

The Effect of Vitamin D Supplementation on the Androgenic Profile in Patient with Polycystic Ovary Syndrome

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ABSTRACT

Background: it is suggested that vitamin D status is associated with androgenic profile in women with PCOS. Although there are a lot of clinical trials known in this regard, the results were varying.

Objective: This study aimed to evaluate the effect of Vitamin D supplementation on androgenic levels (including serum total testosterone, free testosterone and sex hormone binding globulins) in adult women with PCOS were established by the presence of hyperandrogenemia or clinical hyperandrogenism.

Patents and Methods: in the present study, 50 outpatient clinic women were included and divided into two groups, first group consisted of 25 patients who received 4000 IU daily of Vitamin D3 for 6 months, and the other group consisted also of 25 patients who received placebo drug blindly.

Results: the results showed significant difference between the two groups regarding different laboratory tests especially total testosterone level (decreased significantly after vit. D intake) and SHBG (elevated significantly after vit. D intake) and also significant difference in the hirsutism state after vitamin D administration. But in contrast, there was no significant difference between free testosterone level before and after vit. D administration. These results can help in the confirmation of the suggestion that vitamin D intake can help significantly in decreasing the androgenic profile in a woman patient with PCOS and also in decreasing hirsutism symptom.

Conclusion: vitamin D intake can help significantly in decreasing the androgenic profile and hirsutism in a woman patient with PCOS and used as a proper treatment for them.

Keywords: Vitamin D, PCOS, Hirsutism.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder of women of reproductive age affecting about 4-10% of all women^(1,2). Classical features of PCOS include infertility, hyperandrogenism, truncal obesity, abnormal glucose metabolism, insulin resistance (IR), hirsutism, and acne vulgaris, but diagnostic criteria included; chronic oligomenorrhea or amenorrhea, evidence of androgen excess clinical or biochemical, and polycystic ovaries⁽²⁾.

Androgen excess and PCOS (AE-PCOS) Society⁽³⁾ in 2009 cleared Hyperandrogenism includes hirsutism and ovarian dysfunction including oligo-anovulation and polycystic appearing (exclusion of other androgen excess or related disorders). One of the main criteria to establish a diagnosis of polycystic ovary disease is hyperandrogenemia⁽⁴⁾.

1. Serum Testosterone (T):

Serum free testosterone is considered to be a better indication of androgenicity than total testosterone, but the measurement of free testosterone is technically difficult and does not lend itself to routine clinical use. Total testosterone concentration in the saliva is highly correlated with free unbound plasma testosterone and provided a convenient index of free testosterone activity⁽⁵⁾.

2. Serum Androstendione (A):

In polycystic ovary disease, the measurement

of androstendione is probably as important as testosterone measurement, as peripheral conversion of androstendione to testosterone accounts for 50% to 75% of testosterone production. Serum androstendione is elevated in all types of polycystic ovary disease⁽⁵⁾.

3. Serum Di-hydro-testosterone (DHT):

Although DHT is biologically the most active androgen and probably the one that interacts with cutaneous androgen receptors, measurement of this steroid has not added much of clinical utility⁽⁶⁾.

4. Androgens of Adrenal Origin:

Women with polycystic ovaries (obese and non-obese) and hyperinsulinemia have a greater steroidogenic response to ACTH than anovulatory patients with normal insulin levels⁽⁷⁾.

The clinical problem with DHEA-S measurement is the frequent finding of a moderately elevated DHEA-S level in anovulatory patients with polycystic ovary disease⁽⁵⁾.

Vitamin D:

Vitamin D is a steroid hormone that is primarily known for its role in skeletal health and calcium homeostasis, but its deficiency has been related to a number of non-skeletal disorders including obesity, insulin dysregulation, dyslipidemia, hypertension, cardiovascular diseases, and autoimmune diseases⁽⁸⁾.

