Serum concentration of osteopontin and interleukin 17 in psoriatic patients

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Abstract

Background. Psoriasis is a chronic, autoinflammatory disease characterized by activation and differentiation of naive T lymphocytes towards T helper CD4⁺ (including Th1 and Th17) and T cytotoxic CD8⁺. Osteopontin (OPN), which plays an important role in both physiological processes and inflammatory, neoplastic and autoimmune diseases, is also considered in the context of psoriasis pathogenesis. Current data indicates that OPN is a multifunctional protein involved in the modulation of Th1 and Th17 cellular responses, in stimulating keratinocyte proliferation, and in the regulation of cellular apoptosis.

Objectives. The assessment of OPN and interleukin 17 (IL-17) concentrations in the peripheral blood of psoriatic patients in comparison to healthy volunteers as well as the correlations of OPN and IL-17 with the severity of psoriasis.

Material and methods. The study included 107 male psoriatic patients and 41 age-matched healthy men. The serum concentrations of IL-17 and OPN were examined using the enzyme-linked immunosorbent assay (ELISA) method. The skin change severity of psoriasis was assessed using the Psoriasis Area and Severity Index (PASI), Body Surface Area (BSA), Physician Global Assessment (PGA), and Dermatology Life Quality Index (DLQI).

Results. Psoriatic patients had significantly higher concentrations of OPN (31.65 ng/mL on average) than the healthy volunteers (11.42 ng/mL on average) ($p < 0.001$). Interleukin 17 was also higher in psoriatic patients (0.53 pg/mL on average) compared to healthy volunteers (0.09 pg/mL on average) ($p < 0.001$). There was no significant correlation between OPN and IL-17 concentrations in psoriatic patients and in healthy volunteers. Psoriasis severity correlated positively to IL-17 serum concentration, but not to OPN.

Conclusions. Although the study did not show a relationship between OPN and IL-17 concentrations in psoriatic patients, it should be emphasized that serum concentrations were significantly higher in the patients with psoriasis compared to healthy volunteers.

Key words: psoriasis, osteopontin, interleukin 17

Cite as

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Introduction

Psoriasis is an autoinflammatory disease characterized by a chronic skin inflammation with infiltrations containing T lymphocytes, neutrophils and macrophages.^{1–3} Activated Th17 cells, formed from naive CD4⁺ cells under the influence of interleukin 23 (IL-23),⁴ migrate to the skin, where in the presence of pro-inflammatory cytokines, such as IL-1 β , they produce IL-17⁴ which is known to play a key role in the development of psoriatic plaque.⁵

Another protein, osteopontin (OPN), supposedly engaged in the pathogenesis of psoriasis, has a substantial role in certain physiological processes as well as in the pathogenesis of inflammatory disease, cancer and autoimmune diseases. Osteopontin, first described in 1979 by Senger et al.,⁶ is one of the glycoproteins of the SIBLING non-collagen protein family.^{7,8} Initial studies on OPN focused on its role in osteogenesis and cancer metastases,⁹ while recent studies have been mainly concerned with the effect of OPN on cell migration and autoinflammatory mechanisms.⁹ Some data indicates that in chronic systemic inflammation, the increase in peripheral blood OPN concentration may contribute to the development of atherosclerosis and metabolic syndrome as well as psoriasis.¹⁰ Presently, OPN is indicated as a multifunctional protein involved in the modulation of Th1 and Th17 responses and keratinocytes' proliferation as well as in cell apoptosis regulation.^{7,11} Osteopontin is also supposed to play a role in the development of autoimmune diseases since it is capable of stimulating macrophages to produce IL-12 and interacting with the CD44 receptor as well as inhibiting IL-10 production, which enables differentiation of T cells into Th1.^{7,12–14} As a result of these processes, the concentration of IL-27 decreases, which in turn favors differentiation of T cells into Th17.⁷ Due to interaction with $\alpha\beta$ 3 integrin, OPN stimulates Th17 to produce IL-17.^{7,12,14} In addition, OPN increases the production of interferon gamma (IFN γ) by T cells and IL-6 by monocytes, thereby promoting adhesion and migration of lymphocytes.^{12,13} Similar immunological phenomena are also observed in the pathogenesis of psoriatic lesions, which is suggestive of a possible contribution of OPN to the development of local and systemic inflammation in psoriasis.

