Assessment of Serum Level of Adipocyte Fatty Acid Binding Protein in Patients with Psoriasis Vulgaris before and after Treatment with Acitretin

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ABSTRACT

Background: Psoriasis is a common immune mediated and chronic inflammatory skin disorder portrayed as hyperproliferation and maturation impairment of keratinocytes, increased immune cells infiltration and blood vessel formation, and accumulation in proinflammatory cytokines. Psoriasis is now considered a systemic disease where it is associated with psychological, metabolic, arthritic, and cardiovascular comorbidities. Lifespan is reduced as a consequence.

Objective: The aim of this study was to evaluate serum level of adipocyte fatty acid-binding protein (FABP4) in patients with psoriasis vulgaris and to compare it with its level in healthy control.

Patients and methods: Seventy-four were included in this study. They were chosen from the Out-patient Clinic of Dermatology, Andrology & STDs Department, Mansoura University Hospitals. A case study group of 37 patients with psoriasis vulgaris and 37 of healthy people age- and sex-matched were used as a control group.

Results: ROC curve for detection of FABP4 before acitretin validity in differentiating studied cases illustrated excellent area under curve of 0.728 ($p < 0.001$)* with the best detected cut off point was 2.7 yielding sensitivity of 75%, specificity of 81.1% and total accuracy of 78.1%. So, the present study demonstrated that; detection of FABP4 level before acitretin therapy could be used as reliable indicator in differentiating studied cases with high sensitivity and specificity.

Conclusions: Serum FABP4 levels were significantly increased in patients with psoriasis, indicating that this protein may be a potential marker of psoriasis and an independent predictor for the risk of comorbidities or complications in psoriatic patients. Additionally, it could be used also as a reliable indicator of acitretin therapy.

Keywords: Psoriasis, Fatty acid-binding protein, Acitretin.

INTRODUCTION

Psoriasis is an immune-mediated, chronic inflammatory condition affecting about 2-4% of the general population [(1)]. Psoriasis onset is triggered when genetic and/or environmental factors activate plasmacytoid dendritic cells, resulting in the production of numerous proinflammatory cytokines, including tumor necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-17, IL-22, IL-23 and IL-1β. Many of these cytokines stimulate keratinocyte hyperproliferation, which perpetuates a cycle of chronic inflammation [(2)]. Elevated levels of multiple proinflammatory cytokines are found not only in skin lesions, but also in the blood [(3)]. Systemic elevations in these cytokines promote chronic subclinical inflammation (asymptomatic inflammation that can cause tissue damage over time) associated with comorbidities that disproportionately affect patients with psoriasis, including psoriatic arthritis (PsA), cardiovascular disease (CVD), diabetes mellitus, obesity, inflammatory bowel disease and nonalcoholic fatty liver disease (NAFLD) [(4)].

Although a wide range of treatment modalities have been developed for psoriasis over the last two decades, systemic retinoids may have an advantage over other systemic treatments due to their non-immunosuppressive properties and safety profile [(5)].

It has been reported that acitretin could suppress the proliferation of keratinocytes and regulate their differentiation in the treatment of psoriasis, but it has little effect on Th1, Th17, and Tregs [(6)].

There is emerging evidence suggesting an underlying shared chronic inflammatory process between psoriasis and obesity [(7)]. While it is noteworthy to mention that some anti-psoriatic drugs may also influence obesity and obesity-associated comorbidities through their adverse effects [(8)].

Adipocyte fatty acid-binding protein, also called adipocyte protein 2 (aP2) is mainly expressed in adipocytes and macrophages. Besides its pivotal role in lipid metabolism and insulin sensitivity, it has also been recognized as adipokine influencing several [(9)]. Increased levels of FABP4 were associated with obesity, IR, DM, nonalcoholic fatty liver disease (NAFLD), and cardiovascular artery disease (CAD), which in turn are closely related to psoriasis [(10)]. Adipocyte-type FABP has been proposed as a potential therapeutic target for CVD, which points to its high clinical relevance [(9)]. Furthermore, adipocyte-type FABP has been proposed as a potential therapeutic target for heart failure or CVD, which points to its high clinical relevance. Considering psoriasis as an independent cardiovascular predictor, lowering the FABP4 level would be valuable [(11)].

