Serum concentrations of 25-OH vitamin D and the pro-inflammatory interleukins IL-17, IL-23, and IL-18 in patients with plaque psoriasis

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Aims. The present study aimed to assess vitamin D status and serum concentrations of pro-inflammatory cytokines IL-17, Il-23, and IL-18 in patients with chronic plaque psoriasis and their association with various demographic and clinical characteristics.

Methods. The study was conducted during the autumn/winter period on 48 patients with chronic plaque psoriasis and 48 controls. Total serum 25(OH)D level was determined with Roche Elecsys® 2010 Vitamin D total assay. Commercial ELISA kits were used for quantifying the serum levels of IL-17A, IL-18, and IL-23.

Results. Serum 25(OH)D had a median value of 16.95 ng/mL (IQR 10.8–23.50) for patients with psoriasis and 18.80 ng/mL (IQR 15.45–25.85) for the control group (*P*=0.09). A moderate negative correlation was found between PASI score and 25(OH)D levels (r_s=–0.34; *P*=0.02). The serum levels of IL-17 (*P*=0.001), IL-23 (*P*=0.01) and IL-18 (*P*=0.02) were significantly higher in the patient group compared to controls. IL-17 concentrations were higher in patients with moderate to severe psoriasis compared to patients with mild psoriasis (*P*=0.003). No significant correlations were detected between the serum concentrations of 25(OH)D and IL-17, IL-23, and IL-18.

Conclusion. It was confirmed that IL-17 serum level is associated with psoriasis severity. Measurement of 25(OH)D serum concentration can be useful in patients with moderate to severe psoriasis with or without comorbidities. A direct association between 25(OH)D serum concentration and the serum concentrations of IL-17, IL-23, or IL-18 was not identified in this study.

Key words: psoriasis, 25-OH vitamin D, IL-17, IL-23, IL-18

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INTRODUCTION

Psoriasis is a chronic immune-mediated inflammatory skin disorder. It is considered to be a multisystem disease due to the frequent development of serious comorbidities including psoriatic arthritis, cardiovascular diseases, metabolic syndrome or its components (obesity, dyslipidemia, type-2 diabetes mellitus), non-alcoholic fatty liver disease, and osteoporosis[1-5]. In addition to the classic comorbidities such as psoriatic arthritis, inflammatory bowel disease, uveitis and psychiatric disorders, new associations between psoriasis and many other diseases are emerging[3,6]. It has been hypothesized that the presence of chronic inflammation might be the link between psoriasis and many of these associated disease states[7].

In the last decades, psoriasis has been viewed as a T-helper 17 (Th17)-driven inflammatory disease in individuals with genetic predisposition, triggered by environmental factors such as trauma, infection, etc. (ref.[8]). The IL-23/IL-17 pathogenic axis plays a key role in the pathogenesis[9], but other cytokines are also involved. The major cells participating in the pathogenesis of psoriasis in addition to T cells are dendritic cells, macrophages, and keratinocytes[8]. Activated plasmacytoid dendritic cells release IFN-α and TNF-α leading to keratinocyte activation and maturation of myeloid dendritic cells. IL-23 produced by dendritic cells and macrophages promotes Th17 cell effector functions[10] resulting in the production of very high levels of IL-17 and IL-22 leading to keratinocyte proliferation and down-regulation of their differentiation[11].

Vitamin D is also thought to be involved in the pathogenesis of psoriasis by modulating the inflammatory process and affecting the epidermal barrier function. The effects of vitamin D and its metabolites on immune function are pleiotropic and mediated through the vitamin D receptor (VDR), which is expressed by macrophages, dendritic cells, and activated T cells. Vitamin D impairs the capacity of plasmacytoid dendritic cells which are assumed to initiate the inflammatory cascade in psoriasis, to induce T-cell proliferation and IFN-γ secretion[12]. 1,25(OH)2D3, the active form of vitamin D, inhibits the production of inflammatory Th1-cytokines such as IL-2

and IFN-γ, as well as the Th17-derived cytokines IL-17 and IL-21 (ref.[13,14]). Vitamin D promotes differentiation of naive T-cell into T regulatory cells, enhancing the production of anti-inflammatory cytokines (TGF-β, IL-4, and IL-10), and suppressing the production of pro-inflammatory cytokines TNF-α, INF-γ, IL-2, IL-17A, and IL-21 (ref.[15]). In this way, vitamin D is presumed to affect the inflammatory Th1/Th17 pathways.

