Circulating ghrelin and apelin levels in nonobese psoriasis vulgaris patients

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Background
The metabolism and immune system are linked via a network of many mediators known as adipokines. Ghrelin and apelin-36 are unique adipokines; however, their role in psoriasis, an immune-mediated disease, remains unclear.
Objective
To detect the serum levels of ghrelin and apelin-36 in psoriasis vulgaris patients in comparison with controls and to correlate their levels with severity of psoriasis, BMI, lipid profile, and glycated hemoglobin (HbA1c).
Patients and methods
The present case–control study included 70 nonobese psoriasis vulgaris patients and 70 controls. The severity of psoriasis was assessed using the psoriasis area and severity index score. The ghrelin and apelin-36 serum levels, cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, and HbA1c were measured.
Results
Psoriatic patients had significantly higher ghrelin ($P<0.001$), HbA1c ($P<0.001$), cholesterol ($P<0.001$), triglycerides ($P<0.001$), and low-density lipoprotein ($P=0.001$) levels and a lower apelin-36 ($P<0.001$) serum level than controls. Serum ghrelin was negatively correlated with psoriasis area and severity index score ($r=-0.75$; $P<0.001$), whereas serum apelin-36 was negatively correlated with HbA1c mean values ($r=-0.44$; $P=0.004$) and was found to be a good predictor of prediabetes in psoriatic patients ($P=0.012$). Nonsignificant correlation between ghrelin and apelin-36 serum levels was observed in psoriatic patients.
Conclusion
Ghrelin and apelin-36 are dynamic adipokines that might play a role in psoriasis vulgaris pathogenesis. The role of ghrelin and apelin-36 in psoriasis might be mediated through dyslipidemia and impaired glucose metabolism in psoriatic patients, respectively. Targeting both ghrelin and apelin-36 may be of value in management of metabolic syndrome associated with psoriasis. Serum apelin-36 assessment can predict prediabetic state in psoriatic patients.

Keywords:
apelin-36, dyslipidemia, ghrelin, glycated hemoglobin, psoriasis

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Introduction

Psoriasis is a common inflammatory and relapsing immune-mediated disease. It affects the skin and small joints in genetically predisposed persons, affecting ~2% of the population. The precise cause of psoriasis is not known, which could be attributed to the interaction between environmental, genetic, and immunological factors [1].

A significant body of data highlights the association of psoriasis with many comorbidities, including obesity. The increased immunological activity of T-helper (Th1) cells in obese patients suggests that psoriasis may be associated with obesity. Circulatory levels of tumor necrosis factor alpha (TNF-α), soluble TNF-α receptors, and in vitro TNF-α production are elevated in patients with a high BMI [2].

Metabolism and immune system are linked via a network of many soluble mediators identified as adipokines. Adipokines are categorized into good and bad adipokines. Bad adipokines are proinflammatory molecules that produce insulin resistance, local inflammatory reactions, and vascular dysfunction, supporting cutaneous inflammation. In contrast, good adipokines have opposite properties. Proinflammatory cytokines increase the secretion of bad adipokines and decrease that of the good ones. In the last decade, ghrelin and apelin have appeared as distinctive adipokines [3].

Ghrelin is an adipose-derived peptide formed of 28 amino acids. It has modulatory effects on the systemic metabolism. Ghrelin is implicated in insulin sensitivity and modulates lipid metabolism. Moreover, ghrelin has some anti-inflammatory effects resulting from the downregulation of proinflammatory cytokines, such as interleukin 1 beta (IL-1β) and TNF-α [4].

Apelin, an endogenous peptide, is a ligand for the G protein-coupled receptor. It formed of a prepropeptide having 77 amino acids. Based on the amino acid numbers, there are three different forms of apelin: apelin-13, apelin-17, and apelin-36. Apelin-36 is the physiologically active form. It has an extensive tissue distribution and is involved in many physiological (e.g. body fluid homeostasis and energy metabolism) and pathological (e.g. obesity and diabetes) processes. Apelin improves glucose homeostasis and can act as an anti-inflammatory agent [5].

Ghrelin and apelin-36 have emerged as unique adipokines [3]. Nevertheless, their role in psoriasis remains unclear. Therefore, this study aimed to shed light on the possible roles of ghrelin and apelin-36 in psoriasis vulgaris by analyzing their serum levels in those patients in comparison with controls and to correlate their levels with severity of psoriasis, BMI, lipid profile, and glycated hemoglobin (HbA1c).