Nevertheless, the studies on OPN conducted so far, both in the peripheral blood and psoriatic plaque, have produced conflicting results; therefore, the role of OPN in the pathogenesis of psoriasis still awaits elucidation.

Objectives

In light of the recent study results indicative of a stimulating role of OPN in the Th17 response, the aim of our study was to assess the concentration of OPN and IL-17 in the serum of psoriatic patients as well as the correlation between OPN and IL-17 concentrations in the serum and the severity of psoriasis measured with the Psoriasis

Area and Severity Index (PASI), Body Surface Area (BSA), Physician Global Assessment (PGA), and Dermatology Life Quality Index (DLQI).

Material and methods

The study was conducted in 2018 and included 107 male psoriatic patients hospitalized in the Department of Dermatology, Venereology and Pediatric Dermatology as well as 41 age-matched healthy men. All the study subjects signed informed consent and gave information about the duration of psoriasis, family history, comorbidities, and addictions. The patients underwent physical examination and were evaluated for psoriasis severity using PASI, BSA, PGA, and DLQI.

In order to determine serum OPN and IL-17 concentrations, peripheral blood samples were collected from both psoriatic patients and healthy volunteers. Blood samples were centrifuged for 15 min at 1,000 $\times$ g. Then, serum samples were stored at -80°C until tested. The serum concentrations of OPN and IL-17 were examined with the use of enzyme-linked immunosorbent assay (ELISA) kits (R&D SYSTEMS® Quantikine® ELISA Human Osteopontin, R&D SYSTEMS® Quantikine® HS ELISA Human IL-17) (R&D Systems, Inc., Minneapolis, USA).

The data was statistically analyzed using STATISTICA v. 13.0 (StatSoft, Inc., Tulsa, USA) software. Minimum and maximum values, median and interquartile range (IR) were estimated for continuous variables, as well as the absolute numbers (n) and percentages of the occurrence of items for categorical variables.

We used statistical tests as follows:

- Mann–Whitney U test to compare age as well as OPN and IL-17 serum concentrations between psoriatic patients and healthy volunteers;
- Mann–Whitney U test to compare OPN and IL-17 serum concentrations between psoriatic patients with PASI below 25 and between 25 and 45;
- Pearson's correlation coefficient r to correlate: OPN and IL-17 serum concentrations, OPN serum concentration and psoriasis severity, IL-17 serum concentration, and psoriasis severity;
- Kruskal–Wallis H test to compare OPN and IL-17 serum concentrations between 3 groups of psoriasis severity measured with PGA.

The significance level was assumed at 0.05.

Results

Characteristics of psoriatic patients and healthy volunteers

The study included 107 male patients aged 18–77 years, 47 years on average. The age of the health volunteers was 48 years on average and did not significantly differ from

the psoriatic patients ($p = 0.899$). The age of psoriasis onset ranged from less than 1 year to 65 years, 25 years on average. Psoriasis duration was from a few months to 48 years, 19 years on average.

In the patients studied, the severity of psoriatic skin lesions expressed with PASI was between 3 and 45, 13 on average. The PASI was ≤ 5 in 14% of the patients, up to 10 in 17.76%, i.e., 31.78% of the patients had PASI ≤ 10 , whereas 68.22% of them had PASI > 10 . In the group studied, 12 patients (11.21%) had PASI ≥ 25 .

The extent of the psoriatic skin lesions expressed by BSA in the patients was from 5% to 90%, 25% on average; 25.23% of the patients had BSA ≤ 10 , whereas 74.77% were above 10.

Dermatology Life Quality Index was from 1 to 29 points, 12 points on average. Physician Global Assessment was minimal in 13 patients (12.15%), mild in 57 patients (55.74%), moderate in another 35 individuals (32.71%), and severe in 2 patients (1.87%).

