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## Serum Vitamin D3 Level in Patients with Female Pattern Hair Loss

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### Abstract

#### Background:

Female pattern hair loss (FPHL) is the most common cause of alopecia in women, characterized by diffuse nonscarring hair loss in frontal, central, and parietal areas of the scalp. Pathophysiology of FPHL is still not well known, and it is probably a multifactorial genetic trait. FPHL is also observed in women without increased androgen levels, which raises the likelihood of androgen-independent mechanisms and explains the lack of response to antiandrogen treatments in some patients. Vitamin D is a factor that has recently been considered in dealing with these patients. The purpose of this study was to evaluate the serum levels of Vitamin D in patients with FPHL and compare it with healthy controls.

#### Methods:

In this case-control study, 45 women with FPHL were evaluated as well as the same number of healthy women matched for age, hours spent under sunlight per day, and body mass index. Serum 25(OH) D3 level was measured using ELISA.

#### Results:

60% of FPHL patients were in 15–30 years old age group with the mean standard deviation (SD) age of 29.11 (7.30) years. In the majority of patients (66.7%), severity of hair loss was Ludwig I. Mean (SD) serum Vitamin D3 level in patient and control group was 13.45 (8.40) and 17.16 (8.96), respectively. *T*-test showed a significant difference between the two groups in terms of Vitamin D3 serum levels ( $P = 0.04$ ).

#### Conclusions:

This study indicated the correlation between the incidence of FPHL and decreased serum levels of Vitamin D3. It is recommended to evaluate serum Vitamin D3 levels as well as other hormone assays in these patients.

**Keywords:** ELISA, female pattern hair loss, Vitamin D3

## INTRODUCTION

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Female pattern hair loss (FPHL) is one of the most common complaints among female patients referred to dermatology clinics. It is the most common cause of alopecia involving 6–12% of women aged 20–30 years and over 55% of women over 70 years of age. FPHL is clinically characterized by diffuse nonscarring hair loss without obvious hair thinning in frontal, central, and parietal lobes of the scalp. The frontal hairline is characteristically maintained. A similar pattern is observed in men with miniaturized follicles and is known as androgenic alopecia. FPHL designation is preferred in women over androgenic alopecia since the role of androgens in women is not still clear.[1]

FPHL pathophysiology is not well understood yet, and it is likely to be a multifactorial genetic trait. Androgen-independent mechanisms may contribute to this phenotype in addition to androgen-dependent ones.[2] FPHL is also seen in women without elevated androgen levels, raising the likelihood of interference of androgen-dependent mechanisms, and explaining the lack of response to treatment with androgen inhibitors in some FPHL patients.[3,4]

Serum levels of Vitamin D are a factor recently considered in approaching patients with hair loss complaint. In a recent study, it has been suggested to measure Vitamin D level in patients complaining from hair loss in addition to tests such as complete blood count (CBC), thyroid stimulating hormone, ferritin, testosterone, and dehydroepiandrosterone sulfate.[5]

The function of Vitamin D3 receptor is critical in a population of keratinocyte stem cells remaining in the bulge region of hair follicles. Defective Vitamin D function leads to defective stem cell renewal and loss of hair follicle cycle.[6]

It has been suggested that an optimum concentration of Vitamin D3 is essential to delay aging and hair loss, and a possible link has been proposed between the lack of Vitamin D in serum and FPHL.[7]

To confirm this hypothesis, a study was conducted in Egypt in 2013 by Rasheed *et al.* to investigate the role of Vitamin D in women with chronic telogen effluvium or FPHL. Serum level of Vitamin D was considerably lower in women with chronic telogen effluvium as well as women with FPHL relative to the control group ( $P < 0.001$ ). Serum level of Vitamin D was further reduced with increasing severity of alopecia, and measurement of Vitamin D was concluded to be essential in women with hair loss complaint. Prescription of Vitamin D may be useful to grow hair in case of its deficiency.[8] In contrast, in a 2008 study in New Zealand, on 296 men with male pattern alopecia, no correlation was found between the extent and severity of alopecia with serum Vitamin D3 level.[9] In the study by Vegesna *et al.*, therapeutic effect of 1, 25-dihydroxyvitamin Vitamin D3 and its analogs in stimulating hair growth was investigated in mice with congenital alopecia due to inborn lack of Vitamin D receptor (VDR), and histological evidence indicated the presence of hair follicles in the skin biopsies of mice after treatment.[10]

Based on the above evidence, Vitamin D3 deficiency is likely to be involved in the pathogenesis of FPHL. Therefore, we set out to evaluate the serum levels of Vitamin D3 in women with FPHL to investigate this hypothesis.