Patients and methods

This case–control study included 70 nonobese patients having psoriasis vulgaris who were diagnosed based on the patient's history and typical clinical features of sharply demarcated, erythematous, plaques covered with silvery scales [1]. In total, 70 age-matched and sex-matched healthy individuals were selected as the control group.

Each participant signed a written informed consent form before joining the study. The study was approved on September 7, 2016 by the Local Ethical Research Committee at Menoufia University, that was in accordance with the Declaration of Helsinki 1975 (revised in 2013). The ethics committee approval number is 1202/7/9/2016.

Inclusion criteria included nonobese patients having psoriasis vulgaris from both sexes. The selected patients stopped either topical (2 weeks) and/or systemic (1 month) therapy for psoriasis before starting the study.

The exclusion criteria were (a) patients with erythroderma, pustular psoriasis, and psoriatic arthritis, (b) systemic diseases (e.g. diabetes and/or hypertension), (c) pregnancy and lactation, (d) polycystic ovary syndrome or amenorrhea, (e) acute or chronic infection, (f) acute or chronic neurological disorders, (g) hypothyroidism or hyperthyroidism, and (h) obesity (BMI$>$30 kg/m^2).

Data were collected from every patient taking into consideration the patients' files. Additionally, thorough general and detailed dermatological examinations were conducted.

Psoriasis area and severity index (PASI) score was used for assessing psoriasis severity [6]. The body of each patient was divided into four parts: (a) head (h), (b) upper extremity (u), (c) the trunk (t), and (d) lower extremity (l). The area of skin percentage affected was calculated and grading was done as follows: 0, 0% affected area; 1, less than 10% affected area; 2, 10–29% affected area; 3, 30–49% affected area; 4, 50–69% affected area; 5, 70–89% affected area; 6, 90–100% affected area.

Three clinical parameters within each part of the skin (A) were assessed to detect the severity: erythema (E), desquamation (D), and induration (I). These clinical signs were estimated as follows: 0, no signs; 1, mild; 2, moderate; 3, severe; 4, very severe. Then, the sum of the severity scores for the clinical signs was calculated for each area of skin and then multiplied by the score for that affected part and by the weight of this part (0.1 for the head, 0.2 for upper extremities, 0.3 for the trunk, and 0.4 for lower extremities).

Last, the PASI score was calculated as follows: PASI score=0.1 (Eh+Ih+Dh) Ah+0.2 (Eu+Iu+Du) Au+0.3 (Et+It+Dt) At+0.4 (El+Il+Dl) Al.

PASI score ranged from 0 to 72. A PASI score below 7 was defined as mild, between 7 and 12 as moderate, and above 12 as severe disease.

BMI was calculated using weight and height of an individual. The body mass was divided by the square of the body height (kg/m^2). BMI was expressed as underweight: under 18.5, normal weight: 18.5–25, overweight: 25–30, and obese: over 30 [7].

Five milliliters of venous blood was aseptically collected from each participant at 09.00–10.00 in the morning after an overnight fast. Each sample was divided into (a) 1 ml on ethylene diamine tetraacetic acid

tube for HbA1c and (b) 4 ml on a plain tube. Samples in the plain tubes were centrifuged at 4000 rpm for 10 min and the sera were separated, collected in Eppendorf tubes, and then stored at −80°C till the time of analysis.

Laboratory investigations were as follows: (a) lipid profile, including Spectrum Diagnostics liquizyme cholesterol (CH) (normal levels are <200 mg/dl in adults), triglycerides (TGs) (normal reference range, 35–135 mg/dl for females and 40–160 mg/dl for males), high-density lipoprotein (HDL) (normal reference range, 48.6–75 mg/dl for females and 41–58.7 mg/dl for males), and low-density lipoprotein (LDL) (with a desirable level <150 mg/dl) reagents, was intended for their in vitro quantitative, diagnostic determination in human serum on both manual and automated systems. (b) HbA1c test was measured by ion-exchange resin chromatography kits (Stanbio, Boerne, Texas, USA) (procedure no. 0350). The normal reference ranges for HbA1c levels are 4–5.9%. (c) Serum ghrelin levels were studied using a Human Ghrelin Kit (Cat. No. A05106; SPI-Bio, Montigny-le-Bretonneux, France) by the enzyme-linked immunosorbent assay method as per the manufacturer's instructions. Ghrelin normal reference values 520–700 pg/ml for normal weight/controls and 340–450 pg/ml for obese patients prior to diet and levels at 8:00 am–12:00 pm: up to 420 pg/ml. (d) For serum apelin-36 levels, a double-antibody sandwich enzyme-linked immunosorbent assay was used (Shanghai Sunred Biological Technology Co. Ltd, Shanghai, China) (catalog no. 201-12-2038), with assay range of 4–2200 ng/ml.

