Disease Markers 34 (2013) 33–39
DOI 10.3233/DMA-120945
IOS Press

Psoriasin: A novel marker linked obesity with psoriasis

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Abstract. To evaluate the role of psoriasin, koebnerisin, interleukn (IL)-12 and IL-23 in the pathogenesis of psoriasis and their relations to Psoriasis Area Severity Index (PASI) and obesity. Thirty patients had chronic plaque psoriasis and 30 healthy subjects matched in age and sex were enrolled in this study. Serum from all subjects were used for determination of psoriasin, koebnerisin, IL-12 and IL-23 by ELISA kits. IL-23 and psoriasin were significantly higher in skin psoriasis compared to controls and psoriatic arthritis (PsA). There was a correlation between psoriasin and both PASI and obesity. On the other hand, IL-12 was significantly increased in PsA compared to skin psoriasis ($p = 0.000$) and controls. Its sensitivity and specificity were 87%, 93%; respectively. To our knowledge, psoriasin is the first biomarker confirm the link between obesity and psoriasis. The risk of developing psoriasis is directly related to higher BMI.

Keywords: Psoriasis, psoriasin, kobneriasin, IL-12, IL-23, obesity

1. Introduction

The percent of psoriasis in the eastern of Saudi Arabia is 5.3% [1]. Psoriasin (S100A7) and koebnerisin (S100A15) were first identified in inflamed psoriatic skin. They are of major interest because of their putative functional roles in innate immunity, epidermal cell maturation, and epithelial tumorigenesis [2]. They have evolved by gene duplications within the epidermal differentiation complex (chromosome 1q21) and form a novel S100 subfamily in human. Despite the highest homology, psoriasin and koebnerisin are distinct in tissue distribution, regulation, and function. They act differently as antimicrobial peptides and promote inflammation, cell migration and chemoattractants [3, 4].

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Different cytokines play a part in sustaining the two main characteristics of a psoriatic lesion; keratinocyte hyperproliferation and inflammation. IL-23 is a member of the IL-12 family of cytokines with proinflammatory properties. IL-23 shares the same p40 subunit with IL-12. The anti-p40 monoclonal antibody neutralized the activities of both IL-12 and IL-23. These findings point to IL-23, but not IL-12, as the necessary mediator of organ-specific autoimmune diseases [5]. Although IL-23 and IL-12 share structural homologies, they have very distinct biological activities. IL-23 specifically stimulates memory $CD4^+$ T cells, whereas IL-12 is a potent stimulant for naive $CD4^+$ T cells [5]. IL-23 induces strong proliferation of mouse memory T cells, a unique activity of IL-23 as IL-12 has no effect on this cell population. Human IL-12 and IL-23 stimulate IFN-gamma production and proliferation in blast T cells. P19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12 [5]. Ustekinumab binds to the p40 subunit common to IL-12 and IL-23 and prevents their actions. Ustekinumab is approved for treatment of moderate-to-severe plaque psoriasis and psoriatic arthritis [6].

ISSN 0278-0240/13/$27.50

Table 1
Demographic data of all psoriatic patients according to Psoriasis area severity index

	Psoriasis Area Severity Index (PASI)			P
	mild (0–3) ($n = 12$)	moderate (> 3–15) moderate ($n = 11$)	severe (> 15) sever ($n = 7$)	
Sex				
Male (11)	5	6	0	0.05*
Female (19)	7	5	7	
Duration of illness				
$>$ 10 years (16)	12	3	1	0.000*
10–20 years (9)	0	4	5	
$<$ 20 years (5)	0	4	1	
Type of psoriasis				
Skin psoriasis (22)	9	7	6	NS
Psoriatic arthritis (8)	3	4	1	
Respond to treatment				
No response (6)	1	3	2	NS
Mild respond (17)	8	6	3	
Moderate (4)	2	0	2	
Excellent (3)	1	2	0	
Obesity				
Underweight (1)	1	0	0	0.03*
Normal (7)	5	1	1	
Overweight (9)	5	4	0	
Obese (13)	1	6	6	
Family history				
Family history of psoriasis (13)	6	7	0	0.02*
No family history of psoriasis (17)	6	4	7	
Smoking				
Smoker (5)	1	2	2	NS
Non-smoker (25)	11	9	5	
Type of treatment				
Local (18)	12	2	4	0.002*
Systemic (2)	0	2	0	
Local + systemic (10)	0	7	3	

Chi-square used to compare between qualitative parameters. $P \leqslant 0.05$ is significant. *is significant, NS is non-significant.

