Increased plasma lipocalin-2 levels correlate with disease severity and may be a marker of acute inflammatory response in patients with psoriasis

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Abstract

More than a skin disease, psoriasis is also considered a systemic disorder. Lipocalin-2, an adipokine, may be a link between psoriasis and systemic inflammation. We conducted this study to measure the plasma level of lipocalin-2 and investigate its relationship with the clinical manifestations in patients with psoriasis. We assessed 62 patients with psoriasis and 31 healthy controls. Their demographic information and clinical characteristics were determined by physical examination and review of the recorded medical history. Plasma lipocalin-2 levels were measured using an enzyme-linked immunosorbent assay. Plasma lipocalin-2 concentration was significantly higher in patients with psoriasis than in the control group (P<0.001). Patients with acute psoriatic subgroups, including psoriatic erythroderma and pustular psoriasis, had significantly higher plasma lipocalin-2 levels than those with the chronic plaque type. In addition, plasma lipocalin-2 concentration positively correlates with the disease severity index, including the psoriasis area severity index, body surface area, high-sensitivity C-reactive protein, nail psoriasis severity index, and pustular severity index. In patients with psoriasis, increased plasma lipocalin-2 levels correlated with severity and indicated an active disease state. These findings suggest that lipocalin-2 may play an important role in determining the pathogenesis of acute psoriasis and may serve as a valuable clinical biomarker of this disease.

Introduction

Psoriasis is a common immune-mediated disease that affects approximately 2-3% of the population. It mainly affects the skin and joints and increases the comorbidities that lead to many mental problems.[1] The relation of the TNF-a – IL-23 – Th17 – IL-17 axis to the pathogenesis of psoriasis has been proven in the recent decade.[2] Therefore, psoriasis is not only a skin disease but is also a systemic inflammatory condition. Diabetes and metabolic syndrome are the two main comorbidities of psoriasis. Compared to the normal population, patients with psoriasis have twice the risk of developing metabolic syndrome, which is present in approximately 20–50%.[3] The proportion of obesity in psoriatic patients was higher than in the normal population,[4] and the body mass index (BMI) has been positively correlated with the risk of developing psoriasis.[5] Psoriasis and its comorbidities are linked by a chronic inflammatory condition that increases cytokine production, which leads to metabolic disorders, atherosclerosis, and myocardial infarction.[5,6] Adipokines, which are produced by white fat tissue, have been implicated as one of the connections of the complex pathogenesis between psoriasis and obesity as well as metabolic syndrome. These proteins have crucial functions in the metabolism of carbohydrates and lipids and the development of insulin resistance and artherosclerosis.[7] Some adipokines, including leptin, adiponectin, resistin, and visfatin, have been reported to increase in psoriasis and may participate in its pathogenesis.[8,9]

Lipocalin-2 is an adipokine that has recently gained attention because of its role in the pathogenesis of psoriasis. It stimulates neutrophils to release pro-inflammatory cytokines, including IL-6, IL-8, TNF-a, and IL-1a, via the 24p3R receptor on the cell surfaces.[10,11] Recent studies have found a high lipocalin-2 expression in psoriatic lesions and keratinocytes, with lipocalin-2 being produced by neutrophils. Previous studies have also reported an increased level of lipocalin-2 in patients with psoriasis vulgaris compared to normal controls, showing a positive correlation between lipocalin-2 levels and the psoriasis area severity index (PASI),[9,11-14] and pruritus.[15] Another study found high expressions of lipocalin-2 in the affected tissues compared to normal skin.[16]

The role of lipocalin-2 in the pathogenesis of psoriasis is not fully understood. Previous reports have only focused on the correlation between lipocalin-2 and metabolic syndrome characteristics in psoriasis vulgaris.[9,11,14] However, the changes in its levels in different types of psoriasis, including psoriatic arthritis, psoriatic erythroderma, and pustular psoriasis, were not investigated. The pathogenesis of psoriasis in different concepts may lead to a specific approach.[17] Therefore, we performed this study to measure the level of lipocalin-2 in different types of psoriasis and investigate the correlation of its level and clinical and laboratory characteristics of psoriatic patients.

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Materials and methods

Study population

This study was conducted at the Ho Chi Minh City Hospital of Dermatology-Venereology, Vietnam, between November 2019 and July 2020. A total of 62 patients diagnosed with psoriasis and 31 healthy volunteers without a personal or family history of psoriasis or inflammatory disorders were enrolled in the study. We excluded patients with psoriasis treated with systemic anti-inflammatory or immunosuppressive agents within 6 months prior to the study, pregnant patients, lactating patients, and patients with other acute and chronic diseases known to be associated with increased plasma lipocalin-2 levels (infection, renal disease, lupus nephritis, severe pancreatitis, autoimmune diseases, cancer, and immunodeficiency).[10,18] All participants signed an informed consent form after fully understanding the benefits and risks of this study.