The aim of this study was to evaluate serum level of adipocyte fatty acid-binding protein (FABP4) in patients with psoriasis vulgaris and to compare it with its level in healthy control. Also, to compare between serum level of adipocyte fatty acid binding protein

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(faBP4) before and after 12 weeks of treatment with acitretin as anti-psoriatic systemic therapy.

PATIENTS AND METHODS

Seventy-four were included in this study. They were chosen from the Out-patient Clinic of Dermatology, Andrology & STDs Department, Mansoura University Hospitals. A case study group of 37 patients with psoriasis vulgaris and 37 of healthy people as a control group, similar age and gender was included.

Ethical consent:

An approval of the study was obtained from Mansoura University Academic and Ethical Committee (MS.20.09.1235). Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria: Patients with chronic plaque psoriasis above 40 years old.

Exclusion criteria:

Systemic disorders (Diabetes, hypothyroidism or hyperthyroidism), pregnancy and breastfeeding, malignancy, systemic drugs during the last 3 months prior to study, dietary restrictions during the last 3 months prior to the study, liver cirrhosis, and cardiac failure.

The patients were subjected to the following:

1. Detailed history taking regarding age, sex, occupation, marital status, special habits, dietary intake, associated psychological disturbance, associated medical or surgical conditions and drug intake.
2. General and detailed dermatological examination, which included a clinical assessment of psoriasis using the Psoriasis Area and Severity Index (PASI) score. PASI combines the assessment of the severity of lesions and the area affected into a single score in the range 0 (no disease) to 72 (maximal disease) **[12].** The body is divided into four sections [head (H) (10% of a person's skin), arms (A) (20%), trunk (T) (30%) and legs (L) (40%)]. Each of these areas is scored by itself, and then the four scores are combined into the final PASI. For each section, the percent of area of skin involved, is estimated and then transformed into a grade from 0 to 6: (0) 0% of involved area. (1) < 10% of involved area. (2) 10–29% of involved area. (3) 30–49% of involved area. (4) 50–69% of involved area. (5) 70–89% of involved area. (6) 90–100% of involved area. Within each area, the severity is estimated by three clinical signs: erythema (redness), induration (thickness) and desquamation (scaling). Severity parameters are measured on a scale of 0 to 4, from none to maximum. The sum of all three severity parameters is then calculated for each section of skin, multiplied by the area score for that area and multiplied by weight of respective section (0.1 for head, 0.2 for arms, 0.3 for body and 0.4 for legs).
3. All patients underwent laboratory test for their serum level of Adipocyte fatty acid-binding protein (FABP4). After an overnight 12-h fast, 3 ml of venous blood were collected to measure biochemical parameters. Blood was centrifuged, and serum was immediately separated and stored at −80 °C for further analysis. Determination of serum adipocyte fatty acid-binding protein FABP4 was carried out using ELISA kits Cat.No E2036Hu (USA).

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS 2013 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) for non-parametric data and mean ± standard deviation for parametric data after testing normality using Kolmogorov-Smirnov test.

Significance of the obtained results was judged at 0.05 level. Student t-test was used to compare 2 independent groups. Mann-Whitney U test was used to compare 2 independent groups. Wilcoxon signed Rank test to compare between 2 studied periods. The Spearman's rank-order correlation is used to determine the strength and direction of a linear relationship between two non-normally distributed continuous variables and/or ordinal variables. Receiver Operating Characteristic (ROC) curve analysis was used for the diagnostic performance of a test, or the accuracy of a test to discriminate diseased cases from non-diseased cases. Sensitivity and specificity were detected from the curve and PPV, NPV and accuracy were calculated through cross tabulation. P value ≤ 0.05 was considered significant.

RESULTS

Table (1) illustrated a non-statistically significant difference between cases and control group regarding age, weight, height and body mass index ($p > 0.05$). Mean age of the studied cases was 56.59 ± 10.67 years versus 56.59 ± 9.71 years for control group. Mean body mass index was 28.86 ± 6.36 kg/m^2 for cases and 27.17 ± 6.62 kg/m^2 for control.