## METHODS

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In this case–control study, 45 women admitted to the Dermatology Clinics of MUMS Quaem and Imam Reza hospitals with clinical (and if necessary pathologic) diagnosis of FPHL and the same number of healthy individuals without hair loss or family history of hair loss matched in terms of age, hours spent under sunlight during the day, and body mass index (BMI) were enrolled. All patients selected from Northeast of the country were evaluated in autumn to avoid the impact of seasonal variation on Vitamin D levels.

Disease severity in patients was recorded using Ludwig classification by a questionnaire developed for this purpose (Grade I or mild, Grade II or moderate, and Grade III or severe). Other data such as age, family history, simultaneous presence of menstrual disorder, hirsutism, BMI, disease duration, the average time spent outdoor (per hour) were also recorded.

Five milliliters blood was drawn from each patient from the brachial vein. Serum level of 25(OH) Vitamin D3 was measured in the laboratory by ELISA using Vitamin D kit (Biosource, USA). The following criteria were used to interpret Vitamin D level in patients: <20 (Deficient), 20–30 (Insufficient), and over 30 (Sufficient).

Inclusion criteria were the clinical diagnosis or histologic FPHL in specific cases, 15–65 years of age, and residence in the Northeast of Iran. Exclusion criteria included topical treatment with Vitamin D3 compounds or systemic therapy (phototherapy) within the past month, use of Vitamin D3 supplements, and other chronic inflammatory diseases such as multiple sclerosis, inflammatory bowel diseases, rheumatoid arthritis, insulin-dependent diabetes mellitus, systemic lupus erythematosus, lymphoma, nonmelanoma skin cancer, or any history of cancer.

Description of data was done using mean, standard deviation (SD), and frequency distribution. Data analysis was performed using Chi-square, *t*-tests, ANOVA, and the linear regression analysis was used to control of confounding factors. In all tests, the significance level was considered  $<0.05$ . The Statistical Package for the Social Sciences 11.5 (SPSS Inc., Chicago, IL) was used for data analysis.

## RESULTS

The average age in patient and control group was  $29.11 \pm 7.31$  and  $28.82 \pm 7.11$  years, respectively. There were no significant differences between the age of two groups ( $P = 0.85$ ). The median duration of disease was 2 years with an interquartile range of 1–5 years.

In an analysis of patient group, 4 patients (8.9%) had BMI 0–18, 27 patients (60%) had BMI 18.1–25, and 14 patients (31.1%) had BMI  $>25.1$ . In control group, 5 patients (11.1%) had BMI 0–18, 32 patients (71.1%) had BMI 18.1–25, and 8 patients (17.8%) had BMI  $>25.1$ . Chi-square test showed no significant difference in BMI between the two groups ( $P = 0.33$ ). According to Ludwig classification, 28 patients (66.7%) were in mild group, 12 (28.6%) were in moderate group, and 2 patients (4.8%) were in severe group [Table 1].

Mean BMI in patient and control group was  $22.94 \pm 3.27$  and  $22.78 \pm 3.07$ , respectively with no significant difference ( $P = 0.69$ ).

Mean (SD) serum Vitamin D3 level in patient and control group was 13.45 (8.40) and 17.16 (8.96), respectively. *T*-test showed a significant difference between the two groups in terms of serum Vitamin D3 levels ( $P = 0.04$ ).

Moreover, after classification of Vitamin D level into three categories ([0–19.9], [20–29.9], and [30–150]), the evaluation of frequency distribution of Vitamin D levels showed that 36 patients (80%) had Vitamin D 0–19.9, 5 patients (11.1%) had Vitamin D 20–20.9, and 4 (8.9%) had Vitamin D 30–150. In control group, 32 patients (71.1%) had Vitamin D 0–19.9, 6 (13.3%) had Vitamin D 20–20.9, and 7 (15.6%) had Vitamin D (30–150). Pearson Chi-square test showed no significant difference between the three categories of Vitamin D in both groups ( $P = 0.56$ ).