After qualified physicians performed physical examination to confirm the diagnosis of psoriasis, a complete medical history (general health, age, sex, occupation at presentation, course and duration of disease, and family history), clinical examinations, and laboratory tests were obtained from each patient. Three subgroups of psoriasis were collected in a 1:1:1 ratio (psoriatic erythroderma: psoriasis vulgaris: pustular psoriasis). Among them, patients whose symptoms met the Classification Criteria for Psoriatic Arthritis were classified as having psoriatic arthritis. The severity of skin disease was determined using the PASI and BSA. For generalized pustular psoriasis, the severity was evaluated according to a previous report.[19] Nail abnormalities were recorded, and the severity of the affected nails was evaluated using the nail psoriasis severity index (NAPSI) score.

Blood sample preparation

Up to 3 mL of peripheral blood samples were obtained from patients and healthy subjects and stored in plasma separator test tubes with ethylenediaminetetraacetic acid. The blood samples were then analyzed at the Medic Medical Center (Ho Chi Minh City, Vietnam) within 2 h of collection, and the plasma lipocalin-2 level was quantitatively detected using a human NGAL enzyme-linked immunosorbent assay kit (KIT 036 RUO, BioPorto Diagnostics, Denmark). Blood samples from the patients were collected and paired with routine analyses at the first visit.

Statistical analyses

All collected data were coded and analyzed using a standard software (R version 3.6.3 for Mac OS). Qualitative data are described as frequencies and percentages (%). Quantitative data with normal distributions are described using mean and standard error of the mean (SEM), while those with non-normal distributions are described as median and interquartile range.

The chi-square test was applied for the comparison of non-numerical data. For normally distributed data, Student's *t*-test and ANOVA were used to determine the statistical significance of the difference between two or more study group means. The Mann-Whitney and Kruskal-Wallis tests were used to compare two or more groups with non-normal distributions. The Spearman correlation test was used to study the correlation between quantitative parameters. All statistical tests were two-sided, and a P-value <0.05 was considered significant in all statistical tests.

Results

Plasma lipocalin-2 concentrations in psoriasis

Selected demographic, clinical, and laboratory characteristics of patients with psoriasis and healthy controls are summarized in Table 1. There were no statistically significant differences between the two groups with respect to sex, age, and BMI.

The median value of plasma lipocalin-2 level in psoriatic patients was 263.6 ng/mL (interquartile range 207.7–384.1 ng/mL). It was significantly higher than in controls (median 125.8 ng/mL, interquartile range 95.7–165.5 ng/mL; p<0.0001) (Figure 1). Moreover, all subgroups of psoriasis also showed significantly upregulated lipocalin-2 levels in comparison to the control groups. In particular, patients with acute psoriasis, including psoriatic erythroderma