Statistical analysis

For data analysis, Statistical Package for Social Science (SPSS), version 20, program (SPSS Inc., Chicago, Illinois, USA) was employed. Qualitative records were expressed using number and percentage, whereas quantitative data were expressed using the arithmetic mean, SD, median, range, and percentage (%). For comparing qualitative data, the χ^2 test was utilized. For comparison between quantitative variables, Mann–Whitney *U* test was used, while Kruskal–Wallis test (*K*) was used to compare three or more variables. Spearman's correlations (*r*) were used for presenting correlation coefficients. Sensitivity and specificity were detected from the receiver-operating characteristic curve; positive predictive value, negative predictive value, and accuracy were calculated by cross-tabulation. *P* value less than or equal to 0.05 was considered to be statistically significant.

Results

The included psoriatic patients (*n*=70) were 35 (50%) females and 35 (50%) males with an age range of 20–65 years and BMI of 20.2–29.7 kg/m^2. No statistically significant differences were observed between cases and controls regarding sex (*P*=1.0) and age (*P*=0.8); however, BMI was significantly higher in the patient group (*P*=0.005). In terms of the clinical data of the psoriatic patients, the duration of their disease ranged from 1 to 10 years, most of them presented with a moderate form of psoriasis (41, 58.6%), and 12 (17.1%) cases had a positive family history of psoriasis (Table 1).

The laboratory investigations among the studied groups showed dyslipidemia in psoriasis patients in the form of significantly higher CH (*P*<0.001), total cholesterols (*P*<0.001), and LDL (*P*=0.001) and an insignificantly lower HDL (*P*=0.12) serum levels. Moreover, the investigated psoriatic patients had significantly higher HbA1c (*P*<0.001) and ghrelin (*P*<0.001) and significantly lower apelin-36 serum levels (*P*<0.001) (Table 2).

The relationship between circulating ghrelin with the clinical and laboratory data of psoriatic patients revealed significantly higher serum ghrelin levels in the mild form of psoriasis than in the moderate and severe forms (*P*<0.001) (Table 3). Furthermore, in the studied psoriatic cases, serum ghrelin concentrations were negatively correlated with PASI score mean values (*r*=−0.75; *P*<0.001) and disease duration (*r*=−0.27; *P*=0.02), and positively correlated with CH (*r*=0.35; *P*=0.003) and TG (*r*=0.28; *P*=0.02) serum levels as well as BMI (*r*=0.31; *P*=0.009) (Table 4).

However, the association of apelin-36 with the clinical and laboratory data of psoriatic patients showed that the serum apelin-36 concentrations were negatively correlated only with HbA1c mean values (*r*=−0.44; *P*=0.004) (Table 4).

The relationship between ghrelin and apelin-36 with the data of controls showed that only the serum apelin-36 concentrations were negatively correlated with LDL mean values (*r*=−0.30; *P*=0.01) (Table 5).

The receiver-operating characteristic curve analysis for apelin-36 showed that it is a good predictor of hyperglycemia in psoriatic patients at a cutoff value of 29.04 ng/ml with 0.70 area under the curve (95% confidence interval, 0.53–0.88), 90.6%

Table 1 Sociodemographic and clinical criteria among the studied groups

The studied criteria	The studied groups		Test	*P* value
	Cases (*N*=70)	Control (*N*=70)		
Age (years)				
Mean±SD	47.67±11.86	48.16±10.61	*t* test	
Range	20–65	23–66	0.26	0.80
Sex [*n* (%)]				
Male	35 (50.0)	35 (50.0)	χ^2	
Female	35 (50.0)	35 (50.0)	0.0	1.0
BMI (kg/m^2)				
Mean±SD	26.84±2.03	25.86±1.98	*t* test	
Range	20.2–29.7	21.9–29.1	2.85	0.005
Family history [*n* (%)]	12 (17.1)			
Duration of disease (years)				
Mean±SD	4.93±2.76	–	–	–
Range	1–10			
PASI				
Mean±SD	15.19±6.92	–	–	–
Range	3.6–40.4			
Severity [*n* (%)]				
Mild	12 (17.1)	–	–	–
Moderate	41 (58.6)			
Sever	17 (24.3)			

χ^2, χ^2 test; PASI, psoriasis area severity index; *t*, Student *t* test.