Comparison of osteopontin and interleukin 17 serum concentrations between psoriatic patients and healthy volunteers

Osteopontin serum concentration in the psoriatic patients was in the range of 0.15–185.88 ng/mL, 31.65 ng/mL on average, with IR = 16.79. This was significantly higher than in the healthy volunteers (0.09–21.22 ng/mL, 11.42 ng/mL on average, with IR = 5.90) ($p < 0.001$, Fig. 1).

Interleukin 17 serum concentration in the psoriatic patients was in the range of 0.10–18.31 pg/mL, 0.53 ng/mL on average, with IR = 0.73. This was significantly higher than in the healthy volunteers (0.05–0.92 pg/mL, 0.09 ng/mL on average, with IR = 0.10) ($p < 0.001$, Fig. 2).

A correlation between OPN and IL-17 serum concentrations was not found, either in the psoriatic patients ($r = 0.144$, $p = 0.139$) or in the healthy volunteers ($r = -0.107$, $p = 0.501$).

Fig. 1. Comparison of OPN serum concentration between psoriatic patients and healthy volunteers

Fig. 2. Comparison of IL-17 serum concentration between psoriatic patients and healthy volunteers

Osteopontin and interleukin 17 serum concentrations vs clinical severity of psoriasis

No correlation between OPN serum concentration and psoriasis severity measured with PASI, BSA and DLQI was found. However, IL-17 serum concentration correlated positively with psoriasis severity measured with PASI, BSA and DLQI ($r > 0$, $p < 0.05$; Table 2). This means that the higher the IL-17 serum concentration the patients had, the greater the psoriasis severity they had, on average.

Interleukin 17 serum concentration significantly differed between the PGA groups of psoriasis severity in the examined patients ($p = 0.027$, Table 3). The examined patients

Table 1. Characteristics of psoriatic patients

Parameter	Min–Max	Median	IR
Age [years]	18–77	47	21
Age of onset [years]	0.5–65	25	18
Psoriasis duration [years]	0–48	19	20
PASI	3–45	13	10
BSA (%)	5–90	25	35
DLQI	1–29	12	9

PASI – Psoriasis Area and Severity Index; BSA – Body Surface Area; DLQI – Dermatology Life Quality Index; IR – interquartile range.

Table 2. Correlations between OPN and IL-17 serum concentrations and psoriasis severity in the patients examined

Severity of psoriasis	OPN [ng/mL]		IL-17 [pg/mL]	
	r	p-value	r	p-value
PASI	0.160	0.100	0.211	0.029
BSA [%]	0.119	0.224	0.251	0.009
DLQI	–0.053	0.589	0.299	0.002

OPN – osteopontin; IL-17 – interleukin 17; PASI – Psoriasis Area and Severity Index; BSA – Body Surface Area; DLQI – Dermatology Life Quality Index.

Table 3. Osteopontin and IL-17 serum concentrations vs PGA in the psoriatic patients

Proteins	Severity of psoriatic changes (PGA)	Parameter of proteins			Significance of differences	
		min–max	median	IR	H	p-value
OPN [ng/mL]	minimal	14.73–127.81	32.99	12.97	1.309	0.520
	mild	8.60–185.88	30.96	16.18		
	moderate	0.15–78.67	31.69	21.57		
IL-17 [pg/mL]	minimal	0.16–1.08	0.35	0.19	7.238	0.027
	mild	0.10–18.31	0.52	0.83		
	moderate	0.12–13.74	0.74	1.15		

The proteins were not analyzed in severe psoriasis according to PGA, due to the small sample size in this group (n = 2). OPN – osteopontin; IL-17 – interleukin 17; PGA – Physician Global Assessment; IR – interquartile range.

Table 4. Osteopontin and IL-17 serum concentrations vs PASI in psoriatic patients

Proteins	PASI	Parameter of proteins			Significance of differences	
		min–max	median	IR	Z	p-value
OPN [ng/mL]	below 25	0.15–127.81	31.65	17.37	0.977	0.328
	25–45	24.51–185.88	30.80	32.5		
IL-17 [pg/mL]	below 25	0.10–18.31	0.49	0.62	2.987	0.003
	25–45	0.12–6.32	1.59	2.95		

PASI below 25 (n = 95); PASI 25–45 (n = 12). OPN – osteopontin; IL-17 – interleukin 17; PASI – Psoriasis Area and Severity Index; IR – interquartile range.

with moderate severity of psoriatic changes according to PGA had the highest IL-17 serum concentration (0.74 pg/mL on average), the patients with mild changes had lower IL-17 (0.52 pg/mL on average) and the patients with minimal changes had the lowest IL-17 serum concentration (0.35 pg/mL on average). However, OPN serum concentration did not significantly differ between the PGA groups of psoriasis severity in the examined patients ($p = 0.520$).

