Journal of Pakistan Association of Dermatologists. 2021;**31(4)**:614-622.

Original Article

Vitamin D deficiency and associated clinical co-factors in patients with early and late-onset plaque psoriasis

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Abstract

Objective To investigate 25-hydroxyvitamin D (25-OHVD) levels; to perform a comparative analysis between early and late-onset types of plaque psoriasis; and to identify any relationship between 25-OHVD levels and type of plaque psoriasis after controlling for confounders .

Methods This cross-sectional, prospective study had 70 subjects and was conducted in the Dermatology department during September 2018 to August 2019. Demographics and disease-related features were noted down; body mass index (BMI) and Psoriasis Area and Severity Index (PASI) were calculated; and serum levels of 25-OHVD were checked.

Results Mean±SD age was 41.3±13.2 years with equal gender ratio. Family history was positive in 19 (27.1%); presence of psoriatic arthritis (PsA) in 36 (51.4%); use of oral steroids in 14 (20%); while 40 (57.1%) patients had disease for ≤5 years. 42 (60%) and 28 (40%) patients belonged to early-onset and late-onset groups respectively. 35 (50%) patients were obese and median PASI score was 4.45. Mean 25-OHVD levels were 17.1±9.1 ng/mL. Comparative analysis revealed statistically significant differences between 25-OHVD levels (P=0.03), age (P<0.001), duration of psoriasis (P=0.01), use of oral steroids (P=0.01) and family history of psoriasis (P=0.04) of the two psoriatic groups. Stratified analysis disclosed males (P=0.003) who had disease for <5 years (P=0.01) suffered from PsA (P=0.03) were more affected with VDD in early-onset group.

Conclusion VDD is more frequent among early-onset plaque psoriasis cases. Cofactors associated with VDD are early age of presentation, lesser duration of disease, use of oral steroids and positive family history. Stratified analysis detected males of early-onset with disease duration of <5 years and having PsA were more often affected with vitamin D deficiency.

Key words
Psoriasis, body mass index, psoriatic arthritis, 25-hydroxy vitamin D, Psoriasis Area and Severity Index.

Introduction

Psoriasis is a common, multisystem, inflammatory disease which affects all age groups. It predominantly involves skin and mostly have a relapsing and remitting course.[1] It affects 3.2% of the World's population.[2] Plaque psoriasis (psoriasis vulgaris) is the most frequently encountered type. Psoriasis affects adults of both genders equally.[3]

Vitamin D is an oil-soluble vitamin. It is responsible for calcium absorption, mineralization and homeostasis of skeletal system, growth and development. It has

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numerous immunological, physiological, homeostatic and metabolic functions. Vitamin D deficiency (VDD) is now recognized as a pandemic disease affecting all races, genders, age-groups, ethnicities, social classes and low to high-income countries.[4] There is considerable fluctuation in vitamin D levels with seasonal and geographical latitude change.[5,6]

The debate over relationship between VDD and psoriasis is now more than a decade long but no definite conclusion has been drawn yet. Some studies indicated a contributory role of VDD in development and/ or aggravation of psoriasis while others completely denied any association.[4]

This study aimed: to investigate 25-hydroxyvitamin D (25-OHVD) levels in plaque psoriasis patients; to perform a comparative analysis between early and late-onset types of plaque psoriasis; and to identify any relationship between 25-OHVD levels and type of plaque psoriasis after controlling for confounders.

Materials and Methods

This cross-sectional, prospective study was conducted in the Dermatology department of The Indus Hospital, Karachi, Pakistan during September 2018 to August 2019 period. 70 cases who met the selection criteria were selected consecutively after informed consent. Approval from the institutional review board (IRB) was taken prior to the study.

***Inclusion criteria*:** Clinically diagnosed patients with plaque psoriasis for more than 6 months, age ≥ 18 years, either gender, never treated with oral and/or topical vitamin D analogues or stopped their treatment at least 3 months before investigation were included.