Table 2 Laboratory investigations among the studied groups

	The studied groups		Test	*P* value
	Cases (*N*=70)	Controls (*N*=70)		
HbA1c				
Mean±SD	5.99±0.62	5.31±0.52	*t* test	<0.001
Range	4.7–7.8	4.3–6.5	7.07	
TGs				
Mean±SD	127.38±49.78	97.13±25.59	*U*	<0.001
Range	42–288	42–145	3.62	
CH				
Mean±SD	144.3±20.80	79.86±25.20	*U*	<0.001
Range	110–190	35–118	10.15	
HDL				
Mean±SD	155.27±34.59	163.93±30.28	*t* test	0.12
Range	100–214	102–215	1.58	
LDL				
Mean±SD	150.91±53.99	129.31±46.02	*U*	0.001
Range	55–335	55–335	3.24	
AP-36 (ng/ml)				
Mean±SD	26.11±9.59	82.21±78.2	*U*	<0.001
Range	7.89–66.91	4.95–280.96	4.06	
Ghrelin (pg/ml)				
Mean±SD	2455.2±1204.3	426.6±140.7	*U*	<0.001
Range	1001–7744	159–860	10.21	

AP-36, apelin-36; CH, cholesterol; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; *t*, Student *t* test; TGs, triglycerides; *U*, Mann–Whitney *U* test.

sensitivity, and 64.7% specificity (*P*=0.012) (Fig. 1). The ghrelin and apelin-36 serum levels showed a nonsignificant correlation in psoriatic patients (*r*=0.11; *P*=0.38) (Table 4) and in controls (*r*=−0.18; *P*=0.13) (Table 5).

Discussion

To the best of our knowledge, no previous studies investigated both ghrelin and apelin-36 in psoriasis. Herein, ghrelin and apelin-36 serum levels were

Table 3 Relationship between apelin-36 and ghrelin and clinical data of the studied cases

	The studied cases (*N*=70)			
	AP-36 (ng/ml)		Ghrelin (pg/ml)	
	Mean±SD	Test (*P* value)	Mean±SD	Test (*P* value)
Sex				
Male	26.35±9.36	*U*=0.54 (0.59)	2700.5±1416.9	*U*=1.59 (0.11)
Female	25.88±9.95		2209.9±900.8	
Family history				
Yes	25.13±4.65	*U*=0.41 (0.69)	1700.2±685.9	*U*=2.98 (0.003)
No	26.32±10.34		2611.4±1232.9	
Severity				
Mild	26.72±9.88	*K*=1.02 (0.60)	4192.5±1679.0	*K*=47.7(<0.001)
Moderate	26.70±10.62		2442.9±450.7	
Sever	24.28±6.55		1258.4±150.3	

AP-36, apelin-36; *K*, Kruskal–Wallis test; *U*, Mann–Whitney *U* test.

Table 4 Correlation between apelin-36 and ghrelin and clinical data and lab investigations

	The studied cases (*N*=70)			
	AP-36 (ng/ml)		Ghrelin (pg/ml)	
	r	*P* value	*r*	*P* value
Age (years)	0.13	0.29	–0.08	0.49
BMI (kg/m^2)	–0.09	0.46	0.31	0.009
Duration (years)	–0.04	0.77	–0.27	0.02
PASI score	–0.10	0.42	–0.75	<0.001
HbA1c	–0.44	0.004	–0.03	0.79
TGs	0.02	0.85	0.28	0.02
CH	–0.004	0.97	0.35	0.003
HDL	–0.12	0.33	–0.11	0.39
LDL	0.15	0.21	0.11	0.38
AP-36 (ng/ml)	–	–	0.11	0.38
Ghrelin (pg/ml)	0.11	0.38	–	–

AP-36, apelin-36; CH, cholesterol; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PASI, psoriasis area severity index; *r*, correlation coefficient; TGs, triglycerides.