Some studies have reported a deficiency of vitamin D in psoriatic patients[16-19]. Vitamin D has also been implicated in the pathogenesis of many auto-inflammatory, cardiovascular, and infectious diseases. In this regard, the present study aimed to assess vitamin D status and the serum concentrations of pro-inflammatory cytokines IL-17, Il-23, and IL-18 in patients with chronic plaque psoriasis and their association with various demographic and clinical characteristics.

MATERIALS AND METHODS

This study is a part of a project addressing the factors influencing the vitamin D status of psoriasis patients. It includes 96 subjects (48 patients with histologically verified plaque psoriasis and 48 controls) and was conducted during the autumn/winter period (November–March) of 2019–2020 in the Clinic of Dermatology and Venereology, UMHAT "Prof. Dr. Stoyan Kirkovich", Stara Zagora, Bulgaria. Control subjects had no dermatological diseases and were sex and age-matched (±2 years). The following exclusion criteria were defined: age below 18 years, pregnancy, prior malignancy or confirmed psychiatric disorder, consumption of drugs or dietary supplements containing vitamin D during the previous 3 months. Additional exclusion criteria for patients were the treatment with topical vitamin D analogs, phototherapy or thalassotherapy, and the use of systemic immunosuppressants during the previous 3 months.

Participation in the study was consistent with the ethical principles of voluntarism and anonymity and complies with the laws and regulations in the country. Written informed consent from the participants was obtained. The local Ethics Committee approved the study (decision number 10/2019).

Patients

Data were collected by 3 researchers on-site using a specially designed self-completed questionnaire. The questionnaire had 2 versions: one for patients and another for control subjects. It contained information on participants' socio-demographics, health, and lifestyle characteristics (age, gender, weight, height, and sports activity). Data on smoking, alcohol consumption, sensitivity to sunlight, and concomitant cardio-metabolic diseases (CMDs) were also collected. Regular alcohol consumption was defined as the daily ingestion of more than 100 mL of hard liquor or more than 2 standard glasses of wine or beer. Skin phototype was defined according to the Fitzpatrick classification[20].

For coding the main groups of concomitant diseases the ICD-10 was used. The questionnaire for patients included additional questions concerning the duration of the disease and the type of therapy for psoriasis in the previous 3 months. Depending on the onset of the psoriasis, patients were categorized into those with early onset if the first symptoms appeared before 40 years of age and those with late-onset psoriasis – with symptoms appearing after 40 years of age.

Patients were subjected to clinical examination. PASI was calculated using an online calculator[21]. Psoriasis was classified as "mild" (PASI ≤ 10) and "moderate to severe" (PASI ≥ 10) (ref.[22]). Depending on the PASI score psoriasis patients were divided into 2 groups: patients with mild disease and patients with moderate to severe psoriasis. Body mass index (BMI) was calculated according to the Quetelet equation. Normal weight was considered for BMI 18.5–24.9 kg/m^2, underweight for BMI below 18.5 kg/m^2, pre-obesity for BMI 25.0–29.9 kg/m^2, and obesity for BMI above 30 kg/square meter[23].

Methods

Total serum 25(OH)D level was determined with Roche Elecsys® 2010 Vitamin D total assay (ECLIA-electrochemiluminescence immunoassay, Roche Diagnostic, Mannheim, Germany), with a sensitivity of 3.00–70.00 ng/mL (7.5–175 nmol/L). Vitamin D status was defined according to the level of 25(OH)D as deficiency (≤ 20 ng/mL), insufficiency (21–29 ng/mL), and sufficiency (≥ 30 ng/mL) according to Holick[24].

