Serum 25-hydroxy vitamin D levels in patients with *acne vulgaris* and its association with disease severity

Parviz Toossi[1]
Zahra Azizian[2]
Hassan Yavari[3]
Tannaz Hoseinzade Fakhim[4]
Seyed Hadi Sadat Amini[5]
Ramin Enamzade[5]

[1] Professor of dermatology, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2] Resident of Dermatology, Rasoul-e-akram Hospital, Iran University of Medical Sciences, Tehran, Iran
[3] Young Researchers Club, Tehran Medical Branch, Islamic Azad University, Tehran, Iran
[4] Dermatologist, Iran University of Medical Sciences, Tehran, Iran
[5] Dermatologist, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Address for correspondence:
Ramin Enamzade
Shahid Beheshti University of Medical Sciences
Tehran, Iran
E-mail: Raminenamzadeh@yahoo.com

Summary

***Background*. Since vitamin D is a recent known immunoregulatory factor in some diseases which are addressed in immune system disorders such as SLE, [psoriasis] and others.**
***Objective*. To determine the serum levels of 25-hydroxy vitamin D3 [25(OH)D] in patients with *acne vulgaris* and its association with clinical features.**
***Methods*. This cross-sectional study was conducted over months. This study included 39 patients with *acne vulgaris* and 40 healthy controls. Subjects who did not use alcohol, vitamin D supplements, oral steroids or PUVA and/or NBUVB for more than three months were included. Serum 25(OH)D levels were measured. Baseline demographics, family history and comorbidities like PCO were recorded. Statistical analyses were performed using SPSS 16.0.0.**
***Results*. The median concentration of 25(OH)D was 8.4 ng/mL (range: 1.4-99) in patients and 10.4 ng/mL (range: 3.1-56.7) in controls, with no statistical significant difference. PCOS was a significant predictor of the occurrence of acne vulgaris (OR=6.25; 95% CI: 1.52-25.66; p=0.01). There were no significant associations between severity of disease and serum 25(OH)D levels (r_s=-0.12, p=0.45), age (r_s=-0.28, p=0.09), BMI (r_s=-0.12, p=0.46), age at onset of disease (r_s=-0.08, p=0.63) and duration of disease (r_s=-0.10, p=0.54).**
***Conclusion*. Based on the previous studies this is highly suspected that vitamin D would be a prominent factor in acne patients and more performances with bigger sample size could be useful to get positive results.**

KEY WORDS: acne vulgaris; serum 25(OH) vitamin D.

Introduction

Acne vulgaris is a well-known chronic involvement of sebaceous follicles which commonly targets individuals' face, chest and back. The disease is usually triggered in adolescents among whom sebum production is rising as a result of androgenic changes in serum sexual hormones. Otherwise, children would be also affected. Furthermore, this has not been very rare that some cases with *acne vulgaris* suffered from the disease for the rest of their lives (1, 2). An extreme proliferation of *Propionibacter acnes* sounds to be the main predisposing factor in *acne vulgaris*. This gram positive anaerobic bacterium settles in skin follicles which are usually bulged and ruptured due to bacterial proliferation to distribute local inflammation followed by papules and pustules creation (3-7). Acne vulgaris is not (indeed) terminated at the above condition and there are several consequences such as erythema, post-inflammatory hyperpigmentation (PIH) and scars. Serious aftermaths would be named as fulminant acne, *acnea conglobuta*, septic hydradenitis, *acne excoriee* and *acne mecanica* (1, 2). Each of the mentioned outcomes could make challenges for patients to draw them to health providers and physicians as well. Acne vulgaris and relevant consequences are that much common that nearly all the adult people experience it at least once during their whole lives through them 15-20% get [moderate-to-severe] types of the disease. The disease occurred even as frequent as 85% in the second decade of life (8, 9). Genders seem to be out of importance in catching the condition although men show more severe while women get more permanent types (10). Many conditions direct the disease to rise such as exposure to industrial halogenated hydrocarbons, hair styling conditioners, medications like lithium, isoniazid, phenytoin, corticosteroids, anabolic steroids, oral contraceptives as well as iodized antitussives and physical skin effects of sport equipment. There are also some medical conditions which predispose *acne vulgaris* like polycystic ovaries (PCO) and congenital adrenal hyperplasia which need to be evaluated in recurrent referrals. Apart from the named consequences, depression and eating complaints are the most prominent problems (11-13) which expose patients at the risk of mental and dietary factors of severe and resistant disease. Concerning dietary factors, studies have been conducted to show the role of zinc in treatment of drug-resistant cases of depression (14, 15). Also these kinds of performances have done for vitamin D and its effects on *acne vulgaris* (16-18). Vitamin D, as an antioxidant agent, would have positive impression on the disease (19, 20). It seems that vitamin D makes superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) which were found at lower levels in papulo-pustu-