Psoriasis is an inflammatory skin disease often associated with obesity. Several studies found a link of psoriasis with obesity [7]. Both overall and central obesity have been associated with the risk of psoriasis in a prospective study. The study provided evidence linking obesity with the risk of incident PsA among US women [8]. Patients with moderate-to-severe psoriasis have a significantly increased risk of cardiovascular disease and cardiovascular risk factors such as obesity, diabetes mellitus, the metabolic syndrome and smoking compared to the general population. Also, there is a potential excess of cardiovascular events with the newer generation of anti-interleukin-12p40 antibodies used in psoriasis therapies [9]. Psoriatic patients with a body mass index of 27 or more are likely to have vitamin D insufficiency [10]. Obesity may play an additional factor in sever psoriasis that need specific management.

Data on the association between obesity and skin psoriatic or PsA have been sparse. Hence, the aim of this study is to evaluate the role of psoriasin, koebnerisin, IL-12 and IL-23 in the pathogenesis of skin psoriasis and psoriatic arthritis . Also, the relation between PASI, obesity and demographic data of the patients.

2. Patients and methods

This is a case control hospital based study. The study was approved by the Regional Research Ethics Committee, Qassim Province, Ministry of Health, KSA. Written informed consent was obtained from each participant after an information sheet was provided. The study included 30 patients diagnosed as chronic plaque psoriasis and 30 healthy controls matched in age and sex. They were subjected to full history taking, routine laboratory investigations, ESR and uric acid were determined. Body mass index (BMI) and Psoriasis Area Severity Index (PASI), presence of arthritis were recorded. Patients with autoimmune disease like rheumatoid or arthritic lesion like gout were excluded. PASI is the most widely used measurement tool for psoriasis [11]. The patients divided into 3 groups accord-

Table 2
The relation between body mass index and demographic data of cases of psoriasis

		Body Mass Index (BMI)				P
		Underweight (16.0–18.5)	Normal (18.5–25)	Overweight (25–30)	Obesity < 30	
Duration of illness	> 10 years ($n = 16$)	1	6	5	4	0.009*
	10–20 years ($n = 9$)	0	1	0	8	
	< 20 years ($n = 5$)	0	0	4	1	
Psoriasis severity index	Mild(0-3) ($n = 12$)	1	5	5	1	0.03*
	Moderate (> 3–15) ($n = 11$)	0	1	4	6	
	Severe (> 15) ($n = 7$)	0	1	0	6	
Type of psoriasis	Skin psoriasis ($n = 22$)	1	5	7	9	NS
	Psoriatic arthritis ($n = 8$)	0	2	2	4	
Smoking	Smoking ($n = 5$)	0	0	0	5	0.04*
	Nonsmoking ($n = 25$)	1	7	9	8	
Sex	Male ($n = 11$)	0	0	6	5	0.04*
	Female ($n = 19$)	1	7	3	8	
Respond to treatment	No respond ($n = 6$)	0	2	0	4	NS
	Mild respond ($n = 17$)	1	3	8	5	
	Moderate ($n = 4$)	0	2	0	2	
	Excellent ($n = 3$)	0	0	1	2	
Type of treatment	Local ($n = 18$)	1	6	7	4	NS
	Systemic ($n = 2$)	0	0	0	2	
	Local + systemic ($n = 10$)	0	1	2	7	
Family history	Family history ($n = 13$)	0	3	6	4	NS
	No family history ($n = 17$)	1	4	3	9	

Chi-square used to compare between qualitative parameters. $P \leqslant 0.05$ is significant. *is significant, NS is non-significant.