Blood samples for cytokine determination were collected in gel/clot activator vacutainer tubes. The blood samples were allowed to clot at room temperature for 30 min before centrifugation. Serum samples were removed and frozen in small aliquots at −70 °C until the enzyme-linked immunosorbent assay (ELISA) analysis was available.

Commercial ELISA kits (eBioscience, Vienna, Austria) were used for quantifying the serum levels of IL-17A, IL-18, and IL-23 following the manufacturer's instructions. The cytokine concentration was determined using a standard curve constructed with the kit's standards and expressed in picograms per mL (pg/mL). Serum samples were run as duplicates and analyzed in the same analytic batch. The minimum detection levels were 0.5 pg/mL for IL-17A, 9 pg/mL for IL-18, and 4 pg/mL for IL-23. Values below the detection limits were set as zero.

Statistical analysis

Descriptive statistics were used to summarise the data. Variables were tested for normality using the Shapiro-Wilk test. Categorical variables are presented as numbers and percentages. Continuous data are presented as mean and standard deviation or as the median and interquartile range (IQR). Comparisons between groups for categorical variables were made using the Chi-square (χ^2) test or Fisher`s exact test. For comparisons of continuous variables, the Mann-Whitney U test, the independent

samples median test and Kruskal-Wallis test were used. Spearman's rank correlation was used to assess the association between serum cytokine levels, 25(OH)D, and various clinical parameters. A *P*-value <0.05 was considered statistically significant. All statistical analyzes were performed using SPSS, version 19.

RESULTS

A total of 48 psoriasis patients and 48 controls with no skin diseases were included in the study (Table 1).

The mean age of psoriasis patients was 52.85±10.81 (median 55.0; IQR 44.75–59.75) and the mean age of controls was 52.65±11.41 (median 55.0 IQR 44.0–60.5). Menopause was recorded in 10 (20.8%) female participants from the psoriasis group and in 11 (22.9%) females from the control group. The proportion of patients with pre-obesity and obesity was significantly higher in the psoriasis group (χ=18.561; *P*=0.001) and BMI with a median of 30.46 kg/m^2 (IQR 27.76–36.07) was higher (*P*=0.001) in patients compared to controls with BMI 26.24kg/m^2 (IQR 24.30–27.76). More psoriasis patients were engaged in outdoor jobs, but participated in no regular physical activities and were smokers. There were no differences among patients and controls concerning diet, alcohol consumption, and skin phototype.

Concomitant CMDs belonging to the groups "Diseases of the circulatory system" (I00–I99) and "Endocrine, nutritional and metabolic diseases" (E00–E90) affected 26 (54.2%) patients and 13 (27.1%) control subjects (χ=8.4; *P*=0.004). The number of diseases per patient varied from 1 to 3. The most common was hypertensive disease found in 26 (54.2%) patients and 8 (16.7%) controls.

Clinical characteristics of psoriasis patients (Table 2)

Early onset psoriasis was prevalent (34 patients, 70.8%) in the psoriasis patient group. The average duration of the disease was 17.75±11.13 years, with a median of 17.5 (IQR 9.25–21.0). The mean PASI score was 14.80±11.68, with a median of 18.05 (IQR 1.8–25.4). No association was found between psoriasis severity and

Table 1. Demographic, anthropometric, and lifestyle characteristics of patients and controls.

Characteristics	Category	Psoriasis patients (n, %)	Controls (n, %)	*P*
Sex	Male	30 (62.5%)	30 (62.5%)	0.17
	Female	18 (37.5%)	18 (37.5%)	
Regular alcohol consumption	Yes	14 (29.2%)	10 (20.8%)	0.12
	No	34 (70.8%)	38 (79.2%)	
Smoking	Smoker	27 (56.3%)	16 (33.3%)	0.01
	Nonsmoker	21 (43.8%)	32 (66.7%)	
Regular physical activity	Yes	6 (12.5%)	26 (54.2%)	0.001
	No	42 (87.5%)	22 (45.8%)	
Diet	Normal diet	48 (100.0%)	47 (97.9%)	1.0*
	Vegetarian	0 (0%)	1 (2.1%)	
BMI categories	Normal	6 (12.5%)	17 (35.4%)	0.001
	Pre-obesity	14 (29.2%)	23 (47.9%)	
	Obesity	28 (58.3%)	8 (16.7%)	
Skin phototype	III	12 (25.0%)	9 (18.8%)	0.06
	IV	31 (64.6%)	29 (60.4%)	
	V	5 (10.4%)	10 (20.8%)	
Job environment (outdoor)	Yes	19 (39.6%)	8 (16.7%)	0.008
	No	29 (60.4%)	40 (83.3%)	