lar cases of *acne vulgaris* by some Authors (21). Other dietary factors like dairy productions have been raised by investigators in terms of the occurrence of *acne vulgaris*. Proacneic potentials of milk have been focused as a factor to increase serum level of insulin-like growth factor in the mechanism of the disease onset (22). Otherwise, antimicrobial role of vitamin D is the other issue to be raised since ancient era by many authorities and social cultures (23) and focused now as a treatment hint in *acne vulgaris*. Not only *acne vulgaris*, but also psoriasis, rosacea, vitiligo and similar skin disorders have been linked to vitamin D and its determinant impress by several researches (24-33).

This study headed to compare serum levels of 25 (OH) vitamin D between cases of *acne vulgaris* and age- and sex-matched control group to find any relationship between the vitamin and the occurrence of the disease besides comparing the two groups in terms of vitamin D deficiency conditions.

The aim of the present study is to compare the serum level of 25-hydroxy vitamin D in patients with *acne vulgaris* and healthy controls and to assess the association between disease severity and vitamin D deficiency.

Materials and methods

Setting

This cross-sectional study aimed to compare serum concentrations of 25(OH)D, as an index for serum vitamin D content, between patients with *acne vulgaris* on one hand, and healthy (individuals) on the other hand. Participants were referrals to two university hospitals which were well-known centers of dermatology in shohada-e-tajrish and Rasoul-e-Akram hospital Tehran, Iran in 2014.

Patients and controls

Patients with *acne vulgaris* who referred to dermatology departments and clinics at Rasoul-e-Akram and Shohada-e-Tajrish Hospitals, two referral centers of dermatology in Tehran were included in the study.

Case group contained all patients over 18 years of age with *acne vulgaris* regarding dermatologist physical examination. A pilot study was done before the main performance to estimate suitable sample size to achieve 80% research study power and 30 individuals were identified in each group to be enough. Control group included 30 patients or healthy people who did not experience *acne vulgaris* considering their medical history and present illness. Participants were excluded if used alcohol, vitamin D supplements, oral steroids or PUVA and/or NBUVB in recent three months.

Specimen collection

All the participants gave blood samples after answering a Data collection form for demographics, past medical history, family history, and other relevant variables. From all participants 5 ml peripheral venous blood was drawn to be immediately centrifuged before freezing at -80°C.

Laboratory study

Vitamin D was detected in the form "25 (OH) vitamin D" through LIASON chemiluminescent Immunoassay manufactured and provided.

Date Gathering

A data collection form was designed to cover demographics, patients' complaints, severity of *acne vulgaris* by Global Acne Grading System (GAGS), family history, past medical and medication history, treatment seeking history for *acne* and relevant actions, serum vitamin D profile, daily sun exposure rate and vitamin D supplement use. Global Acne Grading System (GAGS) was utilized to score disease severity by the research dermatologist who visited the patients.

Statistics

All data analyses were performed using the statistical software SPSS 16.0.0. (SPSS Inc. Chicago, IL, U.S.A.). Two-sided P-values less than 0.05 were considered statistically significant.

Continuous variables are summarized as mean±SD or as medians with total and interquartile ranges (25^{th}-75^{th} percentiles). Categorical variables were expressed as number (percentage). The Shapiro-Wilk's W-test was applied for checking the normality assumption of continuous variables. Chi-square test and Fisher's exact test, wherever appropriate, were used for data analysis. Independent two-sample t-tests or Mann-Whitney-U tests were applied to compare the continuous variables between the two groups. Kruskal Wallis test was used for comparing the median serum 25 (OH) D levels among the three categories of acne severity. The correlation between acne severity (GAGS score) and other parameters were assessed with Spearman's correlation test. Binary logistic regression models were used to examine the associations between occurrence of *acne vulgaris* and other parameters.

Ethics

All the participants including cases and controls gave their written informed consents after being informed about the aims and process of the study as well as applicable objectives. The principal investigators have kept individual data as private information safely. There was no extra fee to be paid by the participants and the investigators covered all the costs in this regard.

Results

This study included 39 patients with *acne vulgaris* (28 females and 11 males) and 40 healthy controls (28 females and 12 males). Baseline demographics and clinical characteristics of the participants are presented in Table 1. Patients with acne were younger than healthy controls (Table 1). PCO was more frequent in female patients with acne in comparison with healthy female individuals with statistical significant difference between the two groups (Table 1). Eleven patients with acne (28.2%) and four healthy subjects (10%) were exposed to sunlight longer than two hours per day in average (Table 1). In this study, the two groups did not differ significantly in gender, BMI, positive family history of acne and presence of hirsutism (Table 1).