Table 5 Correlations between apelin-36 and ghrelin and the studied data among the control group

	Control group (*N*=70)			
	AP-36		Ghrelin	
	r	*P* value	*r*	*P* value
Age (years)	0.18	0.13	0.01	0.92
BMI (kg/m^2)	–0.10	0.42	–0.13	0.29
HbA1c	0.008	0.94	–0.06	0.62
Triglyceride	–0.03	0.83	–0.04	0.74
Total cholesterol	0.14	0.24	–0.10	0.42
HDL	–0.07	0.59	0.10	0.43
LDL	–0.30	0.01	0.10	0.42
AP-36 (ng/ml)	–	–	–0.18	0.13
Ghrelin (pg/ml)	–0.18	0.13	–	–

AP-36, apelin-36; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; *r*, correlation coefficient.

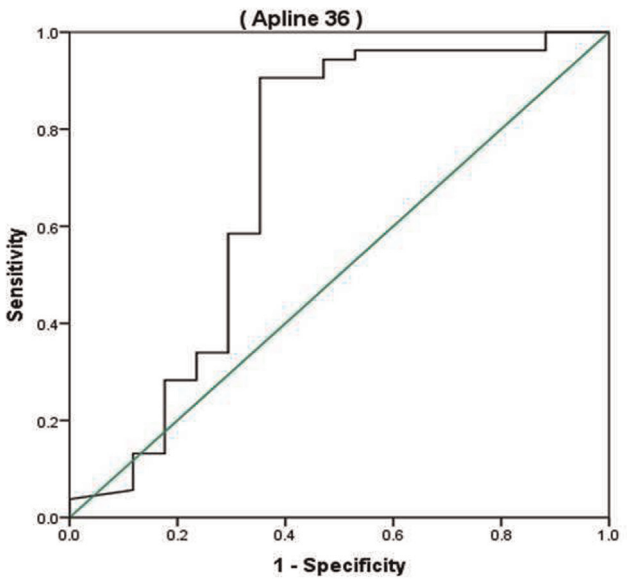
examined in nonobese psoriasis vulgaris patients versus controls. Significant upregulation of ghrelin and downregulation of apelin-36 serum levels were observed in nonobese psoriasis patients. Moreover, it was noticed that ghrelin serum levels were associated with dyslipidemia, while apelin-36 was negatively correlated with hyperglycemia. Therefore, adipose tissues' metabolic dysfunction is related to insulin resistance and metabolic syndrome rather than obesity per se [8].

The observed upregulation of ghrelin serum levels in psoriasis patients was previously reported by Ucak *et al.* [9] However, Ozdemir *et al.* [10] found that the increased ghrelin serum levels in psoriasis cases were insignificant. The difference could be attributed to the limitations in the study by Ozdemir and colleagues, including the relatively small number of patients (*n*=26), and many exogenous and endogenous factors, such as inappropriate dietary behaviors, physical inactivity, and oxidative stress, that could influence ghrelin serum levels.

The increased ghrelin serum levels in our psoriatic patients could be a result of their relative increased BMI, or increased proinflammatory cytokines that might induce the secretion of many adipokines [3]. Ghrelin affects proinflammatory cytokine formation and release, and has antioxidative properties [11]. Thus, we confirmed that the high level of circulating ghrelin in psoriasis could be a compensatory outcome against inflammation, increased insulin resistance in the disease, and/or resulted from the relatively increased BMI [9].

In line with Ucak *et al.* [9], the current study showed that ghrelin serum levels were significantly higher in mild cases compared with those in moderate and severe cases and had a significant negative correlation with PASI score. These findings suggested that since

Figure 1



Receiver-operating characteristic (ROC) curve of apelin-36 to predict hyperglycemia among psoriasis patients showing that area under the curve of 0.70 (95% confidence interval 0.53–0.88), at a cutoff value was 29.04 ng/ml, sensitivity was 90.6%, and specificity 64.7% (P=0.012).

ghrelin has anti-inflammatory properties, it will be decreased as it is consumed in the biochemical conduits to abolish inflammation [12].

Psoriasis is a state of chronic inflammation mediated by increased T-cell activity (Th1 and Th17). The important role of cytokines (e.g. TNF-α, interferon-γ, IL-8, IL-1, IL-6, and IL-17) in the formation of proatheromatous abnormalities, as well as dyslipidemia, was described [13].