*Fisher's exact test.

Table 2. Demographic and clinical characteristics of psoriasis patients.

Characteristics	Mild psoriasis (PASI≤10)	Moderate to severe psoriasis (PASI≥10)	*P*
Number of patients (n, %)	20 (41.7%)	28 (58.3%)	–
Males (n, %)	12 (40%)	18 (60%)	0.76
Females (n, %)	8 (44.4%)	10 (55.6%)	
Age (median, IQR)	55 (IQR53.0–59.0)	54(42.0–60.0)	0.8
BMI (median, IQR)	28.2 (IQR 27.76–30.86)	32.9 (IQR 28.0–36.84)	0.03
Cardio-metabolic disease (n, %)			
Yes	6 (22.2%)	21 (77.8%)	0.002
No	14 (66.7%)	7 (33.3%)	

Table 3. Vitamin D status of psoriasis patients and controls.

Vitamin D status	Psoriasis patients (n, %)	Controls (n, %)
Sufficiency	4 (8.3%)	8 (16.7%)
Insufficiency	13 (27.1%)	13 (27.1%)
Deficiency	31 (64.6%)	27 (56.3%)

the factors "age" and "sex". The weight of patients with moderate to severe psoriasis was significantly higher than the weight of the patients with mild psoriasis (*P*=0.03). Concomitant CMDs were detected more commonly in patients with moderate to severe psoriasis compared to patients with a mild form of the disease (χ=9.6; *P*=0.002).

Vitamin D status of patients and controls (Table 3)

Serum 25(OH)D had a median value of 16.95 ng/mL (IQR 10.8–23.50) for patients with psoriasis and 18.80 ng/mL (IQR 15.45–25.85) for the control group (*P*=0.09). The rate of vitamin D deficiency in patients and controls was similar (χ=1.52; *P*=0.35). Deficiency or insufficiency was detected in 91.7% of psoriasis patients and 83.3% of controls (χ=1.61; *P*=0.47).

The median serum 25(OH)D was 15.25 (IQR 10.7–22.2) for patients with moderate to severe psoriasis and did not differ significantly from the median concentration of 17.45 (IQR 12.02–27.7) for patients with psoriasis of mild severity (*P*=0.21) but was significantly lower than the median serum 25(OH)D level of the controls (*P*=0.04). Moderate negative correlation (Fig. 1) was found between PASI and 25(OH)D levels (r_s=−0.34; *P*=0.02). No correlation was found between serum 25(OH)D level and the duration of psoriatic disease (r_s=0.12; *P*=0.41). No statistical differences in 25(OH)D serum concentrations were detected in psoriatic patients with CMDs compared to patients with no CMDs (*P*=0.14).

Serum levels of IL-17, IL-23, and IL-18 in the study population

The serum levels of IL-17, IL-23 and IL-18 were found to be significantly higher in the group of patients with psoriasis than the level of these cytokines in controls (Table 4). In the examined cohort no correlation was detected between the serum levels of IL-17, IL-23, and IL-18 and age. No differences were found in the investigated interleukins among males and females. The serum level of IL-18 was higher (*P*=0.02) in subjects with preobesity and obesity (mean rank 52.36) than in subjects with normal weight (mean rank 36.26). In the investigated cohort of patients and controls, the serum levels of IL-17