Table 3
The biochemical markers of skin psoriatic and psoriatic arthritis patients

Biomarkers	Control ($n = 30$)	Skin psoriasis ($n = 22$)	Psoriatic arthritis ($n = 8$)	Total cases of psoriasis ($n = 30$)
Interlukin-12 (pg/ml)	24.9 ± 5.18	41.8 ± 12.7	296.5 ± 76.9	109.5 ± 29.8
P value		NS*	$P = 0.000^{*\#}$	$= 0.007^*$
AUC		0.574	0.921	0.763
Interlukin-23 (pg/ml)	123.86 ± 4.60	204.78 ± 24.24	136.56 ± 15.34	186.59 ± 18.93
P value		$=0.000^*$	$= 0.02$#	$= 0.002^*$
AUC		0.767	0.413	0.708
Psoriasin (ng/ml)	4.41 ± 0.26	69.71 ± 32.34	4.75 ± 0.98	52.39 ± 24.16
P value		$= 0.01^*$	$P = 0.01^{\#}$	0.05^*
AUC		0.725	0.416	0.67
Kobneriasin (ng/ml)	17.25 ± 1.58	35.67 ± 8.03	26.35 ± 14.52	33.19 ± 6.96
P value		$= 0.02^*$	NS#	0.02^*
AUC		0.63	0.365	0.559

*Compared to control; #compared to skin psoriasis only. ANOVA test used to compare between groups. AUC: area under the curve of receiver operating characteristic (ROC) curves. NS: non-significant. T-test used to compare between control and total cases of psoriasis.

ing to PASI, mild (> 3), moderate (3–15) and severe (< 15). Five ml blood was collected from each patient and control, centrifuged and serum kept at -80°C for biochemical analysis. CircuLex's S100A7/Psoriasin ELISA Kit (Cat# CY-8073, Japan) was used to estimate psoriasin protein by the quantitative sandwich enzyme immunoassay technique. A polyclonal antibody specific for human S100A7/Psoriasin has been pre-coated onto a microplate. Psoriasin kit could detect psoriasin level from 90.00 ng/ml to 0.12 ng/ml. Kobneriasin measured by Human S100 calcium binding protein A15 (S100A15) ELISA kit WKEA MED Supplies, USA, code # WH-1699. Koebnerisin assay could detect level ranges from 4 ng/ml to 100 ng/ml. IL-12 measured by Human IL-12(P70) RayBio®, ELISA Kit (Cat#: ELH-IL12P70-001). IL-12 is a heterodimeric 70 kDa glycoprotein (IL-12-p70) composed of p35 and p40 subunits. We used here IL-12(p70) not (p40), the whole protein not the subunit IL-12(p40). Human IL-23 ELISA Kit, Glory Science USA -CK-E10077, was used to measure IL-23.

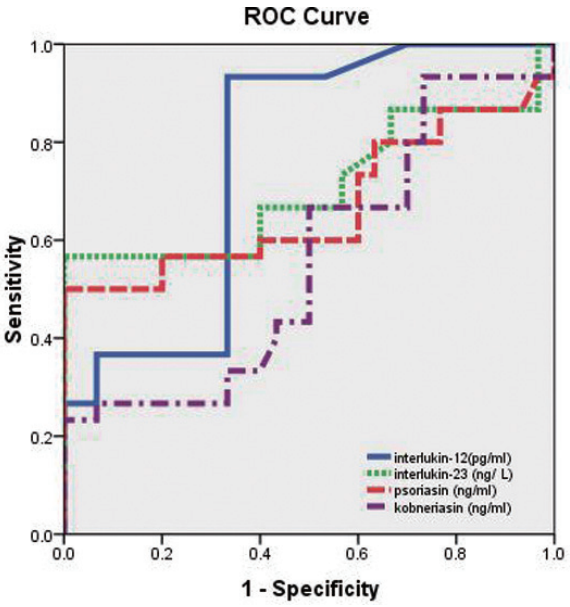

Fig. 1. ROC curves of all cases of psoriasis ($n = 30$) with area under the curve for interlukin-12 (p70) = 0.76; interlkin-23 = 0.7; psoriasin = 0.67; kobneriasin = 0.56. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/DMA-120945)

