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Original Article

High serum resistin levels correlate with the increased severity of psoriasis vulgaris

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Abstract

Background Psoriasis is a chronic inflammatory skin disorder characterized by an increase in epidermal turnover and inflammation of the dermis. Resistin is one of the adipokines that promotes the production of proinflammatory mediators involved in the pathogenesis of psoriasis. This study aimed to assess the correlation between serum resistin levels with the severity of psoriasis vulgaris.

Methods The disease severity was recorded based on Psoriasis Area and Severity Index (PASI) score, and serum resistin levels were obtained for each subject. The independent t test and One-Way ANOVA were applied for comparative analysis and the Pearson test was used to measure correlation analysis.

Results Serum resistin levels didn't differ significantly between men and women (p=0.998) or also between the normal, overweight and obese subjects (p=0.624). Serum resistin levels were significantly higher in subjects with psoriasis vulgaris compared with controls (p<0.001). High serum resistin levels were markedly correlated (r=0.848; p<0.001) with the increased severity of psoriasis vulgaris based on the Psoriasis Area Severity Index (PASI) scores.

Conclusion Serum resistin levels mediates the degree of inflammation of psoriasis and correlates with the severity of psoriasis vulgaris.

Key words
Resistin; Psoriasis vulgaris; PASI score; Metabolic syndrome.

Introduction

Psoriasis vulgaris is an immune-mediated skin disorder that may negatively impact physical and psychosocial well-being. It affects 2-3% of general population worldwide,[1] whereas in Asia, the prevalence of psoriasis is known to be estimated at 0.4-0.7% of the population.[2] The pathogenesis of psoriasis is complex, based on genetic factors and influenced by various biochemical, immunological and vascular abnormalities. Immunological disorders are mainly dominated by T-helper 1 (Th1) lymphocytes, causing the production of various pro-inflammatory cytokines which result in abnormal proliferation of the epidermis.[3] The inflammatory process in psoriasis does not only occur on the skin, but also occurs systemically, which links the psoriasis with several comorbidities, especially metabolic syndrome.[4] Metabolic syndrome is a combination of several medical conditions, such as central obesity,

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hyperglycemia, dyslipidemia, and hypertension. As a major factor that plays a role in metabolic syndrome, central obesity induces the infiltration of macrophages and T cells in adipose tissue and produces inflammatory cytokines which in turn stimulate the release of several soluble mediators called adipokines.[5] Both psoriasis and metabolic disorders could be the primary conditions, or vice versa, these two conditions can form independently due to the same risk factors (genetic or lifestyle).[6]

Adipokines are cell-signaling molecules secreted by white adipose tissue that is found around the internal organs (visceral fat) and under the skin (subcutaneous fat). In addition, other immune cells, especially macrophages, also play a role in secreting adipokines. Proinflammatory adipokine such as resistin, also known as adipocyte-derived secreted factor (ADSF), is an adipokine associated with inflammation, immunity, obesity, and insulin resistance. Human resistin is particularly produced by monocytes and macrophages that are present in adipose tissue and in peripheral blood vessels. Although the biological mechanism explaining the association between resistin and psoriasis is poorly understood, the increased production of proinflammatory mediators in psoriasis (TNF-α, IL-6) could stimulate the formation of proinflammatory adipokines, one of which is resistin.[4,7] Resistin itself would further increase the production of inflammatory mediators involved in the pathogenesis of psoriasis (TNF-α, IL-6, and IL-12), so the inflammatory process could get enhanced through a positive feedback mechanism.[8]

The purpose of this study was to compare the serum levels of resistin among psoriatic patients with matched-healthy controls, and to assess the correlation of resistin levels with disease severity according to PASI score.

Methods

The research was a case-control study carried out in the Allergy-immunology Division, Prof dr. I.G.N.G Ngoerah General Hospital Denpasar Bali in 2019, after the approval by the Local Ethics Committee, and informed consent was obtained from all participants. Inclusion criteria were age of >18 years old, diagnosed with psoriasis vulgaris (both clinically and histopathologically for case), with age- sex- and BMI-matched with each case (for control). Exclusion criteria were patients with other chronic metabolic diseases (diabetes melitus, coronary heart disease, chronic kidney disease, hepatic sirosis), patients with acute or chronic infection (upper respiratory infection or tuberculosis), patients with malignancy, autoimmune disease, pregnancy, immunocompromised state (HIV infection), patients who took systemic corticosteroids, antioxidants, insulin or *thiazolidinedione* (TZD) during 4 weeks before the study.