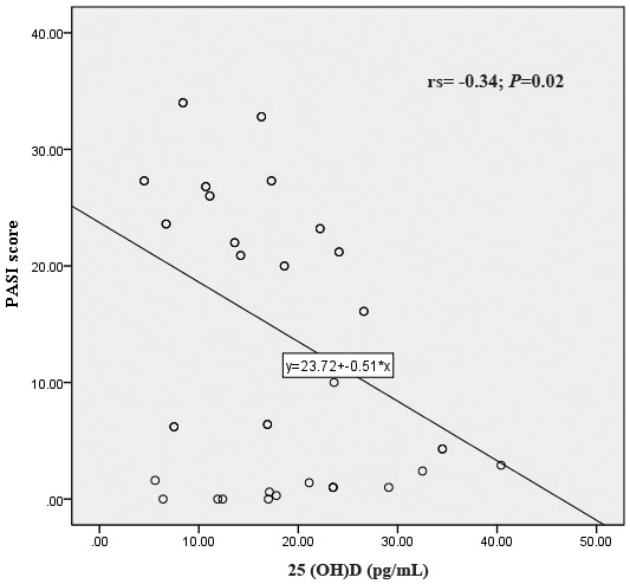

Fig. 1. Linear correlation between serum 25(OH)D concentration and PASI score in psoriasis patients.

(mean rank 56.83 vs 42.55) and IL-18 (mean rank 55.64 vs 43.40) were significantly higher (*P*=0.01 and *P*=0.03 respectively) in the group with CMDs than in the group without any CMDs.

Among psoriatic patients, the presence of concomitant systemic disease (cardiovascular and/or metabolic) was not associated with differences in the serum levels of IL-17 (*P*=0.24), IL-23 (*P*=0.32) and IL-18 (*P*=0.38) although the median levels were higher in psoriasis patients with CMDs (Table 4). IL-23 correlated negatively with the duration of the disease (r_s=−0.56; *P*=0.001). Serum IL-17 correlated positively with the PASI score (r_s=0.42; *P*=0.004). Comparing interleukin serum concentrations in psoriasis patient groups based on the severity of the disease, IL-17 concentrations (Fig. 2) were found to be significantly higher in patients with moderate to severe psoriasis compared to patients with a mild form of the disease (*P*=0.003). No significant differences were detected in the concentrations of IL-23 and IL-18 among these groups.

Table 4. Serum levels of IL-17, IL-23, and IL-18 in psoriasis patients and controls

IL	Psoriasis pts n=48 (median, IQR)	Controls n=48 (median, IQR)	*P*	Pts with CMDs n=27 (median, IQR)	Pts with no CMDs n=21 (median, IQR)
IL-17	4.49 (3.62–6.95)	2.07 (1.59–2.83)	0.001	4.82 (3.76–8.64)	4.17 (3.56–5.22)
IL-23	8.38 (0.0–20.59)	0.13 (0.0–9.77)	0.01	13.7 (0.0–114.03)	7.48 (0.0–18.54)
IL-18	134.21 (39.93–217.07)	70.95 (33.57–101.5)	0.02	154.21 (47.07–217.07)	87.07 (38.5–241.35)

Pts, patients.

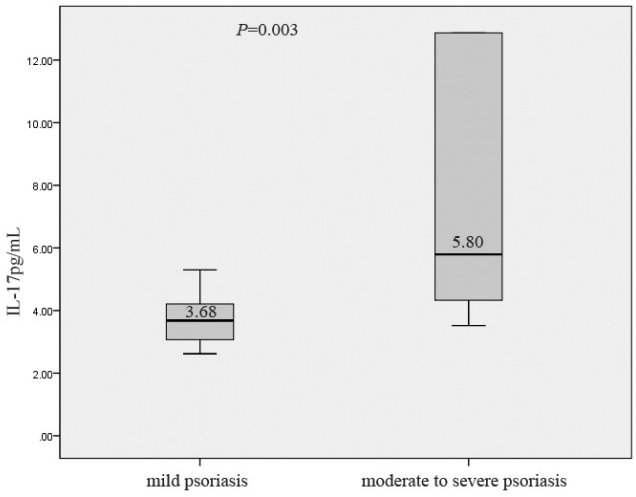

Fig. 2. The serum concentration of IL-17 (medians and IQR) in patients with mild and moderate to severe psoriasis. Mann-Whitney U-test.