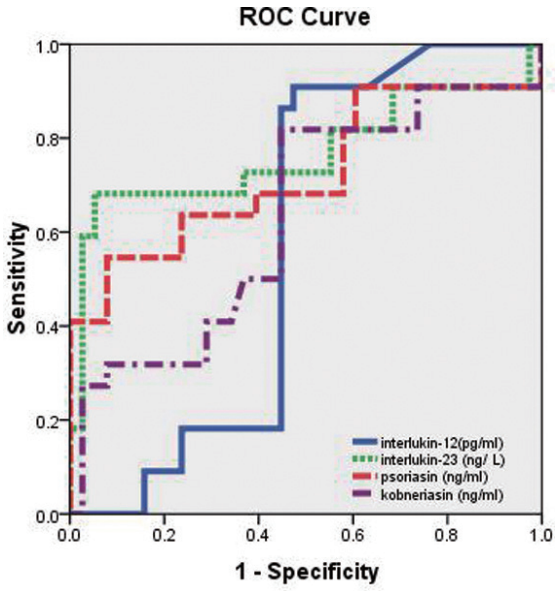

Fig. 2. ROC curves shows cases of skin psoriasis without arthritis ($n = 22$) with area under the curve for interlukin-12(p70) = 0.57; interlkin-23 = 0.76; psoriasin = 0.72; kobneriasin = 0.63. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/DMA-120945)

2.1. Statistical analysis

Data were analyzed using SPSS version 16. Values were expressed as mean ± SEM. Results considered statistically significant at $p \leqslant 0.05$. Difference between values assessed by t- test. One-way analysis of variance (ANOVA) test followed by post hoc test (LSD) used to compare between different types of patients. Person's correlation coefficient was calculated to assess the relation between biomarkers and PASI, response to treatment. Receiver operating characteristic (ROC) curves were done and area under the curve (AUC) was used to compare between markers. Sensitivity and specificity of different markers were determined by choosing from the data result of ROC and the best calculated point achieving the highest sum of sensitivity and specificity was used as cut off value. Chi- square was used to compare between qualitative parameters.

3. Results

Thirty patients proved to be psoriatic were included in the study. The age of patients ranged from 16 to 56 years, 11 are males and 19 are females. Their BMI ranged from 17.5 to 41.5. The age of the control subjects ranged from 16 to 60 years, 10 males and 20 females and their BMI range from 16 to 42.5. Eight out of the thirty patients were fulfilling the CASPAR criteria for psoriatic arthritis (PsA) [12]. The disease duration was from one to 28 years (mean is 10.87 ± 1.7 years). The ESR 1st hour was within normal range in all patients with a mean of 14.05 ± 2.42 mmHg/lst hour. Routine investigations were all normal. The rheumatoid factor was negative in all cases and the serum uric acid was within normal value. There was no significant correlation between the studied markers level and any of the routine laboratory parameters. According to PASI the patients were 12 mild, 11 moderate and 7 severe. The relation between PASI and demographic data of the patients were demonstrated in Table 1. There was significant increase in non-responders to treatment in females than males ($p = 0.03$) by Chi-square. Five out of 6 psoriatic patients that didn't not respond to treatment had no family history of psoriasis ($p = 0.000$) by Chi- square, that indicated the possibility of the presence of another factor most probably obesity. No correlation between PASI and PsA was detected. Table 2 shows the relation between BMI and demographic data of all cases of psoriasis. Psoriasin, koebnerisin, IL-12 and IL-23 were significantly increased in all cases of psoriasis than controls but only IL-12 that was significantly increased in PsA compared to skin psoriasis and controls (Table 3).