Consecutive sampling method was used and each subjects underwent questionairre screening for exclusion criteria, venous blood sampling, and Psoriasis Area Severity Index score calculation in each cases.

Results

Fourty-two subjects, consisted of 21-subjects with psoriasis and 21-matched controls, were recruited. **Table 1** shows the characteristics of the case and control group. Most of the participants were men (76.19%), with normal body mass index in 57.14%. The mean age in both case and control group were beyond fifth decade of life. In the case group, only 23.81% patients had the family history of psoriasis. The average PASI score was 15.02±7.66, with more than 80% of cases with moderate and severe psoriasis. The comparison of BMI levels

Table 1 Comparison of the characteristics of cases and controls.

Variables	*Case group (n=21)*	*Control group (n=21)*
Age	42.24±14.67	40.90±12.97
Gender		
Men	16 (76.19)	16 (76.19)
Women	5 (23.81)	5 (23.81)
Body Mass Index (BMI)		
Normal (18.5-24.9)	12 (57.14)	12 (57.14)
Overweight (25-29.9)	6 (28.57)	7 (33.33)
Obesity (>30)	3 (23.81)	2 (9.52)
Mean±SD (kg/m2)	25.19±4.73	24.73±4.26
Family history of psoriasis		
Yes	5 (23.81)	
No	16 (76.19)	
PASI score		
Mild (<7)	3 (14.29)	
Moderate (7-15)	9 (42.86)	
Severe (> 15)	9 (42.86)	
Mean±SD	15.02±7.66	

PASI: Psoriasis area and severity index.

Table 2 Comparison of BMI based on PASI score.

Severity of Psoriasis	*n (%)*	*BMI (kg/m^2)*
Mild (PASI <7)	3 (14.29)	24.03±4.78
Moderate (PASI 7-15)	9 (42.86)	24.99±4.86
Severe (PASI >15)	9 (42.86)	23.34±5.07

P= 0.855; One-Way Anova

between mild, moderate, and severe psoriasis were not statistically significant (*p*=0.855) (**Table 2**). Resistin levels did not differ significantly between men and women (*p*=0.998) (**Table 3**). With regard to BMI levels, resistin levels were higher in obese group than in normal and overweight groups but not statistically significant (p=0.624) (**Table 3).** The case group had resistin levels higher than the control group (p< 0.001), with mean difference of 1622.37 ng/L (**Table 3)**.

In the case group, serum resistin levels were strongly correlated with increased severity of psoriasis (r=0.848; p <0.001) (**Table 4)**. The determination coefficient (R^2 linier) was 0.72, which means that the effect of increasing serum resistin levels on the severity of psoriasis vulgaris was found to be 72% (**Figure 1**).

Discussion

Psoriasis, as a chronic hyperproliferative skin disease, is found worldwide, with the prevalence of 0.33-0.6% in different races.[9,10] Peak incidence of psoriasis has a bimodal distribution, which divides psoriasis into two types, psoriasis type I with onset at less than 40 years called early-onset psoriasis and type II with onset at more than 40 years or called late-onset psoriasis.[2,11] Early-onset psoriasis suggests greater genetic susceptibility that impacts chronicity of psoriasis due to its association with HLA-Cw6.[12] Meanwhile, late-onset psoriasis is usually not related to HLA, and does not show any genetic susceptibility.

A study conducted by Hellgren *et al*; stated that the risk of developing psoriasis was 8 to 23% in first-degree relatives.[13] In this study, the majority of psoriasis subjects recruited were over 40 years old which indicated that psoriasis vulgaris found in this study had a late onset, and a family history of psoriasis was only found in 23.81%

Table 3 Comparison of serum resistin levels.

	Resistin (ng/L)	*Mean difference, CI 95%*	*P value*
Between gender			
Male	1821.26±1303.99	0.877	0.998
Female	1822.14±1154.49	(-932.16 – 930.41)	
Based on BMI			
Normal (18.5-24.9)	1757.19±1107.16		0.624
Overweight (25-29.9)	1739.60±1388.19		
Obesity (> 30)	2342.89±1720.80		
Between group			
Case group	2627.90±1270.35	1622.37	<0.001*
Control group	1005.53±492.98	(1011.02 – 2233.72)	

CI: Confidence interval; *p< 0.05

Table 4 Correlation of serum resistin levels with the severity of psoriasis vulgaris.

