Available online at www.medicinescience.org

ORIGINAL RESEARCH

Medicine Science International Medical Journal

Medicine Science 2018;7(3):580-6

Increased serum levels of Bisphenol A and Betatrophin in patients with Psoriasis

Suzan Demir Pektas[1], Nigar Yilmaz[2], Ibrahim Kivrak[3]

[1]Mugla Sitki Kocman University, Faculty Of Medicine, Department of Dermatology, Mugla, Turkey
[2]Mugla Sitki Kocman University, Faculty of Medicine, Department of Biochemistry, Mugla, Turkey
[3]Mugla Sitki Kocman University, Mugla Vocational School of Higher Education, Department of Chemistry and Chemical Treatment Techniques, Mugla, Turkey

Received 31 January 2018; Accepted 22 March 2018
Available online 18.04.2018 with doi: 10.5455/medscience.2018.07.8770

Abstract

Psoriasis is a common and serious systemic inflammatory disease. The purpose of this study is to research the relationship between bisphenol A, betatrophin, urocortin 3 and vitamin D levels in patients with psoriasis. Sixty patients with psoriasis (mean age, 34.1±9.6 years) and twenty six age and gender-matched healthy individuals (mean age, 35.5 ±10.5 years) were included in this study. Bisphenol A, betatrophin, urocortin 3 and vitamin D levels were assessed by using enzyme-linked immunosorbent assay in all participants. Serum levels of bisphenol A were detected using UPLC-ESI-MS/MS. In psoriasis patients, the median bisphenol A serum level was 0.537 ng/mL (range 1.1), and significantly higher compared to controls (median 0.2 range 0.9 ng/mL) ($p<0.001$). The median serum level of betatrophin was 270 ng/mL (range 5834.7 ng/mL) in patients with psoriasis, and significantly different from the control group (median 198.7, range 198.2). The median serum level of urocortin 3 was 63.3 (range 129.1) in patients with psoriasis, and it was not significantly different compared to control group (median 27 range 537.9). The median serum level of vitamin D was 23.6 (range 377), and it was significantly lower than the control group (median 156.8 range 247.1) ($p<0.001$). A positive correlation was found between serum bisphenol A and PASI scores in patients with psoriasis ($p<0.001$, $r=0.878$). Furthermore, urocortin positively correlated with the duration of illness ($p<0.001$, $r=0.557$). In ROC analysis, bisphenol A values greater than 0.764 were predicted psoriasis with 88.3% sensitivity and 61.5% specificity. Betatrophin levels greater than 0.819 were predicted psoriasis with 80% sensitivity and 69.2% specificity. We have determined a relationship between bisphenol A, betatrophin and vitamin D levels in the inflammatory process in the pathophysiology of psoriasis. Bisphenol A and betatrophin may be predictive markers for presence of psoriasis and the disease severity.

Keywords: Psoriasis, bisphenol A, betatrophin, urocortin 3, vitamin D

Introduction

Psoriasis is a chronic and recurrent inflammatory skin disease with approximately 1-3% prevalence all over the world. It is characterized with hyper-proliferative disorder of skin in which dermal-epidermal junction drives keratinocyte proliferation and development of psoriatic plaque [1]. Patients with psoriasis, have physical, social and psychological problems which result in disruptions in daily activities and professional responsibilities [1]. For this reason, the treatment of the disease or the understanding of etiopathogenesis is crucial. Although many studies have shown genetic susceptibility, epigenetic and environmental influences are also associated with disease [2-4]. For the treatment of psoriasis, initially corticosteroids are combined with vitamin D or retinoids, and also primary topical treatment agents are preferred for mild to moderate psoriasis.

Vitamin D3 serves as an immune regulator with impact on both innate and adaptive immunity, through its effects on the VDR. Vitamin D may improve outcomes by reducing both local and systemic inflammatory responses as a result of modulating vitamin 1,25-D3 inhibits proliferation of T helper 1(Th1) cells (consequently impairing production of IL-2, tumor necrosis factor α and interferon (IFN)], as well as T helper 17 (Th17) cells, skewing cytokine production toward a T helper 2 (Th2) phenotype [5]. It has shown that the active D vitamin provided differentiation and proliferation of keratinocytes, the balance of immune system and apoptosis balance in the skin [6,7]. It has been expressed that lack of Psoriasis D vitamin was related with severity of the disease [6].