In psoriasis patients no significant correlations were detected between the serum concentrations of 25(OH)D and IL-17 (r_s=0.15; *P*=0.3), IL-23 (r_s=−0.19; *P*=0.21) and IL-18 (r_s=0.22; *P*=0.13).

DISCUSSION

Results from the present study show that vitamin D deficiency and insufficiency are commonly seen in psoriasis patients as well as in control subjects. Indeed low vitamin D status is emerging as a very common condition worldwide[25]. Unlike other studies of psoriasis patients[16,17] vitamin D deficiency was not found to be prevalent in psoriasis patients although the median serum concentrations of 25(OH)D were lower in this group. Lower serum levels of 25(OH)D have been reported for patients with chronic plaque psoriasis in many studies[26-28] but these findings have not been supported by others[19,29,30]. These differences can be attributed not only to the various designs of the studies but also to factors such as ethnicity, diet, sun exposure, and lifestyle characteristics (dressing habits, use of sunscreens). In line with the findings of several studies[17,31-33], we detected a moderate negative correlation between the serum level of 25(OH)D and the severity of the disease evaluated with the PASI score which suggests that 25(OH)D may be implicated in the pathogenesis of psoriasis. A recent immunohistochemistry study of psoriatic skin found a strong significant negative correlation (*P*<0.001, r=0.719) between the expressions of VDR and PASI score[34] that might explain low serum levels of 25 (OH)D in severe psoriasis. The relationship between vitamin D and psoriasis was confirmed in some studies including a recent meta-analysis[35]. However, the data are controversial, and it is still not known if low vitamin D level is the causative factor for psoriasis or the effect of the disease[36].

Available studies suggest that vitamin D deficiency may be a risk for the development of autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and Crohn's disease[37,38]. What is more, vitamin D deficiency appears to be associated with the different components of the metabolic syndrome[39], a common co-morbidity of psoriatic patients. The prominent co-morbidities with systemic inflammatory diseases, such as cardiovascular diseases and metabolic syndrome in psoriasis may result from the underlying inflammatory process[40]. Thus the association between psoriasis and CMDs could be explained by the systemic effects of psoriasis-related inflammation, mediated by Th1 and Th17 cytokines[41,42], as Th17 cells along with Th1 are found in the dermis of psoriatic lesions and produce IL-17 and IL-22 (ref.[43]).

The results of this study show significantly higher serum concentrations of IL-17, IL-23, and IL-18 in patients with psoriasis compared to controls. These data support the involvement of the IL-23/IL-17 immune axis along with the NLRP3 inflammasome in psoriatic patients. It is postulated that immunologically psoriasis is a mixture of autoimmune and auto-inflammatory responses. The balance between the two defines the clinical presentation of the disease with chronic plaque psoriasis having prominent autoimmune responses while pustular psoriasis is dominated by autoinflammatory immune responses[44].

In the current study, it was found that the serum level of IL-23 was higher in psoriasis patients compared to controls but no differences were established between patients with moderate to severe psoriatic disease and patients with mild psoriasis. Data on serum levels of IL-23 in psoriasis is contradictory. A study of 60 patients with severe psoriasis from Poland also established higher serum concentrations of IL-23 compared to healthy controls[45]. Conversely, a meta-analysis of 63 studies comparing the serum levels of 23 markers in psoriasis patients and healthy controls showed that serum levels of IL-23 were not significantly different between psoriasis patients and controls[46]. However, an overproduction of IL-23 by dermal dendritic cells and keratinocytes has been demonstrated in psoriatic lesions[47]. IL-23 has a major role in the initiation of the chain of events resulting in the formation of psoriasis lesions. This may explain the negative correlation with the duration of psoriatic disease[48,49], a finding that was confirmed in the present study. IL-23 produced by activated dendritic cells and macrophages is a key upstream regulator of IL-17 production by stimulating differentiation, activation, proliferation, and survival of Th17 cells[50].