			Severity of Psoriasis Vulgaris (PASI score)	*P*
Resistin serum levels	Correlation coefficient	r	0.848	< 0.001*
	Determination coefficient	R2	0.720	< 0.001*

*P < 0.05. Pearson test.

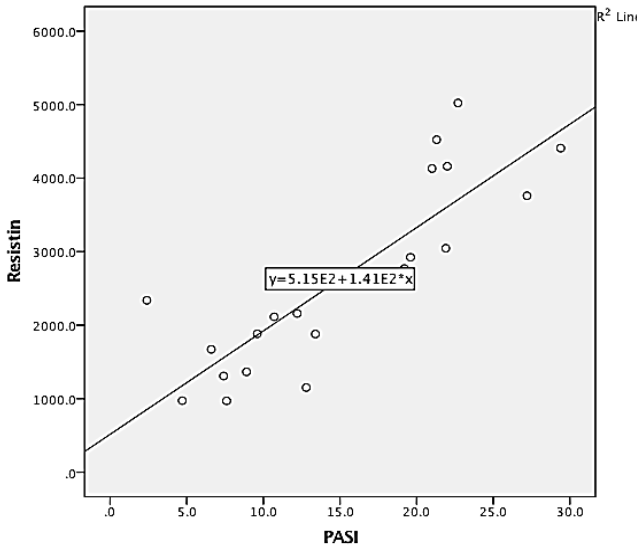

Figure 1 Scattered plot graph of correlation of serum resistin levels with PASI score.

subjects of psoriasis vulgaris. Most of the respondents involved in this study were men (76.19%) both in case group and in control group. The evidence showing the difference in the incidence of late-onset psoriasis between men and women has not been found.[2,14] However, several other studies state that there is an increased incidence of psoriasis in men compared to women. In a study conducted in Taiwan, the ratio of the incidence of psoriasis in males to females was 2.17:1.[15]

The higher prevalence of psoriasis in men could be caused by various factors, one of which is the role of reproductive hormones. Cemil *et al.* stated that estradiol has a protective effect against psoriasis.[16] Female sex hormones influence the clinical severity of psoriasis. High estrogen levels, as seen in pregnancy, and increased estrogen to progesterone-ratios might improve the severity of psoriasis; while progesterone alone does not affect psoriasis.[14] Estradiol has a bipotent effect on monocytes and macrophages, at high concentrations it inhibits the immune response, whereas at low concentrations it can increase inflammation and immunological processes.[17] Low estradiol concentrations can increase polarization of T cells towards Th1, triggering the production of proinflammatory cytokines (IL-1, IL-6, TNF-α, IFN-γ), whereas at high concentrations it can reduce the number of Th17 cells and reduce the production of proinflammatory cytokines.[16,18] Accordingly, estrogens act as a negative regulator for tumor necrosis factor (TNF), the cytokine involved in psoriasis pathogenesis.[14] Arnold *et al.* stated that estrogen has an inhibitory effect on the epidermal ornithine decarboxylase, an enzyme needed for DNA replication, so estrogen has an anti-psoriasis effect because it can inhibit the proliferation of keratinocytes in psoriasis.[19] While the testosterone hormone has an immunological shift effect towards Th2, it was found that testosterone levels in psoriasis patients were lower than controls.[16]

In several studies, it is known that an increase in body mass index (BMI) is associated with psoriasis. In a case-control study in Italy, an odds ratio of 1.9 was found to develop psoriasis in subjects with a BMI above 30 kg/m2.[13] In addition, obesity could increase the severity of psoriasis and is related with a higher failure of psoriasis therapy.[20] A case-control study conducted by Coimbra *et al.* (2010) showed the significant difference in BMI between psoriasis group compared to controls, with the average BMI in psoriasis group of 27.49 kg/m^2.[21] In this study, the BMI characteristics in the case and control groups were found not to differ

significantly in this study due to the matched sampling procedure for cases and controls to avoid obesity confounding factors in resistin measurements. In the psoriasis vulgaris group, the majority of BMI showed a normal range (18.5-24.9 kg/m^2) in 57.14% of patients, with the mean value was 25.19±4.73 kg/m^2. Meanwhile, no significant difference of BMI levels between the mild, moderate and severe psoriasis group was found. This is in accordance with research conducted by Sobhan *et al.* which examined the relationship between obesity and the degree of severity of psoriasis. In that study, there were no significant differences in BMI in mild, moderate, and severe psoriasis.[22] However, in a study in Italy by Bardazzi *et al*; it was found that there was a relationship between an increase in BMI and the severity of psoriasis.[23] The inconsistent relationship between obesity and the severity of psoriasis still requires further study, because the severity of psoriasis is still influenced by various other extrinsic factors such as infection, inadequate use of topical and systemic drugs, and physical/psychological stress.