Betatrophin is a recently discovered protein which is synthesized in the liver and regulates plasma triglyceride levels rather than regulating beta cell division on the pancreas. It has been stated that betatrophin deficiency causes insulin tolerance and it is experienced highly in metabolic syndrome patients [6,8]. It was determined that psoriasis might be related to insulin tolerance and its prevalence was higher in pathologies such as diabetes mellitus (DM), obesity, and metabolic syndrome [7,8]. Furthermore, it has been indicated that hyperlipidemia is a risk factor for psoriasis [8-10].

Bisphenol A belongs to a group of substances named epoxy, which

***Coresponding Author:** Suzan Demir Pektas, Mugla Sitki Kocman University, Faculty of Medicine, Department of Dermatology, Mugla, Turkey
E-mail: suzandpektas@gmail.com

is formed as a result of processing plastics under heat with various hardeners and catalysts. Used in many industrial processes (ship building, metalworking, auto repair, etc.) and health processes (laboratory and dentistry), this substance can cause dermatoses [11]. Nowadays, the most common use of bisphenol A is the production of polycarbonate plastic blocks. These blocks are used in the storage of foods and beverages. Irritant contact dermatitis, allergic contact dermatitis, contact urticaria, and airborne contact dermatitis were stated to be developed upon contact with bisphenol A. It was also shown that this process stimulates cellular immune response with a similar effect with estradiol [11].

Corticotropin-releasing factor (CRF) is a peptide reported to have varying levels in many diseases. High fasting blood sugar, increased epinephrine, adrenocorticotropic hormone, aldosterone, prolactin, growth hormone and estradiol; decreased cortisone and CRF release have been shown in psoriasis [12]. Decreased corticosteroid synthesis on the skin such as urocortin has been suggested to constitute a pathogenic mechanism of psoriasis [13, 14].

To date, there have been no publications reporting serum concentrations of bisphenol A, betatrophin and urocortin 3 in patients with psoriasis. To evaluate the contribution of bisphenol A, betatrophin, urocortin 3 and vitamin D in the pathogenesis of psoriasis, we measured the levels of bisphenol A, betatrophin, urocortin 3 and vitamin D in patients with psoriasis and determined the relation between the parameters and clinical features of psoriasis.

Material and Method

This study has been performed prospectively in Mugla Sitki Kocman University Training and Research Hospital Department of Dermatology and Biochemistry between the dates 01/03/2016 – 01/03/2017 after obtaining the approval of Mugla Sitki Kocman University Medical Faculty Hospital Ethics Committee with no. 04VIII and date 2016. Study protocols were conducted as per Helsinki Declaration, and they had been reviewed and approved by Ethics Committee. A total of 86 consenting subjects were included in the study consisting of 60 patients diagnosed with psoriasis and 26 healthy controls. Age, gender, body mass index (BMI), family history, psoriasis period, psoriasis severity, urocortin, betatrophin, bisphenol A and vitamin D levels of the patients were examined. In order to determine psoriasis severity, Psoriasis Area Severity Index (PASI) was used. Patients with liver disease, renal failure, malignancy, thyroid disease, DM, hypertension, atherosclerotic diseases, heart failure, systemic lupus erythematosus, psychiatric disease, smoking-alcoholism, substance abuse and pregnant and lactating women were included in, and individuals below age 18 were excluded from our study.

Demographic features, anthropometric measures were recorded. Psoriasis duration was obtained by self report of the patients. Age, weight, height and body mass index [BMI; weight (kilograms)/ height (meters) 2] were evaluated at baseline. Fasting plasma glucose (FPG) and lipid profile [total cholesterol, triglycerides (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C)] at diagnosis as metabolic analysis were performed. Low density lipoprotein cholesterol (LDL-C) (LDL=total cholesterol- [HDL + (TG/5)]) were calculated as previously described. Venous blood samples were obtained from the volunteers after at least 8 hours fasting in the morning. Peripheral venous blood samples (10 mL) were collected by venipuncture into tubes and centrifuged for 20 min at 2,000-3,000 rpm, and serum samples were separated and stored in -80°C until the analysis. FPG was measured with Cobas 6000 Analyzer (Roche Diagnostics, USA) by using the UV hexokinase method. Triglyceride and total cholesterol was determined with the enzymatic colorimetric assay, high density lipoprotein (HDL) cholesterol was determined with the homogenous enzymatic colorimetric assay. The level of Betatrophin (Human angiopoetin-like protein 8 Elisa kit supplied by Shanghai Yehua Biological Technology Co, Ltd, China) was measured with the serum using the enzyme-linked immunosorbent assay (ELISA) method. The level of Urocortin 3 was measured using an automated analyzer (human urocortin-3 Elisa kit supplied by Shanghai Yehua Biological Technology Co, Ltd, China). The determination of vitamin D level was performed with Human 25 dihydroxy vitamin Elisa kit (Shanghai Yehua Biological Technology Co, Ltd, China). White blood cell (WBC), neutrophil and platelets counts were measured by an automated blood cell counter (Advia 2120 Hematology Analyzer, Siemens Healthcare Diagnostics Deerfield, IL, USA).