The relationship between serum levels of Vitamin D in FPHL patients with participant characters has been shown in Table 2. There was no significant correlation between serum levels of Vitamin D3 and age ( $r = 0.08$ ,  $P = 0.61$ ), BMI ( $r = -0.06$ ,  $P = 0.69$ ), and FPHL duration ( $r = 0.04$ ,  $P = 0.77$ ). Furthermore, there was no significant relation between serum Vitamin D3 level and family history of FPHL, menstrual disorder, hirsutism, Ludwig score of alopecia severity, and skin type of the patients.

## DISCUSSION

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FPHL is one of the most common causes of alopecia in women. Diffuse reduction in density of the scalp hair is associated with thinning of hair with complete or nearly complete maintenance of frontal hairline. Bitemporal hair recession is observed in 13% and 37% of women before and after menopause, respectively. [11] Follicles are not lost but hair is miniaturized, and the space between hairs is increased so that the head skin is revealed over time. [12] FPHL pathophysiology is still not well known, and it is probably a genetically multifactorial trait. Androgen-dependent mechanisms, as well as androgen-independent mechanisms, may contribute to this phenotype. [2] Estrogen and androgens are the main hormones that regulate the development of FPHL. [1] In addition to sex hormones, FPHL can be associated with insulin resistance, microvascular, and inflammatory disorders. Insulin resistance reduces sex hormone-binding globulin in circulation that leads to early-onset androgenetic alopecia in men. [1] Miniaturization of hair follicles together with diffuse hair loss in frontal lobe can be seen in women without increased levels of androgens, which justifies the lack of response to androgen inhibitors in some women with FPHL. [3,4] On the other hand, FPHL cases in patients with complete androgen insensitivity syndromes support the involvement of other factors in FPHL pathogenesis. [1] Serum level of Vitamin D is one of the factors recently considered in approach to patients with complaints of hair loss [7,13] so that a recent study recommended the measurement of serum Vitamin D level as well as androgen, thyroid hormone assay, and CBC. [5]

So far, except for a single study, the relationship between FPHL and Vitamin D3 deficiency has not been established. In the study of Rasheed *et al.* in 2013 in Egypt, serum Vitamin D3 level in FPHL was significantly lower than the control group. According to this study, low level of Vitamin D3 is associated with hair loss in women with FPHL. A screening test is useful to measure Vitamin D3 level in women referring with hair loss, and dietary supplements can be useful to treat these patients. [8]

In the present study, mean level of Vitamin D3 in patients with FPHL was lower than healthy controls ( $P = 0.04$ ). However, there was no significant difference between the three categories of Vitamin D (deficient, insufficient, and sufficient) in both groups ( $P = 0.56$ ) and this could be due to the high prevalence of Vitamin D deficiency in Iran.

In a study of 296 men with male pattern alopecia, no relationship was found between the extent and severity of alopecia with serum levels of Vitamin D3. [9] In another study on men with androgenic alopecia in 2012, no difference was found between Vitamin D level in patients and the control group. [14] Considering these two studies and the lack of difference between Vitamin D levels and androgenic alopecia in men, it seems that unlike men, Vitamin D deficiency is involved in the development of androgenic alopecia or FPHL through androgen-independent mechanisms.

Alopecia in some families with Vitamin D-dependent rickets raises the likely important role of VDR in hair biology. [15] VDR gene is a negative regulator of a number of genes and reduced suppressor activity of this gene by unliganded VDR leads to derepression of these genes, which may eventually lead to alopecia in these patients. [15]

Histological evidence of hair follicles after treatment with Vitamin D3 analogs in the skin biopsies of beigo/nude/xid mice afflicted with congenital alopecia due to inborn lack of VDR emphasizes the role of VDR in alopecia. Treatment with Vitamin D analogs was associated with natural hair follicle formation and increased the expression of specific Ha7, Ha8, and Hb3 keratins. [10] A certain concentration of Vitamin D is essential to delay aging and hair loss. [7] *In vitro* studies showed that VDR plays a vital role in preserving the hair follicles after birth. Mesodermal papillary cells and keratinocytes of outer root sheath epidermis express varying levels of VDR based on the stage of the hair cycle. In terminal anagen and catagen stages, VDR is increased and is associated with decreased proliferation and increased differentiation of keratinocytes. These changes seem to stimulate the growth of hair cycle. [7,13]