The serum resistin levels didn't differ significantly between men and women. This is in contrast to a study by Stofkova, which stated that resistin expression was found to be higher in men because the hormone testosterone plays a role in triggering resistin expression.[24] The absence of this difference might be due to the fact that most of the samples were in their fifth decade, so that the effect of the testosterone on resistin production had begun to decline.

In addition, this study confirmed the resistin levels in subjects with normal BMI, overweight and obesity did not differ significantly. This result was in accordance with studies conducted by Gerdes and Jamaluddin which stated that although resistin is a pro-inflammatory adipokine, adipose tissue produces resistin in very small amounts, even undetectable, and the percentage of body fat does not affect serum resistin levels.[6,25]

Psoriasis is "more than skin deep" due to psoriasis being strongly associated with several comorbidities, one of which is obesity.[26] Obesity is linked with chronic systemic inflammation, which is characterized by abnormal adipokine production and activation of inflammatory signaling pathways, which would further increase the risk of psoriasis development.[27] In this study, we noted that serum resistin levels were higher in the psoriasis group compared with controls (p <0.001). The results of this study are in accordance with several previous studies.[7,28] A study by Coban *et al.* stated that significant difference in resistin levels was found in psoriasis compared to controls, both before and after therapy, but the comparison of resistin levels in psoriasis group before and after therapy was found to be not significantly difference.[28]

Most of the cases in this study had moderate to severe degree of psoriasis, with normal BMI levels, but the serum resistin levels were significantly higher than controls. This explains that the increase of serum resistin levels in psoriasis is more related to the degree of inflammation rather than obesity. Resistin is a proinflammatory adipokine produced by mononuclear cells by the stimulation of proinflammatory cytokines.[6,8] Psoriatic plaques contain many macrophages, and secrete IL-6, IL-12, IL-23, dan TNF-α.[29] Apart from triggering keratinocyte proliferation, high levels of TNF-α in psoriasis will trigger resistin production, especially by mononuclear cells. Resistin will then increase the production of proinflammatory cytokines (IL-6, IL-8, IL-12, TNF-α) through NFkB signal transduction **(Figure 2)**.[8,25]

Various factors can affect the expression of resistin such as age, sex, obesity, chronic