QuEChERS Methodology

In this study, a fast QuEChERS based method was presented for the analysis of bisphenol A in human serum at low ng/mL (ppb) level. In the comparison of QuEChERS extraction and the following SPE clean-up protocols with other methods, a less toxic reactive was used and a similar detection limit was obtained with faster analysis. The analysis was performed using a tandem mass spectrometer with multiple reaction monitoring (MRM) and negative electrospray ionization mode. BPA D16 internal standard was used to correct the variance of extraction and ionization recovery. The calibration curve was plotted in the range of 0.010-100.000 ng/mL. The average recovery was determined between 84.43% and 98.75%.

QuEChERS methods have been the fastest, easiest, cheapest, most reliable and most robust sample preparation techniques up to this date. This methodology has been used all around the world in the sample preparation of vegetables and fruits for the detection of pesticide residue using GC/MS and/or LC-MS/MS. This extraction and clean-up technology can be applied effectively as an alternative to other bulky sample preparation procedure. Basic requirements for the sample matrix are easy homogenization and appropriate acetonitrile extraction. Furthermore, matrix should contain >75% (w/w) water. This ratio is required for the progressive clean-up of liquid portion.

An additional SPE clean-up step, QuEChERS extraction procedure was applied to human serum. This analysis design provided the detection of low level components without matrix effect and derivation step. Standard SPE protocol increased the number of samples and provided easier process due to the fact that there were no evaporation and derivation steps.

For the effective extraction of a compound using QuEChERS methodology, it is necessary to constitute dispersion between acetonitrile and salt-saturated water, and to have an appropriate dispersion coefficient. Extraction and clean-up step using QuEChERS method for bisphenol A from human serum is

appropriate for the matrix criteria and the liquid/liquid extraction criteria.

Extraction of bisphenol A from human serum

One millilitre of serum was put into 10 mL of centrifuge tube and 1 mL of acetonitrile was added into tube. And then, it was shaken vigorously for 1 minute. 0.75 g of DisQuE pouch products (0.15 g CH3COONa, 0.6 g MgSO4) was added and shaken mightily for 2 minutes, and then centrifuged for 5 minutes at 4000 rpm and 0.5 mL of supernatant was separated into tube for dSPE clean-up. And then 90 mg magnesium sulphate, 15 mg PSA sorbent and 15 mg C18 sorbent were added into tube, then were vortexed strongly for 1 minute, and then were centrifuged for 5 minutes at 4000 rpm. After SPE clean-up, final organic eluate was dissolved with water (50:50). The solution was filtered from Macherey-Nagel Chromafil Xtra PTFE O-20/3mm 0.20µm. UPLC-ESI-MS/MS (Waters Acquity Ultra Performance LC, Xevo TQ-S MS-MS) instrument with an Acquity UPLC BEH 1.7 µm C18 Analytical column, high pH, gradient elution program with methanol/water, ESI negative mode, 3000 V capillary voltages was used in bisphenol A analysis. The instrument analysis parameters were displayed in Table 1.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 22 was used for the statistical analysis of data. Kolmogorov Smirnov test was used for determining distribution range of descriptive statistics. Average, standard deviation (SS), median and range values were used for the expression of data. The expression qualitative data was performed with case number (n) and percentile (%). Student's t-test was used in the analysis of parametric data, while Mann Whitney-U test was used in the analysis of non-parametric data and Pearson's chi-squared test was used in the analysis of quantitative data. Pearson's correlation was used for the examination of qualitative data. ROC curve was used for determining suitable cut-off values and for the determination of sensitivity and specificity with the cut-off values. The results were evaluated with 95% confidence interval and a significance level of $p < 0.05$.

Results

Sixty patients with psoriasis (29 females and 31 males) and twenty-six healthy individuals (12 females and 14 males) were included in the study. Mean age of patient and control groups were 34.1±9.6 and 35.5±10.5 years, respectively (Table 2). No significant differences were determined between the groups in terms of age and gender. Similarly, no significant difference was found with regards to body weight, height, and body mass index (BMI) laboratory findings in patient and control groups ($p>0.05$) (Table 2). The patients had median psoriasis duration of 24.5 months (range: 160). The family history of psoriasis was significantly higher in frequency for the patients. Psoriasis patients consisted of 36 (60%)-mild psoriasis (PASI <10), and 24 (40%)-severe psoriasis (PASI>10) patients. Bisphenol A was significantly higher in patients with psoriasis compared to control group ($p<0.001$). The median bisphenol A serum level was 0.537 ng/mL (range 1.1), and significantly higher compared to controls (median 0.2 range 0.9 ng/mL) ($p<0.001$) (Table2).