The IL-17 family consists of six isoforms IL-17 A-F with similar pro-inflammatory functions in the skin and playing a pathogenic role in psoriatic disease[51]. Findings from many studies show that serum concentrations of IL-17 are higher in psoriatic patients than in controls[28,52-54] although similar differences are not found to be statistically significant by others[55] or are not detected at al.[56]. An important factor that might influence IL-17 levels and explain differences between study populations is age. Sobhan et al. found a significant inverse correlation between IL-17 serum level and age in psoriatic patients[54]. The variations of cytokine levels across studies may be due to different study designs, different genetic back-

grounds, or may reflect the influence of concomitant diseases. A recent study of psoriasis patients without any associated comorbidities using highly sensitive methods of detecting cytokine mRNA provides evidence of increased mRNA expression of IL-17A in blood samples of patients compared to that in normal subjects[57] thus emphasizing the major role of IL-17 in psoriasis.

In the present study, the serum concentrations of IL-17A were significantly higher in moderate to severe psoriasis and a positive correlation with PASI was established. In a large cohort of 623 psoriasis patients evaluating the clinical efficacy of tofacitinib and etanercept, Fitz et al. found that baseline serum IL-17A moderately correlated with disease severity supporting the concept that psoriasis is a systemic disease[58]. The authors concluded that the association between decreases in IL-17A and clinical response suggests that normalization of circulating IL-17A is necessary for psoriasis remission regardless of the target of the therapeutic agent. Thus IL-17A is considered to be an important biomarker of psoriasis severity and response to treatment.

Important findings in the current study are the established significantly higher concentrations of pro-inflammatory IL-17A and IL-18 in individuals with CMDs and obesity (only IL-18) in the study cohort and elevated levels of these cytokines in psoriasis patients with CMDs. Measurement of IL-18 in psoriasis patients with comorbidities is important because IL-18 has been evaluated as a potential predictor of cardiovascular events and mortality in populations with metabolic syndrome[59,60]. IL-18 has been found to be elevated in subjects with metabolic syndrome and increases in parallel with an increasing number of components of the syndrome[61]. Concerning IL-17A, this was higher in all participants with CMDs compared to participants without CMDs, although such differences were not significant for psoriasis patients. High levels of pro-inflammatory cytokines including IL-17A in patients with moderate to severe psoriasis promote chronic subclinical inflammation that increases the risk of several comorbidities including atherosclerotic cardiovascular disease, diabetes, obesity, dyslipidemia, and hypertension[50]. Evidence suggests that psoriasis and atherosclerosis have overlapping pathogenic pathways[62]. The activation of myeloid dendritic cells in psoriasis and the activation of endothelial cells in atherosclerosis lead to Th1 and Th17 responses and secretion of TNF-α, IFN-γ, IL-17A, and IL-22 (ref.[62]). The IL-23/IL-17A pathway emerges as a link between psoriasis and atherosclerosis. In this regard, the clinical importance of the IL-23/IL-17 axis has been validated by the high clinical efficacy of IL-17A and IL-23 inhibitors in the treatment of psoriasis. Thus anti-IL-17A treatment (and other biologics) may be considered promising agents to manage not only psoriasis but also cardiovascular comorbidity[63].

Limitations of the study

The present study has some limitations, including small sample size of patients and control subjects and most of the data regarding control subjects were self-reported.

CONCLUSIONS

The present study established elevated levels of IL-17, IL-23, and IL-18 in psoriasis patients confirming the major role of these cytokines in the pathogenesis of psoriasis. Measurement of serum concentrations of 25(OH) D can be useful in patients with moderate to severe psoriasis with or without comorbidities. A direct association between 25(OH)D serum concentration and the serum concentrations of Th17 cytokines IL-17, IL-23, or IL-18 was not identified. Further large-scale clinical trials are needed to elucidate the complex interplay between vitamin D and pro-inflammatory cytokines implicated in the pathogenesis of a multifactorial disease such as psoriasis and to clarify if oral vitamin D could be a proper adjunct therapy in selected patients with psoriasis.

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