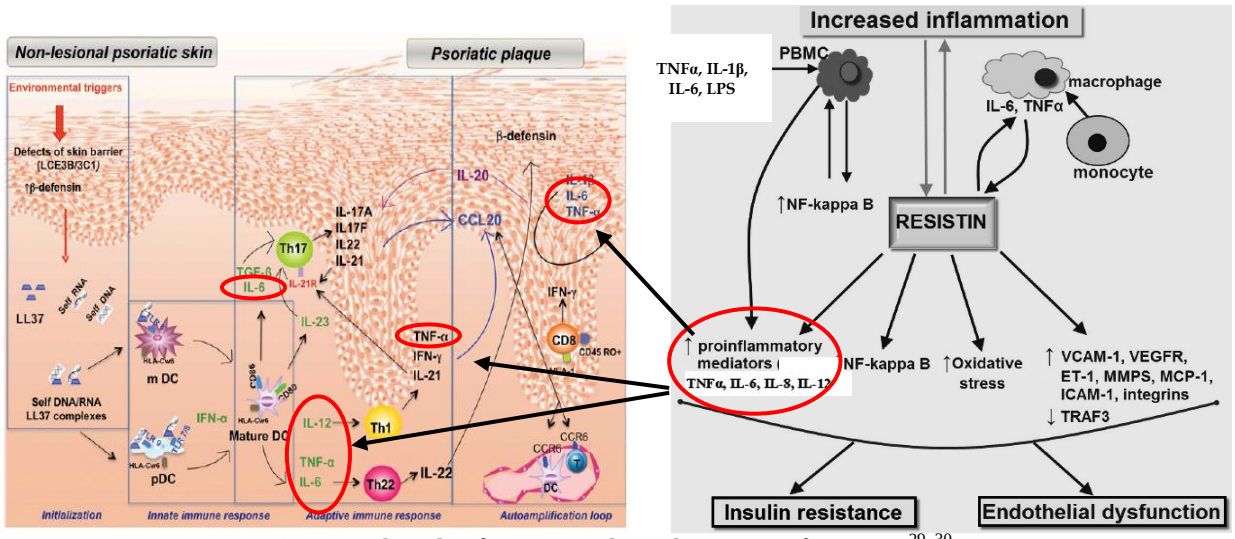

Figure 2 The role of resistin in the pathogenesis of psoriasis[29, 30] (Modified from Monteleone, 2011 and Kizilarslanoglu, 2015).

diseases such as diabetes mellitus, coronary heart disease and chronic kidney failure, acute/chronic infections, internal organ malignancies, other autoimmune diseases, use of corticosteroids, insulin, thiazolidinediones, anti-inflammatory and antioxidants. In experiments on rat adipose cells, resistin expression was induced by corticosteroids, testosterone, prolactin, and somatotropin, and was inhibited by insulin, thiazolidinediones, and epinephrine.[24] The use of thiazolidinediones can reduce resistin levels due to inhibition of resistin expression in adipose tissue. Vitamin C supplementation can reduce resistin levels in healthy individuals.[8] These factors have been controlled into the inclusion and exclusion criteria of this study to minimize the effect of confounding factors on high levels of resistin.

This study found a strong positive correlation (r=0.848; p <0.001) between serum resistin levels and the severity of psoriasis vulgaris as measured by the PASI score, which defined that the higher the serum resistin level, the more severe the psoriasis vulgaris. The magnitude of the effect of increasing serum resistin levels on the severity of psoriasis vulgaris is shown by the coefficient of determination, with a linear R2 value of 0.720 (p <0.001), which indicates that increasing serum resistin levels has an effect of 72% on increasing the severity of psoriasis, while 28% is affected by another factor.

Increased serum resistin levels in psoriasis vulgaris and its correlation with PASI scores has been reported in several studies.[4] Previous research conducted by Pina *et al*; showed that serum resistin levels had a moderate positive correlation with the PASI score (r=0.63, *p*=0.001).[31] A similar study by Hussein *et al.* also found a strong positive correlation (r = 0.918, p <0.001) between serum resistin levels and the severity of psoriasis.[32]

In addition to being correlated with the PASI score, Robati *et al.* found that increased resistin levels in psoriasis had a positive correlation with subclinical atherosclerosis as assessed by the carotid intima-media thickness.[33] The role of resistin in atherosclerosis is mediated by increased expression of adhesion molecules and chemokines by vascular endothelial cells, such as VCAM-1, CCL2, dan *endothelin-1*.[34] However the link between resistin and atherosclerosis in psoriasis was not investigated in this study and still require further research.

The degree of severity of psoriasis vulgaris is

influenced by several factors. In addition to metabolic diseases, there are various other factors such as smoking habits, psychological stress, physical stress, infection, and treatment compliance.[4,35] The coefficient of determination for resistin in the severity of psoriasis vulgaris was found to be 72%, and the other 28% may be determined by other factors, but those were not analyzed in this study.

Conclusion

Resistin is a proinflammatory adipokine contributed by the degree of inflammation in psoriasis. Although resistin is produced by adipose in very small amounts, the percentage of body fat does not affect serum resistin levels. The chronic inflammation in psoriasis may induce the increased production of resistin that may further increase the degree of inflammation in psoriasis. In our study, we found that subjects with psoriasis had higher serum resistin levels than controls, and there was statistically significant correlation between resistin levels and disease severity parameter based on PASI score.

Declaration of patient consent The authors certify that they have obtained all appropriate patient consent.

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Conflict of interest Authors declared no conflict of interest.

Authors' contribution

VT: Study design, acquisition, analysis and interpretation of data, manuscript wiring, critical review, final approval of the version to be published.

DGO: Study design, interpretation of data, critical review, final approval of the version to be published.

PSSS: Study conception, design, analysis and interpretation of data, critical review, final approval of the version to be published.

NYMP: Study design, acquisition and interpretation of data, critical review, final approval of the version to be published.

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