Betatrophin was found significantly higher in patients with psoriasis compared to control group ($p<0.001$). In psoriasis patients, median urocortin 3 level was not significantly different from the controls ($p>0.05$). Median vitamin D serum level in psoriasis patients was significantly lower than the controls ($p<0.001$) (Table 2).

We found a relation between bisphenol levels and PASI scores.

Bisphenol A levels in patients with PASI≤ 10 in the patient group were significantly lower than those in PASI ≥10 patients ($p<0.05$). There were no statistically significant differences found with regards to body weight, height, and body mass index (BMI), laboratory findings in PASI≤ 10 and PASI ≥10 psoriasis patients ($p>0.05$). Moreover, no correlation was found between the parameters themselves (Table 3). A positive correlation was found between urocortin and the duration of psoriasis. Also, we determined a positive correlation between betatrophin and BMI (Table 4). We found that the level of bisphenol A was higher in women with regard to gender ($p<0.001$). There were no statistically significant differences found with regards to body weight, height, and body mass index (BMI), laboratory findings in male and female patients ($p>0.05$).

In this study, appropriate cut-off value of urocortin was determined as 21,15 pg/ml with 86,7% sensitivity and 38,5% specificity; appropriate cut-off value of vitamin D was determined as 82,77 ng/ml with 90,0% sensitivity and 80,8% specificity; appropriate cut-off value of betatrophin was determined as 218,65 ng/ml with 80,0% sensitivity and 69,2% specificity; and appropriate cut-off value of bisphenol A was determined as 218,65 ng/ml with 88,3% sensitivity and 61,5% specificity for psoriasis (Table 5, Figure 1).

Table 1. UPLC instrument parameters

UPLC instrument parameters				
Column	Acquity UPLC BEH C18 column (3.0x100mm, 1.7µm)			
Mobile Phase A	%0.1 NH4OH in H2O			
Mobile Phase B	%0.1 NH4OH in MeOH			
Column Oven Temp	40°C			
Injection Volume	5µL			
Gradient Program	Time (min)	Flow (mL/min)	% Solvent A	% Solvent B
	0.00	0.600	50.00	50.00
	0.20	0.600	50.00	50.00
	3.00	0.600	95.00	05.00
	5.00	0.600	95.00	05.00
	5.10	0.600	50.00	50.00
	10.00	0.600	50.00	50.00

Table 2. Demographic and biochemical data of patient and control groups, and comparison of urocortin, vitamin D, betatrophin and bisphenol A levelsias, u(Cref) values and standard, combined and expanded uncertainty values

		Patient (n:60)	Control (n:26)	p
Age, Average±SD		34,1±9,6	35,5±10,5	0,559
Gender, n(%)	Male	31 (%51,7)	14 (%53,8)	0,853
	Female	29 (%48,3)	12 (%46,2)	
Body mass index (m2/kg), Median (Range)		23 (3,7)	22,7 (1,7)	0,166
Family History	Yes	21 (%35)	0	0,001
	No	39 (%65)	26 (%100)	
Psoriasis period (months) , Median (Range)		24,5 (160)		
Urocortin (pg/mL), Median (Range)		63,3 (129,1)	27 (537,9)	0,529
Vitamin D (ng/mL), Median (Range)		23,6 (377)	156,8 (247,1)	<0,001
Betatrophin (ng/mL), Median (Range)		270,5 (5834,7)	198,7 (198,2)	<0,001
Bisphenol A (ng/mL), Median (Range)		0,537 (1,1)	0,2 (0,9)	<0,001
FPG (mg/dl), Median (Range)		90,5 (182)	86 (164,5)	0,335
Creatinin (mg/dl), Median (Range)		0,8 (9,7)	0,8 (9,7)	0,531
AST (U/L), Median (Range)		18,5 (50)	18 (50)	0,537
ALT (U/L), Median (Range)		16 (93)	14 (13)	0,788
Total protein (g/dl), Median (Range)		7,2 (1,7)	7,1 (1,7)	0,302
Albumin (g/dl), Median (Range)		4,4 (1,6)	4,4 (1,4)	0,077
Total cholesterol(mg/dl), Median (Range)		172 (186)	170 (129)	0,717
LDL (mg/dl), Median (Range)		95,5 (141,2)	90 (94)	0,255
VLDL (mg/dl), Median (Range)		29 (50)	22 (32,4)	0,027
Triglycerides (mg/dl), Median (Range)		111 (267)	110 (265)	0,531
HDL (mg/dl), Median (Range)		49 (73)	51,5 (66)	0,618
WBC (/mm3), Median (Range)		7380 (79800)	6445 (8340)	0,096
Neutrophilcount(/mm3), Median (Range)		4310 (7500)	4260 (3920)	0,196
Leukocytecount (/mm3), Median (Range)		2420 (3680)	2105 (2080)	0,061
Platelets count(/mm3), Median (Range)		245,5 (263)	238 (253)	0,825