***Exclusion criteria*:** Patients with other types of psoriasis (guttate, erythrodermic and pustular); having concomitant inflammatory bowel disease, malabsorption, chronic liver and chronic kidney diseases; infections (tuberculosis, active hepatitis, HIV & AIDS); malignancies; pregnant and lactating mothers; on vitamin D supplements; not giving consent; taking any medications which affect serum vitamin D levels (corticosteroids, bisphosphonates, multivitamin supplements, fish oil) were excluded.

After enrolment of patients; age, gender, presence of psoriatic arthritis (PsA), duration & type of plaque psoriasis, family history and use of oral steroids were noted down. Body mass index (BMI) in kg/m^2 and Psoriasis Area and Severity Index (PASI) were calculated. Serum levels of 25-hydroxyvitamin D through venous samples were checked.

Vitamin D deficiency was assessed by measuring serum levels of 25-hydroxyvitamin D and were categorized as sufficient when level is ≥30 ng/mL; insufficient when level is <30 but ≥20 ng/mL and deficient when level is < 20 ng/mL.[7] PASI was used to define severity of psoriasis accordingly: mild (PASI<7), moderate (PASI 7-12), and severe (PASI>12).[8]

Definition of obesity given by WHO Western Pacific Regional Office for Asians was used. According to this, Asians were categorized as underweight (BMI <18.5 kg/m^2), healthy (BMI=18.5–22.9 kg/m^2), overweight (BMI=23.0–24.9 kg/m^2), and obese (BMI ≥25.0 kg/m^2) respectively.[9]

The classical Henseler and Christophers' division of plaque psoriasis was used. Cases with onset before 40 years were labelled as early-onset plaque psoriasis while those with onset at or above 40 years were labeled as late-onset plaque psoriasis.[3]

Data entered and analyzed by using computer statistical package of social sciences (SPSS) version 25.0. Frequency and percentages were computed for categorical variables. Mean±SD and median (IQR) were computed for quantitative variables. Chi Square, Fisher's exact, Mann-Whitney U tests and Independent sample T-test were applied as appropriate to check out significant difference in 25-hydroxyvitamin D levels between the two psoriatic groups. p-value <0.05 was considered as statistically significant.

Results

A total of 70 patients having plaque psoriasis were enrolled in the study. Half of the patients (n=35; 50%) were males. The mean±SD for age of all patients was 41.3±13.2 years. The duration of plaque psoriasis for majority of patients in this study was ≤5 years (n=40; 57.1%) and the remaining study participants (n=30; 42.9%) had psoriasis for more than 5 years. Regarding type of plaque psoriasis; 42 (60%) patients belonged to early-onset group while 28 (40%) belonged to late-onset group. 36 (51.4%) patients had PsA while 34 (48.6%) did not have PsA. Family history of psoriasis was present in only 19 (27.1%) patients. Only 14 (20%) patients reported the use of oral steroids for psoriasis and/or PsA before presentation to dermatology OPD. In terms of body mass index (BMI); 35 (50%) patients were obese, 14 (20%) were overweight and remaining 21 (30%) were healthy or underweight **(Table 1)**.

Table 1 Demographic details of psoriasis patients.

Age (years)	
Mean ± SD	41.3±13.2
Min-Max	19-66
Gender; n (%)	
Male	35 (50%)
Female	35 (50%)
25-hydroxyvitamin D	
Mean±SD	17.1±9.1 ng/mL
Median (IQR)	15.08 (10.1-23.17) ng/mL
Deficient	47 (67.1%)
Insufficient	19 (27.1%)
Sufficient	04 (5.7%)
Psoriatic Arthritis; n (%)	
Absent	34 (48.6%)
Present	36 (51.4%)
Body Mass Index (BMI); n (%)	
≤ Normal	21 (30%)
Overweight	14 (20%)
Obese	35 (50%)
Duration of Psoriasis; n (%)	
≤ 5 Years	40 (57.1%)
> 5 Years	30 (42.9%)
Type of Psoriasis; n (%)	
Early-onset	42 (60%)
Late-onset	28 (40%)
Family History of Psoriasis; n (%)	
Negative	51 (72.9%)
Positive	19 (27.1%)
Use of Oral Steroids; n (%)	
No	56 (80.0%)
Yes	14 (20.0%)
PASI Score; n (%)	
Mild	46 (65.7%)
Moderate	09 (12.9%)
Severe	15 (21.4%)