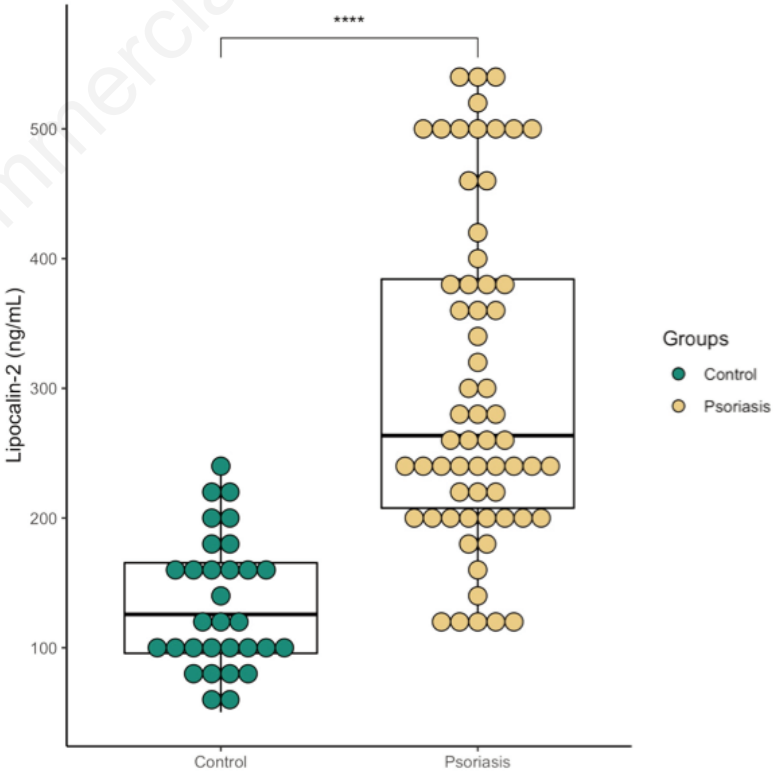

Figure 1. Patients with psoriasis show significantly elevated plasma of lipocalin-2 levels. Plasma lipocalin-2 levels of 62 patients with psoriasis (right) and 31 healthy controls (left) were given. The horizontal bars show the median values. P values < 0.05 is statistically significant. Significance of difference between groups was tested by Mann-Whitney U test (** p<0.0001).**

and pustular psoriasis, had significantly higher plasma lipocalin-2 levels than those with the chronic plaque type (Table 2). These data suggest that lipocalin-2 may be a good marker of the acute inflammatory response in psoriasis.

Plasma lipocalin-2 levels and clinical and laboratory features

In this study, plasma lipocalin-2 levels did not correlate with the demographic characteristics, including age, age of onset, and duration of disease, in patients with psoriasis (Table 3). Despite being an adipokine, we did not detect any relationship between the plasma lipocalin-2 levels and the different metabolic parameters in patients with psoriasis, including BMI, waist circumference, and metabolic syndrome status (Tables 3 and 4). This finding indicates that lipocalin-2 may not play its role as an adipokine but participates in other pathways in the complex pathogenesis of this disease as an inflammatory protein.

Plasma lipocalin-2 levels in correlation with severity markers

Skin

Regarding the markers of skin severity, lipocalin-2 levels positively correlated with BSA and PASI in the subgroup of psoriatic erythroderma and psoriasis vulgaris and the severity score of generalized pustular psoriasis in the subgroup of pustular psoriasis (Table 3).

Table 1. Clinical manifestation of studied groups.

Characteristics	Patients with psoriasis (n = 62)	Control subjects (n = 31)	P value
Sex, n (%)			1.000†
Male	35 (56.4)	17 (54.8)	
Female	27 (43.6)	14 (45.2)	
Age, years	37.0 (26.3-50.8)	38.0 (27.0-50.5)	0.945§
Age of onset, n (%)			
<40 yrs old	48 (77.4)		
≥40 yrs old	14 (22.6)		
Duration of disease, n (%)			
≤10 years	40 (64.5)		
<10 years	22 (35.5)		
BMI (kg/m^2)	21.5±3.4	21.5±2.8	0.921§
BMI Categories, n (%)			0.472¶
Underweight	13 (21.0)	7 (25.0)	
Normal weight	30 (48.4)	13 (46.5)	
Overweight	8 (12.9)	6 (21.4)	
Obese	11 (17.7)	2 (7.1)	
Waist circumference (cm)	80.5±9.6	77.2±8.8	0.115§
Metabolic syndrome, yes (%)	12 (19.4%)	4 (14.3%)	0.751†
Subgroups of psoriasis, n (%)			
Psoriasis vulgaris	21 (33.9)		
Pustular psoriasis	20 (32.2)		
Psoriatic erythroderma	21 (33.9)		
Psoriatic arthritis	16 (25.8)		
Nail psoriasis, yes (%)	41 (66.1)		
Severity of disease: BSA			
Psoriasis vulgaris	19.0 (10.0-54.0)		
Psoriatic erythroderma	98.0 (97.0-99.0)		
Pustular psoriasis	58.5 (35.5-81.5)		
Severity of disease: PASI			
Psoriasis vulgaris	13.0 (5.8-21.7)		
Psoriatic erythroderma	44.4 (34.8-49.8)		
Severity score of GPP	10.4±2.8		
NAPSI			
Psoriasis vulgaris	50.1±21.9		
Psoriatic erythroderma	77.8±31.4		
Pustular psoriasis	60.1±21.0		
Psoriasis arthritis, n (%)			
Only peripheral joints	4 (6.5)		
Both axial and peripheral joints	12 (19.3)		
No	46 (74.2)		
Topical treatment, yes (%)	38 (61.3)		
hs-CRP, mg/L	18.8 (4.6-101.1)	0.6 (0.4-1.1)	<0.001*§

Data were described using mean (± standard error of the mean) for normal distribution and median (interquartile range) for non-normal distribution. Differences between patients and controls was analyzed by using †Chi-quare, ‡Mann-Whitney, §T-Test, and ¶Fisher's Exact Test. BMI: Body Mass Index, BSA: Body Surface Area, GPP: Generalized Pustular Psoriasis, hs-CRP: high sensity C-Reactive Protein, NAPSI: Nail Psoriasis Severity Index, PASI: Psoriasis Area Severity Index. *Statistically significance ($p<0.05$).