FPG: Fasting plasma glucose, AST: aspartataminotransferaz, ALT: alaninaminotransferaz, LDL: Low-density lipoproteins,VLDL: Very low-density lipoproteins,HDL: High-density lipoproteins, WBC: white blood cell.

Table 3. Relation of urocortin, vitamin D, betatrophin and bisphenol A levels in patient and control groups

		Urocortin	Vitamin D	Betatrophin	Bisphenol A
Urocortin	r	1	0,123	0,172	0,042
	p		0,348	0,188	0,749
Vitamin D	r		1	0.044	-0.017
	p			0.740	0.898
Betatrophin	r			1	-0.210
	p				0,107
Bisphenol A	r				1
	p				
Urocortin	r	1	0.304	0.058	0.218
	p		0.131	0.779	0.285
Vitamin D	r		1	0.057	0.253
	p			0.783	0.212
Betatrophin	r			1	-0.249
	p				0.219
Bisphenol A	r				1
	p				

Statistically significant level was determined as p<0.05

Table 4. Relation of demographic characteristics with urocortin, vitamin D, betatrophin and bisphenol A levels in patient group

		Age	BMI	Psoriasis period	PASI
Urocortin	r	0,123	0,242	0,557	0,114
	p	0,351	0,063	<0,001	0,385
Vitamin D	r	0,178	0,160	0,035	-0,050
	p	0,174	0,222	0,791	0,705
Betatrophin	r	0,021	0,310	-0,026	-0,060
	p	0,876	0,016	0,842	0,649
Bisphenol A	r	-0,103	0,147	0,152	0,878
	p	0,432	0,261	0,247	<0,001

Statistically significant level was determined as p<0.05

Table 5. Area, cut-off, sensitivityandspecificity of urocortin, vitamin D, betatrophinandbisphenol A levels

						Asymptotic 95% ConfidenceInterval	
Test ResultVariable(s)	**Area**	**Cut-off**	**Sensitivite**	**Spesifite**	**p**	**LowerBound**	**UpperBound**
Urocortin	0,457	21,15	86,7	38,5	0,529	0,298	0,616
Vitamin D	0,074	82,77	90,0	80,8	<0,001	0,018	0,130
Betatrophin	0,819	218,65	80,0	69,2	<0,001	0,718	0,920
Bisphenol A	0,764	0,23	88,3	61,5	<0,001	0,649	0,879