Median (IQR) PASI score was 4.45 (0.8-43.8). Furthermore, PASI scores of 46 (65.7%), 09 (12.9%) and 15 (21.4%) patients were mild, moderate and severe respectively. The mean and median 25-OHVD levels were 17.1±9.1 ng/mL and 15 ng/mL respectively. Regarding categorization of 25-OHVD levels; 47 (67.1%), 19 (27.1%) and 04 (5.7%) patients were found to be vitamin D deficient, insufficient and sufficient respectively **(Table 1)**.

The baseline characteristics of the exposure groups i.e. early and late-onset groups of plaque psoriasis were compared using T-test and

Table 2 Comparative analysis between early and late-onset plaque psoriasis groups

Variable	*Early-onset Plaque Psoriasis*	*Late-onset Plaque Psoriasis*	*P-value*
Vitamin D (ng/mL) Median (IQR)	13.2 (8.6–22.3)	18.1 (13.3–24.6)	0.03Ŧ
Age (years)(Mean±SD)	32.8±8.4	53.9±7.6	<0.001¶
Gender; n (%)			
Male	18 (42.9%)	17 (60.7%)	0.14§
Female	24 (57.1%)	11 (39.3%)	
Body Mass Index; n (%)			
≤ Normal	14 (33.3%)	07 (25%)	
Overweight	08 (19.1%)	06 (21.4%)	0.80ł
Obese	20 (47.6%)	15 (53.6%)	
Duration of Psoriasis; n (%)			
≤ 5 Years	17 (40.5%)	23 (82.1%)	0.01§
> 5 Years	25 (59.5%)	05 (17.9%)	
Use of Oral Steroids; n (%)			
No	30 (71.4%)	26 (93%)	0.01ł
Yes	12 (28.5%)	02 (07%)	
Family History; n (%)			
Negative	27 (64.3%)	24 (85.7%)	0.04§
Positive	15 (35.7%)	04 (14.3%)	
Psoriatic Arthritis; n (%)			
Absent	19 (45.2%)	15 (53.6%)	0.49§
Present	23 (54.8%)	13 (46.4%)	
PASI Score; n (%)			
Mild	29 (69.0%)	17 (60.7%)	
Moderate	05 (11.9%)	04 (14.3%)	0.76§
Severe	08 (19.1%)	07 (25.0%)	

¶ T-test, Ŧ Mann-Whitney U test, § Chi-Square, ł Fisher Exact

Mann-Whitney U test for quantitative variables. For categorical variables; Chi-Square and Fisher Exact tests were used. Statistically significant differences were detected between the 25-OHVD levels (P-value 0.03), age (P-value <0.001), duration of psoriasis (P-value 0.01), use of oral steroids (P-value 0.01), and family history of psoriasis (P-value 0.04) of the two study groups. No statistically significant difference was observed between gender, BMI, PsA, and PASI scores of the two study groups **(Table 2)**.

Stratified analysis was performed to assess the relationship between the outcome i.e. 25-OHVD levels and the exposure variable i.e. type of plaque psoriasis after controlling for confounders. When controlled for gender; authors found that males having early-onset plaque psoriasis had lesser median (IQR) 25-OHVD levels as compared to males having late-onset plaque psoriasis (P-value 0.003). This discrimination was not found among females of two groups. Similarly, patients who had a ≤5 years duration of psoriasis in early-onset psoriasis group had a lower median (IQR) 25-OHVD level as compared to those who were in late-onset psoriasis group (P-value 0.01). Furthermore, patients in the early-onset plaque psoriasis group who also had psoriatic arthritis,

Table 3 Stratified analysis between vitamin D and types of plaque psoriasis.