Vitamin D is either produced in the skin in

response to direct exposure to sunlight from 3-dehydrocholesterol or obtained from the diet. Vitamin D₃ (cholecalciferol) is converted into 25-hydroxyvitamin D₃ principally in the liver and 1,25-dihydroxy vitamin D₃ in the kidney by two hydroxylation steps. 1,25-dihydroxyvitaminD₃ is an active form of vitamin D, and its action takes place by binding vitamin D receptors (VDR) within cells. In the light of the literature, it has been reported that vitamin D levels are negatively correlated with IR and vitamin D replacement therapy increases insulin sensitivity⁽⁹⁾.

Vitamin D deficiency in PCOS

Vitamin D deficiency is common in women with PCOS, with the 67-85% of women with PCOS having serum concentrations of 25-hydroxy vitamin D (25OHD) <20 ng/ml. It is accepted concept that the metabolic changes in PCOS are related to deficiency of vitamin D and calcium metabolism, which is important in follicular development and normal glucose metabolism⁽¹⁰⁾. Multiple studies have shown that PCOS patients, particularly if obese, have lower serum vitamin D levels⁽¹¹⁾. In addition, have been associated with hyperandrogenism, metabolic syndrome, insulin resistance, and increased body mass index (BMI)⁽¹²⁾.

Aim of the work

This study aims to evaluate the effect of Vitamin D supplementation on androgenic levels (including serum total testosterone, free testosterone and sex hormone binding globulins) in adult women with PCOS were established by the presence of hyperandrogenemia or clinical hyperandrogenism.

PATIENTS AND METHODS

Study setting: This study was carried out in the department of Obstetrics and Gynecology (outpatient infertility clinic), Suez General Hospital.

Type of the study: Prospective randomized controlled study to evaluate the effect of Vitamin D supplementation on androgenic levels (including serum total testosterone, free testosterone and sex hormone binding globulins) in adult women with PCOS were established by the presence of hyperandrogenemia and/or clinical hyperandrogenism. **The study was approved by the Ethics Board of Al-Azhar University and an informed written consent was taken from each participant in the study.**

Patients:

Fifty out patients' clinic women were included in the study fulfilling the following inclusion and exclusion criteria:-

Inclusion criteria:

- 1- PCO women.
- 2- Age 20 – 40 years old.

3- Presence of hyperandrogenemia or clinical hyperandrogenism.

Exclusion criteria:

- 1- Exclusion of other causes of hyperandrogism such as Cushing syndrome, Adrenal hyperplasia and Virilism.
- 2- Any diagnosed case of PCOS who was on and had history of taking vitamin D and calcium supplement within period of one year.
- 3- Patients who were not willing to take part in the study.

They were divided into 2 groups:

Group (A): (n=25), where patients received 4000 IU daily Vitamin D₃.

Group (B): (n=25) placebo group received placebo drug (starch tab).

We used vidrop oral drops from MUP Company, patients received 40 drops daily.

Both studied groups received mentioned treatment for 6 months. Patients who have reported diarrhea, vomiting and severe abdominal distention during treatment were excluded from the study.

Patients included in this study were subjected to:

1- Written consent: was obtain from the outpatient infertility clinic women who were included in the study.

2- Full History Taking Including:

- Personal history: Name, age, occupation and address.
- Present history: infertility, hirsutism, acne.
- Past history: Medical or operative history.
- Family history: of 1st degree relatives with PCO.
- Menstrual history: oligomenorrhea, irregular menses and amenorrhea.
- Obstetric history and 1st day of last menstrual period (LMP)..
- Any drug allergy or obstetric or operative complication.

3- Physical examination

Body weight and height of patients was measured to the nearest 0.1 kg and 0.5 cm using calibrated devices. BMI was calculated as weight (kg) divided by the height squared (m²)⁽¹³⁾.

Hirsutism was evaluated using the Ferriman-Gallwey method⁽¹⁴⁾; it is a scale for hirsutism, it is a score of 1 to 4 is given for 11 areas of the body (the upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, arm, forearm, thigh, and lower leg.), a total score less than 8 is considered normal, a score of 8 to 15 indicates mild hirsutism, and a score greater than 15 indicates moderate or severe hirsutism.

In addition, the methods used to remove hairs and the frequency of using these methods (shaving, plucking) was asked and recorded for better scoring of hirsutism.