Statisticallysignificantlevel is assumed as p<0.05

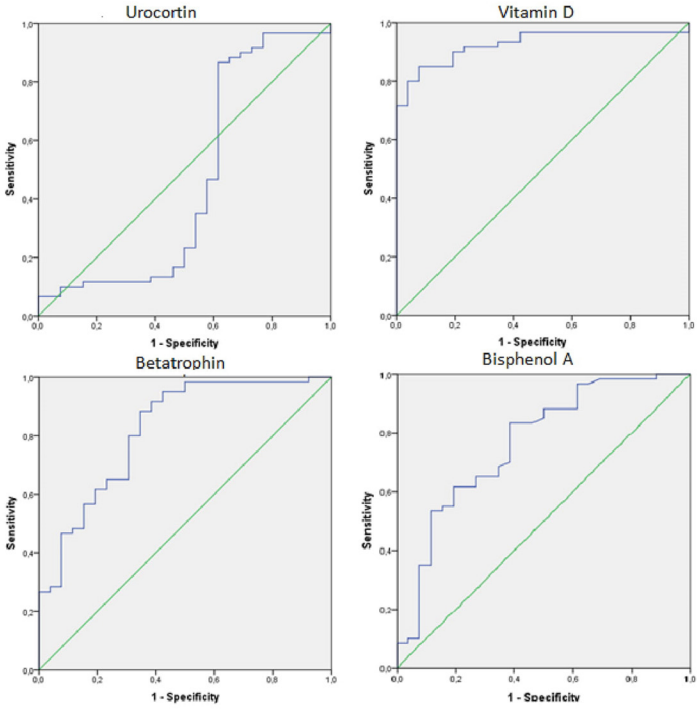

Figure 1. ROC curves of urocortin, vitamin D, betatrophin and bisphenol A

Discussion

Although psoriasis is recognized as a disease involving the immune system, its etiology is not known exactly [14-16]. Vitamin D is a key modulator in inflammatory process [17]. It has been shown that the active metabolite of vitamin D shows an anti-inflammatory effect of human monocyte/macrophages and inflammatory profile and regulates the expression and production of many pro-inflammatory cytokines (TNF-α, IL -1, IL-6 and IL-8) [18,19]. With vitamin D, cytokine-induced differentiation of T-cells, increased proliferation and increased production of immunoglobulin may be experienced. Increased inflammatory effects due to vitamin D deficiency have been associated with psoriasis in some studies. It has been demonstrated that Vitamin D causes the stimulation of in vitro keratinocyte proliferation at low concentrations and inhibition (≥10 -8 M) at higher concentrations [20,21]. Wadhwa and friends stated that administration of vitamin D supplements contributed in reducing inflammation and reversion of some changes occurring in psoriatic lesion [20]. It was shown that decrease in mRNA expression caused by promotor polymorphism of vitamin D receptors affected cutaneous barrier and the development of psoriatic lesions [19,22]. A previous study reported that there was a significant difference in allele frequencies and vitamin D receptors genotypes between normal controls and psoriasis patients, especially with early onset. This suggests that allelic variance in vitamin D receptors or genes in linkage disequilibrium with the vitamin D receptors gene, may be a risk factor for development of psoriasis [23]. In our study, it was determined that vitamin D level was significantly lower in patient group, and it was not determined to be associated with PASI score and other parameters. We consider that vitamin D deficiency contributes in psoriasis by disrupting immunity, keratinocyte differentiation and apoptosis balance. In previous studies, the researchers stated that patients with psoriasis had a 31% increased probability of multiple sclerosis compared to the general population. They determined a relation between psoriasis with multiple sclerosis due to increasing systemic inflammation. Systemic inflammation leads to insulin resistance and subsequently triggers endothelial cell dysfunction, promoting cardiovascular disease [24-26]. Mattozzi and friends determined a correlation between vitamin D and clinical severity of psoriasis calculated with PASI score. And also, they stated that the level of vitamin D is in correlation with the clinical severity of psoriasis [27]. Severe-to-moderate psoriasis effects are defined as a PASI score >10. In previous studies, psoriasis, especially the moderate-severe form, was determined to behave as a systemic inflammatory disease associated with metabolic syndrome [28].

Crujeiras and friends stated in their study that betatrophin level was significantly higher in individuals with metabolic syndrome, obesity, and impaired lipid profile and glucose tolerance [6]. Fenzl and friends have shown a significant correlation between betatrophin level and plasma atherogenic lipids in morbid obese patients and patients with type 2 DM, however, no relation was determined with control group [29]. Fu and friends has shown a positive correlation between betatrophin and BMI [30]. It has been determined that the prevalence of psoriasis increases in metabolic diseases, primarily in hyperlipidemia [8,19,21,28]. It was determined in our study that betatrophin level was significantly higher in patients with psoriasis, showed positive correlation with BMI in patient group; and it was not associated with other demographic data, PASI score, and other parameters.

Psoriasis is an immunological reaction in which tissue reaction occurs as a result of severe inflammatory component and abnormal keratinocyte differentiation. It is developed in the consequence of activation of T cells migrating to skin through the activation of immune system elements such as keratinocytes and dendritic cells, and some cytokines [31]. Aytekin and friends have shown that effect mechanism of Bisphenol A on the skin is developed due to the stimulation of cellular immune response [11]. In this study, bisphenol was studied with highly efficient and highly sensitive UPLC-ESI-MS/MS. It was determined in our study that Bisphenol A levels increased in psoriasis patients, bisphenol A levels increased with increasing PASI score; and they were not associated with other demographic data and other parameters apart

from gender. We think that bisphenol A causes psoriasis as a result of the cellular immune reaction it produces. Since immunological reactions are more common in female patients, we consider that Bisphenol A level increases in female psoriasis patients.