Osteopontin serum concentration did not significantly differ between psoriatic patients with PASI below 25 and between 25 and 45. Interleukin 17 serum concentration was significantly higher in psoriatic patients with PASI 25–45 (1.59 pg/mL on average) than in psoriatic patients with PASI below 25 (0.49 pg/mL on average; Table 4).

Discussion

Elevated levels of OPN lead to reduction of IL-17 secretion, causing a modulation of Th17 response, which may be suggestive of the existence of a positive feedback between IL-17 and OPN. Studies in mice with model autoimmune encephalomyelitis (EAE) showed that, due to an interaction between OPN and integrin receptor $\beta 3$ of CD4⁺ T cells, OPN is also capable of increasing IL-17 secretion directly. Moreover, anti-OPN treatment reduced the production of IL-17 and reduced the clinical symptoms of EAE.¹⁵ Murugaiyan G. et al. also evaluated OPN expression in the dendritic cells and found it was significantly higher in patients with multiple sclerosis (SM) than in healthy volunteers.¹⁵ In the SM patients studied, OPN

secreted by the dendritic cells stimulated Th17 cells to increase production of IL-17.¹⁵

It has also been suggested that OPN activates the immune response of the Th1 cell subpopulation.⁷ Buback et al. found a strong expression of OPN in the psoriasis plaques, which confirms a possible relationship between OPN and both Th1 and Th17 response.⁷ They surmised that in individuals genetically predisposed to psoriasis, OPN stimulates the antigen presenting cells, i.e., dendritic cells and Langerhans cells, in response to an injury or bacterial antigens.⁷ Buommino et al. found that expression of OPN was associated with an increased expression of IL-1 β , INF γ and tumor necrosis factor α (TNF- α) with simultaneous low expression of IL-10 and IL-4 in psoriatic patients.¹⁶ These results are consistent with the data showing a possible role of OPN as an early protein responsible for lymphocyte differentiation towards Th1 responses in patients with psoriasis.¹⁶ It is known that OPN, by interacting with integrins and the CD44 molecule, strengthens the Th1 response and suppresses Th2, which is explained by lack of OPN expression in patients with atopic dermatitis.¹⁶

In our study, however, no significant correlation between the serum concentration of OPN and IL-17 was observed in the study subjects with psoriasis ($p = 0.139$) and the healthy volunteers ($p = 0.501$), which may have been a result of no significant correlation between the OPN concentration and the clinical severity of psoriasis in the subjects of our study. In contrast, serum IL-17 concentration was found to correlate positively with PASI, BSA, PGA, and DLQI. Thus, it is likely that the relationship between OPN

and IL-17 is complex and may be independent of psoriasis severity.

In imiquimod-induced psoriasis experimental animal models, Frenzel et al. observed that increased OPN concentration may promote an inflammatory process mediated by Th17 cells, whereas the OPN-deficient mice studied presented an altered composition of inflammatory cells in the skin, lymph nodes and spleen.¹⁷ A decrease in OPN concentration, however, was found to be associated with a decrease in the Th17 lymphocyte subpopulation in the lymph nodes and CD8⁺ NK cells and antigen presenting cells (APC) in the skin.¹⁷ The findings of the Frenzel et al. studies infer that OPN attracts these cells to the inflammation sites and that the absence of chemotaxis stimulated by OPN may cause a partial reduction in the influx of the immune cells.¹⁷ The authors also observed that in mice with OPN deficiency a lack of B cell expression in the lymph nodes and spleen may further confirm the participation of OPN in the modulation of systemic inflammation.¹⁷ This is in agreement with the results of other studies carried out on animal models in which OPN promoted polyclonal B cell activation.¹⁸