Acne was assessed based on the early involvement of the face in the areas of forehead,

cheeks and nose.

Biochemical measurements: Venous blood sample was obtained from studied population to measure:

- LH and FSH.
- Serum Total Testosterone, Free Testosterone and SHBG. Measured at the start of the study and after 6 months.
- Serum 25-Hydroxyvitamin (OH) level. Measured at the start of the study and after 6 months.
- Random Blood Sugar (RBS)

Ultrasound Examination: Polycystic ovaries defined as the presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter and/or increased ovarian volume (>10 ml; calculated using the formula $0.5 \times \text{length} \times \text{width} \times \text{thickness}$)⁽¹⁴⁾.

Statistical analysis

Analysis of data was done using SPSS (Statistical Program for Social Science) statistical

software, v. 15.2, Echosoftware corp., USA, 2004 as follow:

- Description of quantitative variables as mean, SD and range.
- Description of qualitative variables as no and %.
- Analysis of variance (ANOVA) to compare between 2 groups.
- Spearman correlation rank test was used to investigate the possible correlation between two variables which either positive correlation or inverse correlation.
- P value > 0.05 insignificant.
- P value < 0.05 significant.
- P value < 0.01 highly significant.

RESULTS

This table shows no statistical significant difference (p-value > 0.05) between studied groups as regard demographic data.

Table (1): comparison between studied groups as regard demographic data

Variables		Vit D group (N = 25)	Placebo group (N = 25)	P-value
Age (years)	Mean	27.76	26.48	0.15
	±SD	2.91	3.28	
BMI	Mean	30.84	30.36	0.65
	±SD	3.51	3.99	
Height (cm)	Mean	160.72	161.20	0.79
	±SD	6.47	6.38	
Weight (kg)	Mean	79.96	78.60	0.42
	±SD	4.70	7.03	

This table shows:

- Highly statistical significant difference (p-value < 0.001) between (Vit. D, Total testo and SHBG) before and after therapy in Vit. D group.
- Statistically significant difference (p-value < 0.05) between hirsutism before and after therapy in Vit. D group.
- No statistical significant difference (p-value > 0.05) between Freetesto before and after therapy in Vit. D group.

Table (2): comparison between (Vit.D, Free Testosterone, Total Testosterone, SHBG, Hirsutism) before and after therapy in Vit. D group.

Vit. D group		Before (N = 25)	After (N = 25)	P-value
Vit. D (ng/mL)	Mean	12.56	24.81	< 0.001*
	±SD	1.85	5.31	
Free Testosterone (ng/dL)	Mean	2.78	2.75	0.86
	±SD	0.56	0.59	
Total Testosterone (ng/dL)	Mean	82.08	52.12	< 0.001*
	±SD	15.48	7.35	
SHBG (nmol/L)	Mean	40.38	58.70	< 0.001*
	±SD	9.05	13.05	
Hirsutism	Negative	11 (44%)	19 (76%)	0.02**
	Positive	14 (56%)	6 (24%)	

*: p-value < 0.001 is considered highly significant. **: p-value < 0.05 is considered significant.

This table shows no statistical significant difference (p-value > 0.05) between (Vit. D, Free testo, Total testo, SHBG and hirsutism) before and after therapy in placebo group.

Table (3): comparison between (Vit.D, Free Testosterone, Total Testosterone, SHBG&Hirsutism) before and after therapy in Placebo group.

placebo group		Before (N = 25)	After (N = 25)	P-value
Vit. D (ng/mL)	Mean	12.77	13.18	0.21
	±SD	1.17	1.18	
Free Testosterone (ng/dL)	Mean	2.65	2.68	0.79
	±SD	0.34	0.31	
Total Testosterone (ng/dL)	Mean	82.60	82.88	0.9
	±SD	9.84	11.82	
SHBG (nmol/L)	Mean	43.08	43.99	0.72
	±SD	10.13	8.31	
Hirsutism	Negative	14 (56%)	14 (56%)	1.0
	Positive	11 (44%)	11 (44%)	

This table shows no statistical significant difference (**p-value > 0.05**) between studied groups as regard (Vit.D, Free Testosterone, Total Testosterone, SHBG &Hirsutism) before therapy.