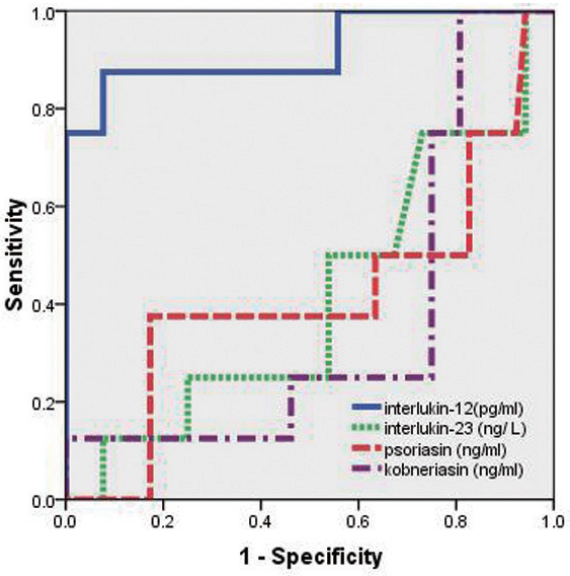

Fig. 3. ROC curves shows cases of psoriatic arthritis ($n = 8$) with area under the curve for interlukin-12 (p70) = 0.92; interlkin-23 = 0.4, psoriasin = 0.4; kobneriasin = 0.3. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/DMA-120945)

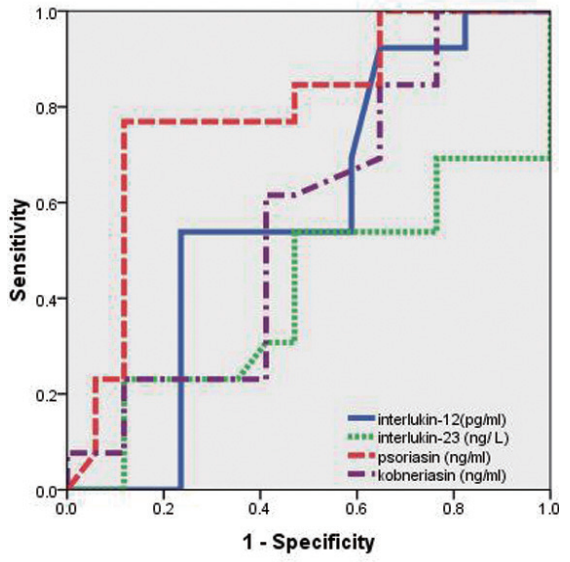

Fig. 4. ROC curves shows psoriatic cases with body mass index < 30, ($n = 13$) with area under the curve for interlukin-12 (p70) = 0.57; interlkin-23 = 0.4, psoriasin = 0.79; kobneriasin = 0.56. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/DMA-120945)

ROC curves of all cases of psoriasis ($n = 30$) showed that IL-12 had the best area under the curve (= 0.76) as in Fig. 1. Cases of skin psoriasis ($n = 22$) shows IL-23 and psoriasin have AUC = 0.76 and 0.72, as in Fig. 2. Psoriatic arthritis cases ($n = 8$) shows IL-12 has AUC = 0.92 as in Fig. 3. IL-23 and psoriasin had sensitivity and specificity in skin psoriasis at cut-off 129.35 and 5.18 ng/ml (73%, 64% and 68%, 61%; respectively). Whereas, IL-12 had the highest sensitivity and specificity in PsA at cut-off 64.2 pg/ml (87%, 93%; respectively). Figure 4 showed that psoriasin has the largest area under the curve = 0.79 in cases of BMI < 30, ($n = 13$). The total cases of psoriasis showed a correlation between PASI and both psoriasin ($r = 0.4$; $P = 0.02$) and BMI ($r = 0.58$, $P = 0.001$). This study demonstrated that the risk of development of psoriasis was directly related to BMI more than 30 ($r = 0.7$, $P = 0.007$). There is a correlation between IL-23 and kobneriasin ($r = 0.3$; $P = 0.006$). Also, there was a correlation between IL-12 and the response to treatment ($r = 0.4$; $P = 0.03$). By using regression analysis, IL-12 was a good predictor of psoriasis ($P = 0.000$).

4. Discussion

Psoriasis is a common complex genetic disease characterized by hyperplasia and inflammation in the skin. However, the relative contributions of epidermal cells and the immune system to disease pathogenesis remain unclear. Linkage studies have defined a psoriasis susceptibility locus (PSORS4) on 1q21, the epidermal differentiation complex, which includes genes for small calcium-binding proteins (S100) [13]. This is in agreement with this study as psoriasin (S100A7) and koebnerisin (S100A15), were significantly increased in all cases of psoriasis and skin psoriasis compared to controls. There was a correlation between psoriasin and both PASI and BMI. The correlation increased when BMI was more than 30. This could be explained by the constitutive expression of elevated concentrations of psoriasin and koebnerisin in the epidermis of psoriatic skin. Mice expressing elevated amounts of doxycycline-regulated mS100a7a15 in skin keratinocytes were genetically modified. These mice had exaggerated inflammatory response when challenged by exogenous stimuli such as abrasion (Koebner phenomenon), potentiated inflammation by acting directly as a chemoattractant for leukocytes [13]. Differential Toll-like receptor (TLR4/2) genes expression on psoriatic peripheral blood mononuclear cells were correlated with regulatory proinflammatory cytokines and damage-associated molecule (S100A9) that emphasize innate immune response role in psoriasis [14].