Serum levels of 25 (OH) D

The two groups did not differ significantly in median serum concentrations of 25 (OH) D (P value=0.14, Table 2). Thirty-five patients with acne (89.7%) and 36 healthy subjects (90%) had hypovitaminosis D (<30 ng/mL), with no significant difference between the two groups (P value=0.97, Table 2). According to the subgroup analysis stratified by sun-exposure time, no significant differences were observed in

Table 1 - Baseline demographics and clinical characteristics of patients with *acne vulgaris* and healthy controls.

Characteristic	Patients with *acne vulgaris* (n=39)	Healthy controls (n=40)	P-value
Gender			0.86
Female	28 (71.8%)	28 (70.0%)	
Male	11 (28.2%)	12 (30.0%)	
Age, years			0.04
MeanSD	24.23±6.45	27.18±5.87	
Median (range)	23 (12-42)	28 (16-42)	
BMI			0.27
MeanSD	22.58±3.57	23.56±4.07	
Sun-exposure time > 2 hours per day	11 (28.2%)	4 (10.0%)	0.04
Positive family history of acne	26 (66.7%)	26 (65.0%)	0.88
Hirsutism[#]	13 (46.4%)	8 (28.6%)	0.17
PCOS[#]	12 (42.9%)	3 (10.7%)	0.01
Age at onset of disease, years			
Median (range); IQR	17 (10-29); (15-19)	-	
Duration of disease, years			
Median (range); IQR	5 (1-25); (2-10)	-	
Site of acne		-	
Face	19 (48.7%)		
Trunk	-		
Both	20 (51.3%)		
Active acne	39 (100%)	-	
GAGS		-	
MeanSD	24.92±10.57	-	
GAGS categories*		-	
Mild	12 (30.8%)		
Moderate	17 (43.6%)		
Severe	5 (12.8%)		
Very severe	5 (12.8%)		

Values are no. (%) unless otherwise noted.
Abbreviations: BMI, Body Mass Index (calculated as weight in kilograms divided by height in meters squared); IQR, Interquartile range (25^{th} -75^{th} percentiles); PCOS, Polycystic ovary syndrome; GAGS: Global Acne Grading System.
[#] the proportions were calculated in the group of females; * A GAGS score of 1-18 is considered mild; 19-30, moderate; 31-38, severe; and >39, very severe.

serum 25 (OH) D of the two groups in both conditions (Table 2). Furthermore, there were no significant differences in median serum concentrations of 25 (OH) D among patients with mild, moderate and severe/very severe acne (P value=0.29, Table 2).

Factors associated with acne vulgaris

According to the results of binary logistic regression analysis, PCO was a significant predictor of the occurrence of *acne vulgaris* (OR=6.25; 95% CI: 1.52-25.66; P=0.01). The occurrence of *acne vulgaris* was not significantly associated with severe vitamin D deficiency (<10 ng/mL) (OR=1.6; 95% CI: 0.65-3.91; p=0.30), BMI (OR=0.93; 95% CI: 0.83-1.05; p=0.27), hirsutism (OR=2.17; 95% CI: 0.72-6.55; p=0.17) and positive family history of acne (OR=1.08; 95% CI: 0.42-2.73; p=0.88).

Correlation between disease Severity (GAGS) and evaluated parameters

The mean GAGS score was significantly higher in female patients with PCO compared to the patients without PCO (28.58±8.21 *vs* 21.06±8.79, p=0.03, respectively). However, there were no significant associations between severity of disease and serum 25 (OH) D levels (r_s=-0.12, p=0.45), age (r_s=-0.28, p=0.09), BMI (r_s=-0.12, p=0.46), age at onset of disease (r_s=-0.08, p=0.63) and duration of disease (r_s=-0.10, p=0.54). Furthermore, no significant difference was found in mean GAGS score of patients who had exposed to sunlight less than two hours per day and patients with sun-exposure time longer than two hours per day (23.82±9.77 *vs* 27.73±12.39, p=0.36, respectively). The mean GAGS score did not differ significantly between the female patients with

Table 2 - Serum concentrations of 25-hydroxyvitamin D [25 (OH) D].