Table (4): Comparison between studied groups as regard (Vit.D, Free Testosterone, Total Testosterone, SHBG & Hirsutism) before therapy.

Before		Vit D group (N = 25)	Placebo group (N = 25)	P-value
Vit. D (ng/mL)	Mean	12.56	12.77	0.63
	±SD	1.85	1.17	
Free Testosterone (ng/dL)	Mean	2.78	2.65	0.34
	±SD	0.56	0.34	
Total Testosterone (ng/dL)	Mean	82.08	82.60	0.9
	±SD	15.48	9.84	
SHBG (nmol/L)	Mean	40.38	43.08	0.32
	±SD	9.05	10.13	
Hirsutism	Negative	11 (44%)	14 (56%)	0.39
	Positive	14 (56%)	11 (44%)	

This table shows:

- Highly statistical significant difference (**p-value < 0.001**) between studied groups as regard (Vit. D, Total Testosterone and SHBG) after therapy.
- Statistically significant difference (**p-value < 0.05**) between studied groups as regard hirsutism after therapy.
- No statistical significant differences (**p-value > 0.05**) between studied groups as regard Free Testosterone after therapy.

Table (5): comparison between studied groups as regard (Vit.D, Free Testosterone, Total Testosterone, SHBG &Hirsutism) After therapy.

After		Vit D group (N = 25)	Placebo group (N = 25)	P-value
Vit. D (ng/mL)	Mean	24.81	13.18	< 0.001*
	±SD	5.31	1.18	
Free Testosterone (ng/dL)	Mean	2.75	2.68	0.59
	±SD	0.59	0.31	
Total Testosterone (ng/dL)	Mean	52.12	82.88	< 0.001*
	±SD	7.35	11.82	
SHBG (nmol/L)	Mean	58.70	43.99	< 0.001*
	±SD	13.05	8.31	
Hirsutism	Negative	20 (80%)	12 (48%)	0.02**
	Positive	5 (20%)	13 (52%)	

*: p-value < 0.001 is considered highly significant. **: p-value < 0.05 is considered significant.

DISCUSSION

It is suggested that vitamin D status is associated with androgenic profile in women with polycystic ovarian syndrome (PCOS). Although there are a lot of clinical trials known in this regard, the results were varying⁽⁹⁾.

Therefore, this study was performed aiming to clarify the possible effect of vitamin D supplementation on the androgen levels in adult females with PCOS (including serum total testosterone, free testosterone and sex hormone binding globulins). Women were established by the presence of hyperandrogenemia or clinical hyperandrogenism.

In the present study, 50 out patients clinic women were included and divided into two groups, first group consisted of 25 patients who received 4000 IU daily of Vitamin D3 for 6 months, and the other group consisted also of 25 patients who received placebo drug blindly.

The results showed significant difference between the two groups regarding different laboratory tests especially total testosterone level (decreased significantly after vit.D intake) and SHBG (elevated significantly after vit.D intake) and also significant difference in the hirsutism state after vitamin D administration. But in contrast, there was no significant difference between free testosterone level before and after vit.D administration. These results can help in the confirmation of the suggestion that vitamin D intake can help significantly in decreasing the androgenic profile in a woman patient with Polycystic Ovary Syndrome and also in decreasing hirsutism symptom.

The two groups were nearly of the same demographic data, regarding age, they were in their twenties, with body mass index (BMI) about 30, height was approximately 160 cm and their weight was approximately 79 kg.

In agreement with a previous study⁽¹²⁾, levels of 25(OH)D were inversely associated with BMI in PCOS patients, the less the vitamin D level, the higher the BMI. Obesity is a well-recognized risk factor of vitamin D deficiency. An inverse correlation between BMI and serum 25(OH)D concentrations in PCOS women was demonstrated in this study and previous reports⁽¹⁵⁾. Regarding laboratory data before the supplement's intake, there was no statistically significant difference between studied groups in random blood sugar (mean about 116 mg/dl in vit.(D) Group and 114 mg/dl in placebo group), FSH (mean about 4.45 in vit.(D) Group and 4.53 in placebo group), and LH (mean about 7.08 in vit.(D) Group and 7.09 in placebo group). Before any drug intake, there was no statistically significant difference (**p-value > 0.05**) between studied groups.