Thus, targeting the S100-amplification loop could be a beneficial anti-inflammatory approach in skin psoriasis. In agreement with our results was that Gambichler et al. [15], as the psoriasin level in psoriatic patients was significantly higher than control group (79.4 $\pm$ 32.7 ng/ml; 3.1 $\pm$ 0.7 ng/ml, $P = 0.0001$). However, when these psoriatic patients received fumaric acid esters therapy, the level was decreased but this may be due to the effect of treatment [15]. IL-23 has the ability to enhance the expansion of T helper type 17 (Th17) cells indicating the responsibility for many of the inflammatory autoimmune responses [16]. In this study, IL-12 and IL-23 were significantly increased in all cases of psoriasis than controls. On the other hand, IL-23 decreased in psoriatic arthritis, whereas IL-12 increased compared to skin psoriasis and controls . However, there was no correlation between PSAI and IL-23 or IL-12 in this study. This is in disagreement with El Hadidi et al. 2008 as they found that IL-23 was over expressed in skin and serum of patients with psoriasis and psoriatic arthritis and its level was correlated with disease severity [17]. IL-12 in PsA had the highest sensitivity and specificity among the studied markers. IL-12 is produced mainly by macrophages and dendritic cells, and induced activation of natural killer cells, production of interferon-gamma (IFN-γ) and differentiation of naive T cells to Th1 cells [18]. In this study, IL-12 was the only marker that increased significantly in psoriatic arthritis and had the highest sensitivity, specificity and AUC of ROC curves in PsA. Contrary, other markers decreased in psoriatic arthritis.

The chronic inflammation and hyperhomocysteinemia found in psoriatic patients may explain the association with atheroma plaque and metabolic syndrome [19]. In a cohort study, obese patients were more likely to have severe psoriasis, patients with severe psoriasis were frequently obese. Importantly, the pathophysiology of both psoriasis and obesity showed many shared cytokines that are known to contribute to features of the metabolic syndrome, such as hypertension, dyslipidaemia and insulin resistance. The strong association between psoriasis and obesity potentially makes psoriasis an important healthcare issue that requires an update in its standard of care [20]. In this study, 7 cases with severe PASI were females without family history of psoriasis, 6 of them were obese. This study reported that the risk of developing psoriasis was directly related to increase in BMI more than 30 ($r = 0.7$, $P = 0.007$). So, the obesity will play an another factor plus the genetic factor in developing psoriasis.

The pathogenesis of psoriasis is not clear till now. This study provided a new evidence about the role of IL-12 in the pathogenesis of psoriatic arthritis. Moreover, to our knowledge, for the first time these findings suggested that psoriatic arthritis may have a separate pathogenic pathway as IL-12 significantly increased in psoriatic arthritis. While psoriasin, kobneriasin and IL-23 could play a role in the pathogenesis of skin psoriasis. However, other studies are required to further investigate the differences in these two possible pathological pathways for psoriasis. In conclusion, psoriasin is the first biomarker confirm the link between obesity and psoriasis. Psoriasin and IL-23 will be important new therapeutic targets for patients with skin psoriasis. Whereas, targeting of IL-12 or its receptor is a potential therapeutic approach for psoriatic arthritis. The obesity of psoriatic patients may reflect a common pathophysiology and not simply a sedentary behavior derived from the disfiguring cutaneous condition.

Acknowledgements

The authors declared that this research granted from Scientific Research Deanship of Qassim University, Ministry of Higher Education, Kingdom of Saudi Arabia grant # SRD-2011-623.

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