin may reflect the lipid profile abnormalities in the psoriatic patients. In agreement with Gisondi et al. as well as Nakajima et al. we were not able to show any statistically significant correlation between serum chemerin levels and PASI and between this adipokine and BMI (16, 39). It is worth noting, that these scientist observed the association of the circulating chemerin levels with efficacy of general treatment. In their studies the concentration of chemerin did not show a correlation with severity of the skin lesions measured by the PASI score but rather with disease activity. A growing body of data indicates that serum chemerin levels may play important roles in inflammatory processes therefore own study has been undertaken to investigate the possible association between this adipokine and inflammatory markers such as CRP and SR. In our study serum chemerin level showed statistically significant positive correlation with CRP and SR. The observed significant positive correlation between inflammatory markers (CRP, SR) and chemerin suggests that this adipokine may be in association with the psoriatic inflammation and thus could be useful in monitoring the psoriatic inflammatory process.

CONCLUSIONS

Results of our study demonstrated that patients with psoriasis have elevated serum levels of PEDF and chemerin compared to healthy controls,

therefore these adipokines may be involved in the pathophysiological processes leading to the development of psoriasis. Among the examined adipokines, PEDF appears to have strong association with the body mass abnormalities in the psoriatic patients and chemerin appears to have association with abnormalities of lipid profile in the psoriatic patients.

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