Variables	*Study Groups*		*P-value*
	Early-onset Plaque Psoriasis group Median (IQR)	*Late-onset Plaque Psoriasis group Median (IQR)*	
Gender			
Male	13.2 (9.6 – 16.2)	18.2 (15.2 – 24.6)	0.003Ŧ
Female	13.4 (7.9 – 25.3)	14.4 (8.9 – 23.1)	0.66Ŧ
Age			
≤ 40	12.9 (8.4 – 18.6)	17.8 (16 – 19.8)	0.31Ŧ
> 40	24.3 (11 – 27.7)	18.1 (13.3 – 24.6)	0.56Ŧ
Body Mass Index			
≤ Normal	13 (10.1 – 15)	15.5 (13.3 – 22.4)	0.1Ŧ
Overweight	12.7 (10.1 – 21.9)	21.6 (18.2 – 24.6)	0.15Ŧ
Obese	15.8 (6.7 – 23.6)	18 (9.6 – 24.8)	0.2Ŧ
Duration of Psoriasis			
≤5 Years	11.6 (8.2 – 17.4)	18.2 (13.4 – 24.6)	0.01Ŧ
>5 Years	14.2 (10.1 – 24.3)	14.4 (13 – 24.8)	0.71Ŧ
Psoriatic Arthritis			
Absent	11.5 (6.3 – 16.4)	16 (13 – 24.6)	0.03Ŧ
Present	13.9 (10.1 – 25.3)	19.7 (15.1 – 23.1)	0.36Ŧ
PASI Score			
Mild	13.9 (7.7 – 24.2)	16 (13.4 – 24.8)	0.16Ŧ
Moderate	13.3 (13.1 – 15)	18.1 (13.4 – 27.5)	0.14Ŧ
Severe	11.3 (9.8 – 18.5)	19.78 (13.3 – 24.6)	0.22Ŧ

Ŧ Mann-Whitney U Test, PASI: Psoriasis Area and Severity Index

had a median (IQR) 25-OHVD level lesser than those patients from the late-onset plaque psoriasis group who had psoriatic arthritis (P-value 0.03). Stratification was done for age, BMI and PASI score but failed to detect any statistically significant association **(Table 3)**.

Discussion

Vitamin D is a fat-soluble vitamin, discovered in cod liver oil during first quarter of the 20th century. Later on, rickets in children and osteomalacia in adults due to vitamin D deficiency were confirmed and subsequently Adolf Windaus, a German organic chemist, received the Nobel Prize in 1928 for this breakthrough discovery.[10] Vitamin D (also known as calciferol) can be produced in the body by the help of ultraviolet B (UVB) radiation and also obtain from diet. Vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) are the two major biologically inactive precursors of vitamin D.[11] Vitamin D2 is obtained from plants, mushrooms and yeasts while vitamin D3 is found in certain animal-based foods like fatty fish, liver and fat from mammals and egg-yolks.[5,10] Vitamin D3 is also formed in the human skin from 7-dehydrocholesterol by irradiation effect of UVB. Both precursors of vitamin D are converted to 25-hydroxyvitamin D (25-OHVD) in liver and then to 1,25-dihydroxyvitamin D [1,25(OH)2VD] or calcitriol, active form of vitamin D, predominantly in proximal renal tubules.[10]

The physiological actions of vitamin D are mediated by vitamin D receptor (VDR) which is

a member of nuclear receptor super-family. VDRs are ubiquitously distributed in human body and have highest affinity for 1,25(OH)2VD. The long half-life (3 weeks) molecule 25-OHVD is commonly used to detect vitamin D status or deficiency in humans as the active form 1,25(OH)2VD is involved in homeostasis and regulatory functions, and has a very short half-life of 4 to 8 hours.[10-13]

Psoriasis is an immune-mediated disorder and involves both innate and acquired immune systems. Cutaneous T-lymphocytes, keratinocytes, histiocytes, mastocytes, dendritic cells and vascular endothelial cells play their complex roles in development of inflammation, leading to an imbalance between Th1 & Th2 immune responses with a diversion towards Th1 response. This systemic inflammatory condition on one hand, produces erythematous, scaly plaques of psoriasis over skin and scalp, while on the other side it is also responsible for development of psoriatic arthritis (PsA), cardiovascular diseases (CVD) and metabolic syndrome (MetS).[1]