Chen et al. observed that an increased OPN level correlated positively with the level of IL-17 in the synovium of the joints in the course of rheumatoid arthritis.¹⁹ Similarly to IL-6 and IL-1 β , OPN promotes differentiation of T cells towards Th17 cells.¹⁹ Interestingly, anti-OPN treatment in the animal model of SM resulted in alleviation of the disease symptoms even though no change in IL-6 activity was observed.¹⁹

Zheng et al. found a positive correlation between OPN concentration and the expression of the 2 known inflammation modulators, i.e., CD29 and CD44 receptors in patients with acute coronary syndrome.²⁰ They surmised that the blockage of the CD44 receptor in OPN-stimulated cells significantly reduces the differentiation of Th17 cells.²⁰

In our study, a significantly higher concentration of OPN in the group of psoriatic patients in comparison to the healthy volunteers ($p < 0.001$) was observed, which is in agreement with the results reported by other authors.^{21–24}

In 2016, Abdel-Mawla et al. observed significantly higher OPN expression in the psoriatic plaques in comparison to the healthy skin as well as to the unchanged skin in psoriatic patients.²⁵ Moreover, the expression of OPN in the unchanged skin of psoriatic patients was significantly higher than in the healthy skin of the healthy volunteers. It is worth noting that the expression of OPN in the healthy volunteers was limited to the basal layer, whereas in the unchanged skin in patients with psoriasis it was also present in the other layers of the epidermis. The authors also showed a positive correlation of OPN expression with the density of inflammatory infiltration in the skin.²⁵ This study confirms the participation of OPN in the local inflammatory process occurring in psoriatic lesions. It seems that an increased concentration of OPN in the unchanged skin of psoriatic patients

may stimulate chemotaxis of inflammatory cells towards the predisposed site and contribute to the development of psoriatic plaque.

Amin et al. also observed the presence of OPN in the vascular endothelial cells of patients with psoriasis, which could suggest its role in angiogenesis.²⁶ This may be confirmed by the influence of OPN on the stimulation of vasodilatation observed by Gürsoy et al., which is associated with IL-1 activation and its effect on endothelial cells as well as the stimulation of phagocytic mononuclear cell chemotaxis.¹¹

El-Eishi et al. noticed that after the applied anti-psoriatic treatment, OPN expression was still significantly higher than in the healthy volunteers.²⁷ The greatest decrease in OPN expression was observed in patients undergoing PUVA (psoralen and ultraviolet A) therapy despite their lowest PASI reduction.²⁷ Conversely, the greatest PASI improvement was observed in the patients treated with ciclosporin in whom a decrease in the OPN concentration was smaller.²⁷

In our study, no correlation between OPN serum concentration and clinical severity of psoriasis was found. What is more, OPN concentration did not significantly differ between the group of patients with mild psoriasis and the group with moderate or severe disease severity ($p = 0.713$). Similar results were obtained by other authors who did not find a relationship between plasma OPN concentration and PASI value^{16,21,24,28–30} either. However, different data was presented by Kadry et al., who showed a positive correlation between plasma OPN concentration and the clinical severity of psoriasis.²² Abdel-Mawla et al., using immunohistochemistry, also observed a positive relationship between the OPN expression in the affected psoriatic skin and PASI.²⁵

In our study, there was no significant correlation between the OPN concentration and the PGA value ($p = 0.520$) as well as between the OPN concentration and the DLQI value ($p = 0.589$). Similarly, Chen et al., in their study group of 40 patients, did not observe a relationship between the OPN concentration and the PGA index either.²¹

Conclusions

In light of recent studies, there is an undeniable link between OPN and IL-17. The aforementioned scientific studies provide evidence that increased serum concentrations of OPN and IL-17 contribute to the development of autoinflammatory and autoimmune diseases, including psoriasis.

Although our study did not reveal a correlation between the OPN and IL-17 values in the psoriatic patients studied, it should be emphasized that their concentrations were significantly higher in comparison to the healthy volunteers, which is undoubtedly a signal of some ongoing pathological process. Yet, this issue still awaits further research.

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