Urocortin is one of the substances affecting CRF receptor, and it is stated to be found on the skin [32,33]. Singh and friends stated that urocortin levels decreased in psoriasis, and this caused increased permeability as a result of mast cell degranulation through orthodromic stimulation of the trigeminal nerve in acute psychological stress [13]. Zangeneh and friends have reported that most stress hormones increase due to increased stress in psoriasis, and CRF and cortisone release have not changed. The researchers well described the pro-inflammation role of CRF which is synthesized by cutaneous cells and immune cells in human skin, such as CRF-induced activation of mast cells in the phenomenon of stress related of cutaneous inflammatory diseases [34]. Moreover, mast cells express CRF receptors, and their activation causes selective release of cytokines and other pro-inflammatory mediators [12]. It has been stated that increase in endogenous glucocorticoids and CRF/urocortin decrease at the tissue level may disrupt permeability barrier and cause psoriasis [35]. CRF is up-regulated in psoriasis, as the stress-integrating peptide which involved in the inflamed tissues of patients with psoriasis [34]. It was determined in our study that urocortin level did not change in psoriasis, and it was not associated with age, BMI and disease severity. Nevertheless, a positive correlation was determined between urocortin level and psoriasis period. Although hormones were related to stress, we consider that this shows urocortin increases with adaptive mechanisms in a long time rather than acutely.

In literature, no studies were determined that evaluate the relationship between vitamin D, bisphenol A, betatrophin and urocortin levels in psoriasis. Also, no correlation was determined among these parameters with each other in our study. This suggests that these four parameters may play a role in psoriasis through separate ways. Also, the possibility that these markers may be effective on attack frequency and lesion development in psoriasis led to the conclusion that it does not provide any opinions for its presence in the etiology.

In literature, no studies were determined that evaluate the sensitivity and specificity of vitamin D, bisphenol A, betatrophin and urocortin levels in psoriasis. It was considered in our study that vitamin D, bisphenol A and betatrophin levels were effective on their own since they had high sensitivity and specificity in psoriasis; while urocortin level was not considered to be effective on its own since it had high sensitivity and low specificity. This brings us to the conclusion that these recently described biomarkers may play a role in clinical use in the near future.

Conclusion

Our study shed light on the psoriasis by investigating the relationship between bisphenol A, betatrophin, urocortin 3 and D vitamin. We suggest that increased levels of bisphenol A, betatrophin and decreased level of D vitamin can be used as a predictive marker of psoriasis and disease severity.

Competing interests
The authors declare that they have no competing interest

Financial Disclosure
The financial support for this study was provided by the investigators themselves.

References

1. Melikoglu M. Sleep Quality and its Association with Disease Severity in Psoriasis. Eurasian J Med. 2017;49:124-7.
2. Kumar P, James W. Psoriasis, Plaque. StatPearls. Treasure Island. 2017.
3. Balci DD, Balci A, Karazincir S, et al. Increased carotid artery intima-media thickness and impaired endothelial function in psoriasis. J Eur Acad Dermatol Venereol. 2009;23:1-6.
4. Neimann AL, Shin DB, Wang X, et al. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol. 2006;55:829-35.
5. Jurgen Schauber, Richard L, Gallo. The vitamin D pathway: a new target for control of the skin's immune response? Exp Dermatol. 2008;17:633-9.
6. Crujeiras AB, Zulet MA, Abete I, et al. Interplay of atherogenic factors, protein intake and betatrophin levels in obese-metabolic syndrome patients treated with hypocaloric diets. Int J Obes. 2016;40:403-10.
7. Gisondi P, Ferrazzi A, Girolomoni G. Metabolic comorbidities and psoriasis. Acta Dermatovenerol Croat. 2010;18:297-304.
8. Gisondi P, Galvan A, Idolazzi L, et al. Management of moderate to severe psoriasis in patients with metabolic comorbidities. Front Med. 2015;2:1.
9. Bajaj DR, Mahesar SM, Devrajani BR, et al. Lipid profile in patients with psoriasis presenting at Liaquat University Hospital Hyderabad. J Pak Med Assoc. 2009;59:512-5.
10. Mysliwiec H, Baran A, Harasim-Symbor E, et al. Serum fatty acid profile in psoriasis and its comorbidity. Arch Dermatol Res. 2017;309:371-80.
11. Aytekin A, Togral AK, Yilmaz ÖH. Epoxy Resins and the Relationship with Occupational Dermatoses. Ankara Med J. 2015;15:96-101.
12. Zangeneh FZ, Fazeli A. The significance of stress hormones in psoriasis. Acta Medica Iranica. 2008;46:485-8.
13. Singh LK, Boucher W, Pang X, et al. Potent mast cell degranulation and vascular permeability triggered by urocortin through activation of corticotropin-releasing hormone receptors. J Pharmacol Exp Ther. 1999;288:1349-56.
14. Hannen R, Udeh-Momoh C, Upton J, et al. Dysfunctional Skin-Derived Glucocorticoid Synthesis Is a Pathogenic Mechanism of Psoriasis. J Invest Dermatol. 2017;137:1630-7.
15. Reich A, Wójcik-Maciejewicz A, Slominski AT. Stress and the skin. G Ital Dermatol Venereol. 2010;145:213-9.
16. Slominski A, Zbytek B, Nikolakis G,et al. Steroidogenesis in the skin: implications for local immune functions. J Steroid Biochem Mol Biol. 2013a;137:107-23.
17. Mehmood ZH, Papandreou D. An updated mini review of vitamin D and obesity: Adipogenesis and inflammation state. Open Access Maced J Med Sci. 2016;4:526–32.
18. Zhang Y, Leung DY, Richers BN, et al. Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1. J Immunol. 2012;188:2127–35.
19. Neve A, Corrado A, Cantatore FP. Immunomodulatory effects of vitamin D in peripheral blood monocyte-derived macrophages from patients with rheumatoid arthritis. Clin Exp Med. 2014;14:275-83.
20. Wadhwa B, Relhan V, Goel K, et al. Vitamin D and skin diseases: A review. Indian J Dermatol Venereol Leprol. 2015;81:344-55.
21. Barrea L, Savanelli MC, Di Somma C, et al. Vitamin D and its role in