25 (OH) D	Patients with *acne vulgaris* (n=39)	Healthy controls (n=40)	P-value
25 (OH) D, ng/mL	8.4 (1.4-99); (5-14.1)	10.4 (3.1-56.7); (6.58-20.25)	0.14
25 (OH) D categories[#], no. (%)			
Severe vitamin D deficiency	24 (61.5%)	20 (50.0%)	
Moderate vitamin D deficiency	9 (23.1%)	10 (25%)	
Vitamin D insufficiency	2 (5.1%)	6 (15%)	
Vitamin D sufficiency	4 (10.3%)	4 (10%)	
Sun-exposure time			
< 2 hours per day	8.25 (1.4-99); (4.05-14.62)	10.4 (3.1-56.7); (6.58-20.08)	
≥ 2 hours per day	8.5 (3.3-22.2); (7.7-14.1)	13.5 (5.5-21); (6-20.62)	
GAGS[*]		-	
Mild (n=12)	8.45 (1.7-34.6); (3.08-16.35)		
Moderate (n=17)	8.6 (1.4-99); (7.2-21.3)		
Severe/very severe(n=10)	7.05 (3.3-12.8); (3.7-10.3)		

Values are median (range); IQR of serum 25-hydroxyvitamin D, unless otherwise stated.

Abbreviations: IQR, Interquartile range (25^{th} -75^{th} percentiles); GAGS: Global Acne Grading System

[#] Subjects were divided into four categories: Severe vitamin D deficiency [25(OH)D <10 ng/ml], moderate vitamin D deficiency [25(OH)D 10 to <20 ng/ml], vitamin D insufficiency [25(OH)D 20 to <30 ng/ml] and vitamin D sufficiency [25(OH)D≥30 ng/ml]

* A GAGS score of 1-18 is considered mild; 19-30, moderate; 31-38, severe; and >39, very severe

and without hirsutism (22.23±9.67 *vs* 26.07±8.71, p=0.28, respectively) and between patients with and without family history of acne (24.96±10.59 *vs* 24.85±10.92, p=0.97, respectively).

Discussion

The current study was the first, to our knowledge, in the evaluation of serum concentration of "25(OH) vitamin D" in patients with *acne vulgaris* which compared cases and controls in this regard. There was no significant association between the occurrence of *acne vulgaris* and serum 25(OH) vitamin D level. Likely, no difference was found between the disease and sunlight exposure among the patients, although the event occurred as high as three times more when compared with controls. The mechanism of vitamin D functions in some medical conditions has been focused by several researches. Youssef et al. as well as other investigators explained an antibiotic effect for vitamin D and its derivatives which help infection prevention too (23, 34). This could show extended impression on a wide microbial spectrum via strengthening innate and acquired immunity in serum and skin. Vitamin D is also known by some authorities as a preventive factor against cancers (35, 36) and skin inflammatory diseases like psoriasis, ictiosis, etc. in addition to mediating the beneficial dermatologic effects of light (37).

Not only infections, cancers, *acne* and inflammatory conditions, but also some regular problems like *rosacea* would be under controlled by vitamin D and its derivatives. Ekiz et al. in 2014 indicated higher rate of vitamin D serum level among rosacea patients comparing with healthy subjects (38).

In terms of therapeutic potentials of vitamin D and its products, comedolytic effects of the vitamin was introduced by Ekiz in 2014 (18). *Propionibacter acnes* is known as the main microorganism in *acne vulgaris* and studies have shown that the bacterium stimulated genes which were linked to expression of some immunologic factors and cytokines, especially in human T lymphocytes in order to block vitamin A and vitamin D. This is the main provider of suitable environment for more microbial proliferation on the skin level in *acne vulgaris* (39, 40).

The current work failed to find correlations between history of PCO and hirsutism and also family history of *acne vulgaris* on one hand and the disease, on the other. Unlikely, current PCO involvement was significantly more frequent among patients. Coincidence of PCO and *acne vulgaris* is not a new issue in this matter. Orio et al. found PCO syndrome and nonfunctional adenoma in addition to severe hirsutism in a young woman with acne (41). This would be a hint to address complementary endocrine studies on individuals with hirsutism, virilism and unusual early onset of *acne vulgaris*, especially in their twenties.

Among the evaluated parameters through the current study, PCO was the only parameter which had a significant association with *acne vulgaris*. Serum "25(OH) vitamin D" was not significantly associated with the occurrence of *acne vulgaris*. This would be partially explained by recall bias which reminds the fact that people usually forget previous involvement in such a disease as a common complaint. Furthermore, low serum vitamin D contents among Iranians would be a general problem which rationally bothers the above cor-

relation because cases and controls in the mentioned population face hypovitaminose D. This factor limited us to conclude that vitamin D was lower in cases when compared with controls.

Comprehensive studies with more participants can probably make vitamin D differences more obvious between the two groups and finally get a correlation in this regard.

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