But after drug administration in both groups, there was highly statistically significant difference (**p-value < 0.001**) between studied groups as regard to Vit. D, Total Testosterone and SHBG and hirsutism after therapy.

Vitamin D level:

In the present study, there was highly statistically significant difference between groups as regard to Vit. D. The mean Vit.(D) level in placebo group was about 13.18 ng/ml and in vit.(D) group after vit. (D) administration was about 24.81 ng/ml.

Similar to our results, **Sirmans *et al.***⁽¹⁶⁾ reported lower serum vitamin D level in women with PCOS (n=545) compared to control (n=145) (25.7 vs 32.0 ng/ml, respectively).

Total testosterone level & Sex Hormone Binding Globulin (SHBG)

Through this study, it was also found that there was highly statistically significant difference between studied groups regarding Total Testosterone and SHBG after therapy.

There was significant decrease in total testosterone in the 1st group after administration of vitamin (D) comparing to placebo group (**82.08 ± 15.48 vs 52.12 +7.35, p<0.001**).

Also it was found highly significant increase in SHBG level in patient who received the drug compared to placebo group (**58.70 +.13.05 vs 43.99 +. 8.31p0.001**).

Similarly, clinical trial performed by Garg *et al.* talking about the effect of vitamin D administration on the androgenic effect in women with PCO mainly total testosterone (used 4 000 IU/day of vit. D but given once a month as an oral dose, 120 000 IU) showed that vitamin D supplementation significantly reduces serum total testosterone concentrations⁽¹⁷⁾.

Free Testosterone

It was found that there were no statistically significant differences (p-value > 0.05) between studied groups as regard to free Testosterone after therapy. That was similar to three clinical trials done by **Wehret *et al.***⁽¹²⁾, **Selimogluet *et al.***⁽¹⁸⁾ and **Raja *et al.***⁽¹⁹⁾ with 91 PCOS participants had data on serum free testosterone. It failed to find any significant effect of vitamin D supplement on serum free testosterone levels.

Hirsutism

Regarding hirsutism which is one of the core results found, before drug intake in both groups, there was no statistically significant difference (**p-value > 0.05**) between them. But after vit (D) intake, there was statistically significant difference (**p-value < 0.05**) between them. About 52% of the patients who were received vitamin (D) show significant improvement of hirsutism.

Similar to our results, study done by **Foroosanfard *et al.***⁽²⁰⁾ (comparing using of 4000 IU/day for 4 months and 1000 IU/day) found significant improvement of hirsutism after administration of vit D in first group (-1.1 - 1.1 vs. -0.8 - 1.2, p=0,001).

Unlike to our results, **Fouzia et al.**⁽²¹⁾ found that there is insignificant relationship present between severity of hypovitaminosis D and hirsutism (P=0.669), acne (P=0.480) and alopecia (P=0.317) among PCOS patients.

And to confirm the results in our study, comparing the results within the same group before and after drug intake shows that in the vitamin D group, there was significant difference between Vit. D, Total testosterone and SHBG and hirsutism but no statistically significant difference between free testosterone before and after drug intake.

This proves that the usage of vitamin D supplements to decrease androgenic effects was significant and valuable.

CONCLUSION

The results of the present study found that vitamin D supplement decreases total testosterone and increase SHBG in patients with PCOS and also decreased hirsutism symptoms. These results can help in the confirmation of the suggestion that vitamin D intake can help significantly in decreasing the androgenic profile and hirsutism in a woman patient with PCOS and used as a proper treatment for them. Long-term interventions with double-blind placebo-controlled design are highly recommended to confirm our results.

RECOMMENDATIONS

According to the results in our study, we recommend administration of 4000 IU of vitamin D daily for 6 months in patients with polycystic ovary syndrome specially those who suffer from hyperandrogenism.

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