Table (1): Socio-demographic characteristics of the studied groups

	Control	Cases	Test of significance
	n=37	n=37	
Age/years	56.59 ± 9.71	56.59 ± 10.67	t=0.0 p=1.0
Weight/kg	73.51 ± 16.71	79.51 ± 16.82	t=1.54 p=0.128
Height /meter	1.65 ± 0.074	1.67 ± 0.091	t=0.890 p=0.377
BMI(Kg/m^2)	27.17 ± 6.62	28.86 ± 6.36	t=1.21 p=0.266

t: Student t test, p:probability, parameters described as mean ± SD

Table (2) showed that median disease duration was 8.0 years ranging from 1.0 to 40 years and median PASI score was 15.4 ranging from 1.9 to 65.4.

Table (2): Distribution of disease duration and PASI score among studied cases

Cases	n=37
Disease duration (years) median (min-max)	8.0 (1.0-40.0)
PASI median (min-max)	15.4 (1.9-65.4)

Mean blood pressure, random glucose and lipid profile illustrated non-statistically significant difference between cases and control group except for cholesterol that was statistically significant higher among cases than control group (170.49 versus 153.67, respectively) and for ALT, which was statistically significantly lower among cases than control group (36.62 versus 41.46, respectively) as shown in table (3).

Table (3): Blood pressure and laboratory findings of the studied groups

	Control	Cases	Test of significance
	n=37	n=37	
SBP (mmHg)	119.32±8.59	121.14±10.36	t=0.818 p=0.416
DBP (mmHg)	78.78±8.11	82.16±7.22	t=1.89 p=0.063
Random glucose (mg/dl)	106.41±17.58	108.76±17.98	t=0.569 p=0.571
Cholesterol (mg/dl)	153.67±28.16	170.49±38.37	t=2.15 p=0.035*
TAG (mg/dl)	106±7.90	111.19±6.78	t=0.524 p=0.602
HDL (mg/dl)	48.97±10.68	53.35±10.32	t=1.79 p=0.08
AST (IU)	24.24±8.26	21.86±7.39	t=1.31 p=0.196
ALT (IU)	41.46±9.14	36.62±3.26	t=2.14 p=0.036*

t: Student t test, p:probability, parameters described as mean ± SD

Median FABP4 before acitretin showed a statistically significant higher median value among cases than control group (2.95 versus 2.6). A non-statistically significant difference was detected between cases and control group regarding after acitretin (p=0.751). Median FABP4 was decreased from 2.95 to 2.4 before and after acitretin with statistically significant change (p<0.001) (Table 4).

Table (4): FABP4 before and after acitretin therapy between studied groups

FABP4	Control n=37	Cases n=37	Test of significance (Mann Whitney U test)
Before acitretin	2.6(1.2-16)	2.95(1.4-16)	z=3.38 p=0.001*
After acitretin	2.6(1.2-16)	2.4(1.3-15.0)	z=0.318 p=0.751
Wilcoxon signed rank test		z=4.51 p<0.001*	

*statistically significant if p<0.05. Parameters described as median (range)

ROC curve for detection of FABP4 before acitretin validity in differentiating studied cases illustrated excellent area under curve of 0.728 (p < 0.001) with the best detected cut off point was 2.7 yielding sensitivity of 75%, specificity 81.1% and total accuracy of 78.1% (Table 5 & figure 1).

Table (5): Validity of FABP4 in psoriatic cases

	AUC (95%CI)	P value	Cut off point	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
FABP4	0.728 (0.608-0.848)	0.001*	2.70	75.0	81.1	79.4	76.9	78.1

AUC: Area Under curve, PPV: Positive predictive value, NPV: Negative predictive value