Vitamin D shifts the immune balance towards a more tolerogenic status by regulating both innate and adaptive immune systems via VDRs. 1,25(OH)2VD induces modulation of dendritic cells, a major component of innate immune response, which results in reduced expression of major histocompatibility complex class II and cluster of differentiation (CD) molecules like CD40, CD54, CD80, and CD86 by these cells. 1,25(OH)2VD also inhibits interleukins (IL) 6, IL 12 and IL 23 production from dendritic cells which are the main inducer of inflammation in psoriasis, and promotes IL 10 production via B lymphocytes to promote immunoregulation.[10,14]

1,25(OH)2VD exerts its anti-inflammatory effects over macrophages through several ways. One is inhibition of cyclo-oxygenase-2 expression by targeting thioesterase superfamily member 4 gene which is responsible for production of pro-inflammatory cytokines.[15] Second is by downregulation of pro-inflammatory molecules (IL 1β, IL 6, tumour necrosis factor α and nuclear factor kappa-B ligand) and upregulation of anti-inflammatory marker (IL 10) and cascade (mitogen-activated protein kinase phosphatase-1 pathway). Third is upregulation of potent anti-oxidative mechanisms to reduce generation of free radical oxygen species.[10,11,16,17]

T lymphocytes and T helper (Th) lymphocyte pathways are influenced by 1,25(OH)2VD via both direct and indirect methods. Indirectly by downregulation of inflammatory molecules from antigen presenting cells (i.e. dendritic cells, monocytes, macrophages), followed by decline in proliferation and subsequent apoptosis of reactive T lymphocytes. Directly by blocking generation of cytokines of Th1 (IL 2, interferon-γ), Th17 (IL 17, IL 21), and Th9 (IL 9) pathways; facilitation for formation of Th2 cytokines (IL 4, IL 5, IL 10); and surge in regulatory T cells. All above changes can convert a pro-inflammatory Th1 and/or Th17 immune response to a pro-tolerogenic Th2 phenotype. This is required in psoriasis to control the inflammation.[18,19]

In this study; mean age of patients was 41.3±13.2 years. Similar ages were also reported by Maleki *et al*. from Iran (42.8±13.68 years), Chandrashekar *et al*. (44.6±12 years) and Srirama from India (47.8±12.8 years), and Orgaz-Molina *et al*. from Spain (44.33±8.71 years).[20-23]

Mean 25-OHVD level was 17.1±9.1 ng/mL in this study. Abdalla *et al*. (19.5±10 ng/mL), Pavlov *et al*. (12.07 ng/mL), Srirama

(18.24±4.55 ng/mL) and Chandrashekar *et al*. (13.3±6.9 ng/mL) mentioned analogous results in their studies.[21,22,24,25]

This study reported that 25-OHVD level of early-onset plaque psoriasis group is lower than late-onset plaque psoriasis group and it was statistically associated with age, duration of psoriasis, use of oral steroids and family history of psoriasis, while it was not correlated with gender, BMI, presence of PsA and PASI score. Pavlov *et al*. described no differences in 25-OHVD levels between two groups of plaque psoriasis, neither any correlation when above-mentioned confounders were compared.[25]

In early-onset plaque psoriasis group; males with ≤5 years disease duration and associated with PsA were more affected with vitamin D deficiency in this study. Abdallah *et al*. denied any relationship of gender and duration of disease with vitamin D levels.[24] Srirama highlighted no association of vitamin D deficiency/insufficiency with age, gender, BMI and PASI score.[22] On the contrary; Zuchi *et al*. reported lower levels of 25-OHVD in psoriatic women as compared to men in their study.[26] Orgaz-Molina *et al*. and Ricceri *et al*. evaluated identical variables but gender related differences were not identified in their studies.[23,27] Possible reasons for differences between this study and above-mentioned studies could be due to racial, geographical, ethnical and disease-related differences between Pakistani population and the Western World.

Conclusion

This study concluded that VDD is common among plaque psoriasis patients. It is more frequent among early-onset cases. Cofactors associated with VDD are early age of presentation, lesser duration of disease, use of oral steroids and positive family history. Stratified analysis detected males of early-onset with disease duration of ≤5 years and having psoriatic arthritis were more often affected with vitamin D deficiency.

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