psoriasis: An overview of the dermatologist and nutritionist. Rev Endocr Metab Disord. 2017;18:195-205.

22. Richetta AG, Silvestri V, Giancristoforo S, et al. A-1012G promoter polymorphism of vitamin D receptor gene is associated with psoriasis risk and lower allele-specific expression. DNA Cell Biol. 2014;33:102–9.

23. Byung-Soon Park, Jeong-Soo Park, Dong-Youn Lee, et al. Vitamin D Receptor Polymorphism is Associated with Psoriasis. J Invest Dermatol. 1999;112:113-6.

24. Coimbra S, Oliveira H, Neuparth MJ, et al. Metabolic syndrome in psoriasis patients. Residual inflammation and pro-inflammatory IL17 signaling reduce length of remission. A follow-up study. Br J Dermatol. 2015;174:414-6.

25. Boehncke WH, Boehncke S, Tobin AM, et al. The 'psoriatic march': a concept of how severe psoriasis may drive cardiovascular comorbidity. Exp Dermatol. 2011;20:303-7.

26. Shlyankevich J, Mehta NN, Krueger JG, et al. Accumulating evidence for the association and shared pathogenic mechanisms between psoriasis and cardiovascular-related comorbidities. Am J Med. 2014;127:1148-53.

27. Mattozzi C, Paolino G, Salvi M, et al. Correlation between plasmatic levels of Vitamin D and PASI score: our experience and mini-review of the literature. G Ital Dermatol Venereol. 2018;153:155-60.

28. Rodríguez-Zúñiga MJM, García-Perdomo HA. Systematic review and meta-analysis of the association between psoriasis and metabolic syndrome. J Am Acad Dermatol. 2017;77:657-666.e8.

29. Fenzl A, Itariu BK, Kosi L, et al. Circulating betatrophin correlates with atherogenic lipid profiles but not with glucose and insulin levels in insulin-resistant individuals. Diabetologia. 2014;57:1204-8.

30. Fu Z, Abou-Samra AB, Zhang R. An explanation for recent discrepancies in levels of human circulating betatrophin. Diabetologia. 2014;57:2232-4.

31. Alper S, Akyol M, Atakan N, et al. Turkish Guideline for the Treatment of Psoriasis. Turkderm. 2012;46:1

32. Theoharides TC, Donelan JM, Papadopoulou N, et al. Mast cells as targets of corticotropin-releasing factor and related peptides. Trends Pharmacol Sci. 2004;25:563-8.

33. Gupta MA, Gupta AK. Age and gender differences in the impact of psoriasis on quality of life. Int J Dermatol. 1995;34:700-3.

34. Andrzej T. Slominski, Michal A. Zmijewski, Blazej Zbytek, et al. Theoharides, and Jean Rivier. Key Role of CRF in the Skin Stress Response System. Endocr Rev. 2013;34:827-84.

35. Choi EH, Brown BE, Crumrine D, et al. Mechanisms by which psychologic stress alters cutaneous permeability barrier homeostasis and stratum corneum integrity. J Invest Dermatol. 2005;124:587-95.