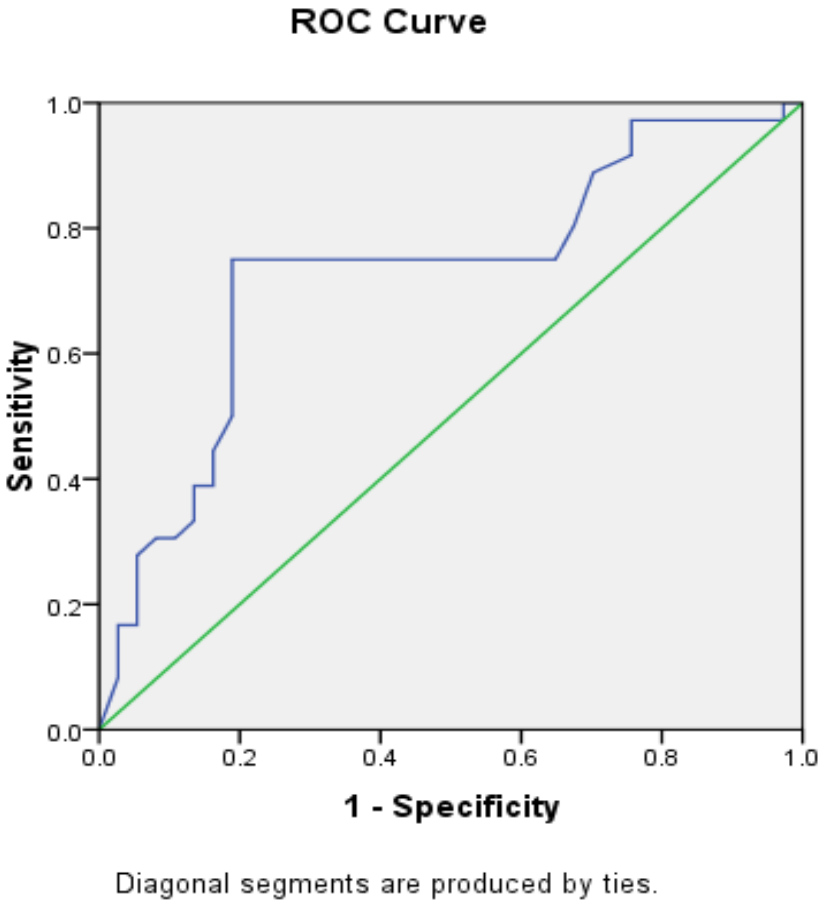

Figure (1): Receiver Operating characteristics of FABP4 in psoriatic cases

Table (6) illustrated that there was statistically significant negative correlation between FABP4 and AST (r= -0.370, p=0.024) among control group.

Table (6): Correlation between FABP4 and clinical & laboratory among control group

		FABP4
Age	r	-0.166
	p	0.325
weight	r	0.296
	p	0.075
height	r	-0.038
	p	0.823
BMI	r	0.294
	p	0.077
SBP	r	-0.157
	p	0.355
DBP	r	-0.218
	p	0.194
Cholesterol	r	0.300
	p	0.071
TAG	r	0.096
	p	0.573
HDL	r	0.264
	p	0.115
AST	r	**-0.370***
	p	**0.024**
ALT	r	-0.268
	p	0.109

r: Spearman correlation co-efficient, *statistically significant if p<0.05

Table (7) illustrated that there was statistically significant positive correlation between FABP4 and PASI score (r= 0.437, p=0.008) and between FABP4 & cholesterol level (r=0.398, p=0.016) among cases group.

Table (7): Correlation between FABP4 and clinical, laboratory& disease characters among psoriasis cases

		FABP4
age	r	0.283
	p	0.094
PASI	**r**	**0.437****
	p	**0.008**
disease duration/ years	r	-0.063
	p	0.714
weight	r	0.196
	p	0.253
height	r	0.245
	p	0.149
BMI	r	0.097
	p	0.574
SBP	r	0.223
	p	0.192
DBP	r	0.011
	p	0.949
Random glucose	r	0.000
	p	0.999
Cholesterol	**r**	**0.398***
	p	**0.016**
TAG	r	0.009
	p	0.960
HDL	r	-0.171
	p	0.318
AST	r	0.100
	p	0.561
ALT	r	0.018
	p	0.919

r: Spearman correlation co-efficient , *statistically significant if p<0.05

DISCUSSION

In the present study, there was a non-significant difference between cases and control group regarding age, weight, height and body mass index ($p > 0.05$). Mean age of the studied cases was 56.59 ± 10.67 years versus 56.59 ± 9.71 years for control group. This mean age was in accordance with **Pezzolo *et al.*** [13] which was 59.7 ± 12.3 & 60.8 ± 16.3 years respectively.