Table 2. Plasma lipocalin-2 in subgroups of psoriasis.

	Controls n = 31	Psoriasis vulgaris n = 21	Psoriatic erythroderma n = 21	Pustular psoriasis n = 20	Psoriatic arthritis n = 16
Lipocalin-2 (ng/mL)	125.8 (95.7-165.5)	203.9 (165.0-237.9)	381.7 (297.7-500.0)	257.9 (236.4-365.8)	338.4 (226.3-479.7)
p (*vs.* controls)		<0.0001*	<0.0001*	<0.0001*	<0.0001*
p (*vs.* PV)			<0.0001*	0.001*	0.001*

Data were presented as median (range) and its range is 25-75th percentiles. Statistically analysis is done using Mann-Whitney test. *Statistically significance (p<0.05). PV: Psoriasis vulgaris.

Nail involvement

As nails are known to be highly impaired in patients with psoriasis, we detected a significant positive association (p=0.044, Table 3) upon analysis of the relationship between lipocalin-2 levels and the nail psoriasis severity index (NAPSI). However, there was no statistical difference in the lipocalin-2 concentrations between patients with and without nail lesions (p>0.05, Table 4).

Joint involvement

Although plasma lipocalin-2 levels in patients with psoriatic arthritis were found to be significantly higher than those in the control group (p<0.0001, Table 2), no significant increase in plasma lipocalin-2 levels was observed in patients with both axial and peripheral joint involvement compared with patients with only peripheral joint involvement and patients without joint involvement (p>0.05, Table 4).

Laboratory findings

High-sensitivity C-reactive protein (hs-CRP) is a sensitive marker of systemic inflammation in psoriasis (20). In our study, both the plasma hs-CRP and lipocalin-2 levels in patients with psoriasis were significantly higher compared to that of healthy controls (Table 1 and Figure 1). Furthermore, a significant positive correlation between lipocalin-2 levels and hs-CRP levels was detected (p<0.001, Table 3).

Table 3. Spearman correlation between lipocalin-2 level and different variables.

	Plama lipocalin-2 (ng/mL) Correlation (r)	p
Age (year)	0.080	0.538
BMI (kg/m^2)	0.023	0.859
Waist circumference (cm)	0.164	0.202
Age of onset (year)	0.146	0.257
Duration of disease (year)	-0.121	0.349
BSA (%)	0.578	<0.001*
PASI	0.607	<0.001*
Severity score of GPP†	0.668	0.002*
NAPSI	0.316	0.044*
hs-CRP (mg/L)	0.424	<0.001*

BMI: Body Mass Index, BSA: Body Surface Area, GPP: Generalized Pustular Psoriasis, hs-CRP: high sensity C-Reactive Protein, NAPSI: Nail Psoriasis Severity Index, PASI: Psoriasis Area Severity Index. *Statistically significance (p<0.05).

Table 4. Comparison of plasma lipocalin-2 levels according to the clinical variables.

	Plasma lipocalin-2 (ng/mL)	p
BMI Categories		0.311†
Underweight	297.7 (214.4-380.3)	
Normal weight	249.4 (201.4-378.6)	
Overweight	221.8 (199.9-279.6)	
Obese	294.3 (249.7-440.8)	
Metabolic syndrome		0.345‡
Yes	296.3 (227.7-500.2)	
No	254.3 (206.2-380.3)	
Nail psoriasis		0.294‡
Yes	274.9 (207.4-462.1)	
No	q244.5 (211.9-310.7)	
Psoriasis arthritis		0.628†
Only peripheral joints	297.4 (212.7-412.6)	
Both axial and peripheral joints	338.4 (256.9-497.8)	
No	242.0 (204.5-363.4)	

Data were presented as median (range) and its range is 25-75t^h percentiles. Differences between two or more groups were tested by †Kruskal-Wallis test and ‡Mann-Whitney test. P values <0.05 is statistically significant.

Discussion

To emphasize the importance of our findings, we propose three points for discussion.