Extensive studies on animal models show that VDR plays an important role in the cycle of the hair follicle, especially in the anagen phase. It has recently been shown that 1.25(OH)<sub>2</sub> Vitamin D, VDR, and β-catein stimulate the differentiation of hair follicle.[16]

Environmental factors such as longitude, season, weather conditions (e.g., cloudy) and air pollution affect Vitamin D3 level in serum.[13] In this study, we attempted to minimize the role of environmental factors by choosing the patients from a specific region in the country (Northeast) during one season (autumn). Individual variables are the factors affecting serum levels of Vitamin D3, including age, weight, skin type, and exposure to the sun.[13] Since the two groups were matched in terms of age, BMI, skin type and exposure to the sun, the impact of these confounding factors on our results was negligible.

In this study, among 45 patients, 60% were in the age group 15–30 years, 37.77% in 31–40 years age group, 0% in 41–50 and 2.22% in the age group over 50 years with a mean age of  $29.11 \pm 7.30$  years. In the study of Sarda *et al.* in 2015 on FPHL patients, 68% were in the age group 18–30 years, 14% in 31–40 years age group, 8% in 41–50 years age group, and 10% in the age group over 50 years.[4] The mean age of FPHL patients in the studies of Sarda *et al.*, Zhang *et al.*, and Deloche *et al.* was  $29.22 \pm 13.01$ ,  $34.4 \pm 10.6$ , and  $34.9 \pm 11.1$  years, respectively.[4,17]

The severity of hair loss was Ludwig I in the majority of our patients (66.7%), which was similar to the study of Sarda (66%).[4] 27.3% of our patients had a family history of FPHL, which was 38% in the study of Sarda.[4] In the study of Zhang *et al.* and Aktan *et al.*, Ludwig I pattern was the most common in FPHL patients.[17,18]

## CONCLUSIONS

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According to this study, the risk of FPHL was associated with decreased serum levels of Vitamin D3, and it is recommended to evaluate serum D3 level along with other hormone assays to check the patient's status. It is also suggested to evaluate the therapeutic effects of oral Vitamin D3 supplements and topical compounds such as calcipotriol in the treatment of FPHL. The limitation of this study was lack of a standard to assess diet in patients to match the control and patient groups in terms of the level of dietary D3 intake.

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## Conflicts of interest

There are no conflicts of interest.

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## Figures and Tables

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### Table 1

Participant characteristics	<i>n</i> (%)		<i>P</i>
	Case	Control	
Subject to sunlight (h)			
<2	40 (49.4)	41 (50.6)	Fischer's exact test <i>P</i> =0.63
≥2	4 (50.00)	4 (50.00)	
Body mass index			
0–18	4 (8.9)	5 (11.1)	Chi-square test <i>P</i> =0.33
18.1–25	27 (60.00)	32 (71.1)	
>25.1	14 (31.1)	8 (17.8)	
Ludwig classification			
Mild	28 (66.7)		
Mod	12 (28.6)		
Severe	2 (4.8)		
Skin type			
2	10 (22.2)		
3	30 (66.7)		
4	5 (11.1)		
Positive family history	12 (27.3)		
Have men's disorder	13 (27.3)		
Have hirsutism	6 (13.3)		

Participant characteristics factor in case and control groups

## Table 2

Serum Vitamin D level	Mean±SD	P
Exposure (h)		
<2	13.07±8.15	0.71*
≥2	14.7±11.69	
Family history		
Yes	15.05±9.98	0.39*
No	12.58±7.81	
Men's disorder		
Yes	13.91±8.43	0.83*
No	13.28±8.66	
Hirsutism		
Yes	10.93±12.53	0.43*
No	13.84±7.72	
Ludwig		
Mild	13.90±7.56	0.92**
Moderate	13.80±10.84	
Sever	11.35±3.32	
Skin type		
2	10.35±8.37	0.23**
3	14.94±8.50	
4	10.06±6.53	

\*T-test; \*\*ANOVA. SD – Standard deviation

Relationship between serum levels of Vitamin D in female pattern hair loss patients with other variables in this study

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