In the current study, the mean body mass index was 28.86 ± 6.36 kg/m^2 for cases and 27.17 ± 6.62 kg/m^2 for control group. **Similarly,** our results come in agreement with the results of **Pietrzak *et al.*** [14] who reported that no statistical difference in BMI between cases and control groups**.** This supports the finding that obesity occurs at some point after the manifestation of psoriasis. Mechanisms by which this occurs emphasize the frequent self-perceived cosmetic disfigurement caused by psoriasis, resulting in social isolation, unhealthy nutrition habits, depression, and alcohol consumption [15]**.** In the contrast, **Praveenkumar *et al.*** [16] and **Elobeid *et al.*** [17] found that obesity (high body mass index) significantly increased the risk of psoriasis. In addition, published observational data by **Budu-Aggrey *et al.*** [18] showed an association of higher BMI with psoriasis. This supports the prioritization of therapies and lifestyle interventions aimed at controlling weight for the prevention or treatment of this common skin disease.

In the present study, the median PASI score was 15.4 ranging from 1.9 to 65.4, which is in agreement with **Daglioglu *et al.*** [19] study where PASI scores ranged from 0.9 to 48, and the mean PASI score was 14.34 ± 10.13.

In the current study, the mean blood pressure, random blood glucose, liver enzymes and lipid profile illustrated non-statistically significant difference between cases and control group except for serum cholesterol that was statistically significantly higher among cases than control group (170.49 ± 38.37 versus 153.67 ± 28.16 respectively) & ALT, which statistically significantly was higher among cases than control group (41.46 ± 9.14 versus 36.62 ± 10.26, respectively). Regarding the blood pressure**,** our results were in contrary with **Duan *et al.*** [20]**,** who found that prevalence of hypertension was significantly higher in psoriasis patients than in controls. This is explained by **Hu *et al.*** [21] who stated that vascular inflammation and hypertension occur when psoriasis-related inflammation persists. Future studies are needed to identify the distinct pathways linking psoriasis with hypertension. **Furthermore,** recognition and evaluation of cardiovascular comorbidities and systemic inflammation are recommended to provide a comprehensive therapeutic approach for patients with psoriasis. Regarding lipid profile, the correlation between dyslipidemia and psoriasis is variable in different studies. **Snekvik *et al.*** [22] reported that analyses of the separate components of metabolic syndrome showed positive associations with risk of psoriasis for triglycerides, high-density lipoprotein (HDL) and cholesterol. Same as, **Pietrzak *et al.*** [14] who found lipid metabolism abnormalities and an oxidative imbalance among patients with psoriasis versus controls. The lack of statistical significance in our study can be explained by our small sample size. Since this is a novel finding of lipid profile, it needs to be investigated further by large population-based studies as well as experimental studies to elucidate the molecular etiopathogenetic links.

Regarding liver enzymes, elevation of liver enzymes was defined idiopathic in patients without an identified risk factor, 4% of mild-moderate and 8% of severe elevation of liver function tests [23]**.**

In the present study, the median FABP4 before acitretin showed a statistically significant higher median value among cases than control group (2.95 versus 2.6). This comes in accordance with **Baran *et al.*** [24] who conducted their study on a total of 37 patients with relapse of plaque-type psoriasis and 16 healthy volunteers. They displayed that the median FABP4 serum levels were significantly increased ($p = 0.038$) in psoriatic patients compared to the controls.