As previously reported [14], the present study demonstrated dyslipidemia in psoriatic patients in the form of significantly high CH, TGs, and LDL serum levels and insignificantly low HDL serum levels. Moreover, significant positive correlations between ghrelin with CH and TG serum levels were observed in our studied psoriatic patients.

Increased CH and LDL in psoriatic patients' serum modified the apolipoprotein composition and increased oxygen metabolite production, resulting in a great impact on inflammation detected in psoriasis. Besides, these lipid disturbances are linked to many immunological abnormalities. As a result, psoriasis was classified as an immune-metabolic disease [15]. Therefore, we postulated that the role of ghrelin in psoriasis might be mediated by associated dyslipidemia.

Regarding apelin-36 serum level, our findings revealed that psoriatic patients had significantly lower levels compared with controls. In agreement with our findings, Capo *et al.* [16] concluded that apelin-36 had lower mean values in the psoriatic population than their matched peers. Additionally, in atopic dermatitis, a cutaneous inflammatory Th1 skin disease, apelin serum level was significantly decreased compared with the control group [17].

Apelin reduces the concentrations of monocyte chemotactic protein-1 and 3, vascular endothelial growth factor A, macrophage inflammatory protein-1 α and β, TNF-α, and angiopoietin-2. Additionally, apelin inhibits the expression of caspase 9/3 in RAW264.7, thus protecting the macrophages from apoptosis [18]. Furthermore, the incubation of rat peritoneal macrophages by apelin results in decreasing the expression of IL-6 and TNF-α, chemotactic, and phagocytic activity of these macrophages [19].

In psoriasis, it was demonstrated that macrophages accumulate in psoriatic lesions and produce many chemokines and cytokines, such as interferon-γ, IL-6, IL-1β, monocyte chemoattractant protein-1, and inducible nitric oxide synthase [20]. Therefore, we suggested that apelin-36 participates in psoriasis development by its anti-inflammatory effects. The demonstrated low apelin-36 serum levels in our investigated cases could result in impaired suppression of activated inflammatory mediators and consequently upregulated inflammatory process in those patients.

In this study, a nonsignificant correlation between serum apelin-36 levels and the severity of psoriasis was observed. In line with these results, Alataş and Kökçam [21] reported that apelin may play a role in the psoriasis pathogenesis, but it is not a severity marker.

In the present study, the HbA1c level was significantly higher in the studied psoriatic patients than controls. In accordance with this result, it was found that HbA1c was significantly high among the psoriatic group [22]. Additionally, a significant relationship between type 2 diabetes mellitus and psoriasis was demonstrated [23]. Moreover, psoriatic patients are prone to a prediabetic state even in mild-to-moderate forms of psoriasis [16]. HbA1c is glucose-bound with hemoglobin, revealing the average blood glucose concentration for 3 months. Compared with fluctuating blood sugar levels, HbA1c tends to be stable. Consequently, it can be used as an objective measurement to detect the occurrence of insulin resistance [24].

In a proinflammatory setting, such as psoriasis, insulin resistance may occur, which is associated with many adipokines and cytokines produced from adipose tissue. These cytokines and adipokines have several roles in the systemic inflammation noticed in psoriasis [25].

As previously reported [26], the present study revealed a statistically significant negative correlation between serum apelin-36 and HbA1c. Insulin stimulates the synthesis and secretion of apelin from adipose tissue. Therefore, in diabetes mellitus, the decreased insulin or increased insulin resistance leads to decreased serum apelin level [27]. Moreover, the present study showed that apelin-36 was a good valid test in detecting prediabetic cases in the psoriatic group. As a result, diabetes and its complications can be prevented by early detection of prediabetes in psoriasis patients. Approving our results, Ma *et al.* [28] reported that the apelin concentration could predict incident diabetes.

Conclusion

Ghrelin and apelin-36 are dynamic adipokines that might participate independently in the psoriasis vulgaris pathogenesis in nonobese patients. The role of ghrelin in psoriasis might be mediated by dyslipidemia, whereas the role of apelin-36 could be a result of impaired glucose metabolism in psoriatic patients. Therefore, targeting ghrelin and apelin-36 may be of value in management of metabolic syndrome associated with psoriasis. It is also concluded that serum apelin-36 assessment can predict the prediabetic state in psoriatic patients, consequently avoiding diabetes and its complications in those patients.

The small number of investigated participants was the main limitation of this study.

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Conflicts of interest

There are no conflicts of interest.

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