Plasma lipocalin-2 plasma levels were significantly increased in patients with psoriasis compared to those in the control groups

This finding is consistent with other previous studies,[9,11-14] but our data particularly pointed out that patients with acute psoriasis, including psoriatic erythroderma and pustular psoriasis, had significantly higher plasma lipocalin-2 levels than those with the chronic plaque type. The pathways involved in acute inflammatory conditions and the chronic type in psoriasis vulgaris may be different, though the majority of the process have not been understood. The main cells that actively participate in these responses include keratinocytes and neutrophils. Keratinocytes produce chemokines and lipocalin-2, which recruit neutrophils to migrate into the lesional area and produce oxidation stimulation and various cytokines and peptides, including lipocalin-2.[21] Lipocalin-2 regulates the function of neutrophils, including activation, migration, and infiltration,[15,22] and stimulates neutrophils to produce pro-inflammatory cytokines, such as IL-6, IL-8, IL-1a, and TNF-a, via specific 24p3R on these cell surfaces.[11,23] Therefore, neutrophil dysfunction may lead to severe diseases.

Both IL-17 and TNF-α are important cytokines in the pathogenesis of psoriasis. The expression of lipocalin-2 has been shown to be enhanced by IL-17A stimula-

tion.[24] It may also trigger inflammation in psoriasis by enhancing the Th17 pathway,[25] causing the production of Th17 cytokines (IL-17A, IL-17F, IL-22, IL-23p19, and IL-23p40), which then leads to an inflammatory response.[25] The neutralization of this peptide showed a decrease in epidermal proliferation, inflammation, and neutrophilic infiltration in psoriatic lesions in an imiquimod-induced psoriasis model.[23] As the lesions faded over time, the expression of lipocalin-2 decreased, highlighting its correlation with disease progression.[26] This finding suggests that lipocalin-2 may participate in the pathogenesis of psoriasis through the regulation of neutrophil function during the acute immune response. As such, it may be a potential treatment target in the future.[23] Another report found a correlation between lipocalin-2 levels and TNF-α in patients with psoriasis.[11] Lipocalin-2 can be produced from the local skin tissue and a wide range of cells, including neutrophils, macrophages, adipocytes, and epidermal cells.[10,11,25]

Lipocalin-2 may have a pathogenic role in the acute types of psoriasis

Lipocalin-2 may take part in the inflammatory response by stimulating and causing the migration of neutrophils and activating the Th17 pathway.[23,25] To date, there have been no reports of lipocalin-2 levels in pustular psoriasis. In a recent report, the author found high lipocalin-2 expression in the lesions of patients with palmoplantar pustular psoriasis, and IL-1β was the active cytokine stimulating the expression of lipocalin-2.[27] IL-1β has been proven to be the main cytokine that drives the acute response in pustular psoriasis.[17] Therefore, increased lipocalin-2 in the plasma may be mediated by the IL-1β pathway, leading to neutrophil infiltration and formation of the typical pustules in pustular psoriasis.

In erythrodermic psoriasis, the inflammatory pathway is mediated by a large amount of IFN type I from pyruvate dehydrogenase complexes, which is different from the traditional TNF-IL-23-Th17 pathway in psoriasis vulgaris.[17] The overexpression of antimicrobial peptides in the lesion may activate the immune response,[28] with lipocalin-2 being one of the highly expressed antimicrobe peptides in the lesions.[29] Therefore, we assumed that lipocalin-2 plays a crucial role in the pathogenesis of this acute systemic type of psoriasis.

Plasma lipocalin-2 positively correlates with disease severity

In contrast to previous reports on the role of lipocalin-2 in metabolic syndrome,[30] insulin resistance, and diabetes,[31] we did not detect any relationship between the plasma lipocalin-2 levels and the different metabolic parameters, including BMI, waist circumference, and metabolic syndrome status. However, we noticed a positive correlation between the peptide levels and severity indices, including PASI, BSA, NAPSI, pustular severity index, and hs-CRP. Lipocalin-2 is an acute phase protein that makes it a potential biomarker for the early diagnosis,[32] follow-up, prognostication of several inflammatory diseases, including lupus nephritis, severe pancreatitis, colitis, acute renal disease; and the assessment of the severity of chronic renal disease.[10] Therefore, our results are in line with other reports that lipocalin-2 is one of the most important pro-inflammatory cytokines that may drive the inflammatory response in the active phase of psoriasis.

We should point out that there was a limitation in our present study because we substituted circulating lipocalin-2 levels instead of their expression within the affected tissue. Further studies including a large number of patients will be required to validate the possible contributions and underlying mechanisms of different immunologic pathways in psoriasis pathogenesis.

Conclusions

Increased plasma lipocalin-2 levels in patients with psoriasis correlate with severity and particularly indicate an active disease state. In the current study, we assumed that lipocalin-2 may play an important role in the pathogenesis of acute psoriasis and may serve as a valuable clinical biomarker of disease severity. Further investigation is needed to provide more insight into the pathogenesis of psoriasis.

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