A further link between FABP4 and psoriasis may be a correlation with tumor necrosis factor-α (TNF-α), which is one of the major cytokines involved in the pathogenesis of this dermatoses. Treatment with TNF-α inhibitors was found to lead to a significant reduction in cytokine levels. FABP4 has been linked to angiogenesis and vascular endothelial growth factor (VEGF), which are also highly disturbed in psoriasis [25]**.**

In the current study, median FABP4 is decreased from 2.95 to 2.4 before and after acitretin with statistically significant change ($p<0.001$). This comes in the same line with **Baran *et al.*** [24] who displayed that FABP4 was decreased [before acitretin therapy 27,286 (20,344-32,257) vs. after acitretin therapy 23,034 (18,320-29,874) pg/ml] ($p = 0.12$), losing its basal significance. Thus, they concluded that FABP4 could be used as a marker for psoriasis. In accordance, **Baran *et al.*** [11] did not show any significant effect of treatment with MTX and acitretin together on serum FABP4. But, it resulted in decrease and loss of the baseline significance in each of the three PASI subgroups of patients compared to controls. However, what is far more valuable, serum adipocyte-type FABP level, which was statistically decreased after administering acitretin. Considering that the elevated serum FABP4 level has been linked with the development of DM, or CVD, interplay of acitretin and FABP4, or even more precisely the protein inhibitors, might be a potential therapeutic approach against CVD in psoriatic patients. They displayed that after total therapy, FABP4 did not statistically change ($p = 0.07$), but significantly decreased after administration of acitretin ($p = 0.03$). Thus, they concluded that FABP4

could be used as a potential marker of psoriasis as well as clinical outcome after therapy with acitretin.

In the instant study, there was a statistically significant positive correlation between FABP4 and PASI score (r= 0.437, p=0.008). On the other hand, **Baran *et al.*** [24] displayed that there was no significant correlation between FABP4 and PASI. Also, **Baran *et al.*** [11] revealed that no relationship between FABP4 and psoriasis severity expressed through psoriasis area and severity index (PASI) was noted in their study (p = 0.57). Thus, both previous studies have reported that FABP4 was not useful in monitoring the severity of psoriasis because there was no significance in both researches **Baran *et al.*** [24] and **Baran *et al.*** [11]. The data obtained differ slightly in relation to groups depending on severity. Of note, significantly elevated FABP4 was found in patients with mild-type psoriasis (p = 0.002) [24], while the **Baran *et al.*** [11] study was found in moderate (p = 0.04) and only marginally in mildly-affected patients (p = 0.05). These discrepancies among results even among two studied performed by the same authors **Baran *et al.*** [24] **and Baran *et al.*** [11] could be due to some methodological nuances or other modifying factors within the studied groups.

In the current study, there was a statistically significant negative correlation between FABP4 and AST (p=0.024) among control group. On the contrary, **Baran *et al.*** [11] found that FABP4 did not correlate with liver enzyme activity (as revealed by ALT and AST).

In the present study, there was a statistically significant positive correlation between FABP4 & cholesterol level (r=0.398, p=0.016) among psoriatic group. Several studies have noted positive correlations between FABP4 and high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triacylglycerol, or adiponectin and TNF-**α** [26, 27]**.** In addition, **Lin *et al.*** [28] displayed that serum A-FABP was positively correlated with triglycerides, total cholesterol, and HOMA-IR. In the same line, clinical studies have shown that elevation of serum FABP4 is associated with obesity, insulin resistance, hypertension, and atherosclerosis [29, 30]**.** Additionally, it was reported that serum FABP4 level predicts long-term cardiovascular outcomes [25]. On the contrary, **Baran *et al.*** [11] have displayed that there was no statistically significant correlation between FABP4 and lipid profile.

In our study, ROC Curve for detection of FABP4 before acitretin validity in differentiating studied cases illustrated excellent area under curve of 0.728 (p<0.001) with the best detected cut off point is 2.7 yielding sensitivity of 75%, specificity of 81.1% and total accuracy of 78.1%. So, the present study demonstrated that detection of FABP4 level before acitretin therapy could be used as reliable indicator in differentiating studied cases with high sensitivity and specificity. Despite the promising outcomes of the current study, small sample size remains the main limitation.

CONCLUSIONS

Serum FABP4 levels were significantly increased in patients with psoriasis, indicating that this protein may be a potential marker of psoriasis and an independent predictor for the risk of comorbidities or complications in psoriatic patients. Additionally, it could be sued also as a reliable indicator of acitretin therapy.

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