OPEN ACCESS
Scholars International Journal of Obstetrics and Gynecology
Abbreviated Key Title: Sch Int J Obstet Gynec
ISSN 2616-8235 (Print)|ISSN 2617-3492 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article

# Effect of Vitamin D Supplementation on Metabolic Syndrome in women with Polycystic Ovary Syndrome

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**DOI:**10.36348/sijog.2021.v04i08.002 | **Received:** 06.07.2021| **Accepted:** 11.08.2021| **Published:** 18.08.2021

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## Abstract

***Background*:** Metabolic syndrome is common in women with polycystic ovary syndrome. Some studies have suggested that vitamin D deficiency may play role in metabolic disturbance and vitamin D supplementation improves metabolic profile of these patients. ***Objective*:** To evaluate the effect of vitamin D supplementation on the metabolic profile in the polycystic ovary syndrome patients. ***Methods*:** Seventy seven diagnosed cases of vitamin D deficient polycystic ovary syndrome patient with metabolic syndrome, age range 18-45 years were administered standard therapy of oral vitamin D $(OH)_2$ 40000 IU weekly for seven weeks followed by maintenance therapy of oral vitamin D2 2000 IU daily. Follow up vitamin D was done 3 months after initiation of vitamin D supplementation. The changes in features of metabolic syndrome namely, waist circumference, blood pressure, fasting plasma glucose, fasting serum triglyceride and high density lipoprotein levels were recorded. Paired't' test was done to see if the changes were significant. ***Result:*** Mean serum vitamin D was significantly increased (11.5±4.0 ng/ml vs. 36.8±10.7 ng/ml) after the vitamin D supplementation ($p<0.05$). Triglycerides level decreased (180.7±62.3 vs 148.1±46.2 mg/dl) and HDL level increased (38.2±11.3 vs 47.1±10.3 mg/dl) which were statistically significant ($p<0.05$). But the changes were not significant for the waist circumference (93.9±8.6 vs. 93.4±8.2), blood pressure (SBP-117.6±12.4 vs 117.5±11.9 mm Hg; DBP- 80.9±7.6 vs 80.8±7.8 mmHg), fasting glucose (5.77±1.02 mmol/L vs. 5.74±0.99 mmol/L). ***Conclusion:*** Vitamin D supplementation have favorable effects on features of metabolic syndrome.

**Keywords:** Metabolic syndrome, vitamin D, blood pressure, polycystic ovary syndrome.



## INTRODUCTION

The Polycystic Ovarian Syndrome (PCOS) manifests itself as menstrual irregularity, hyperandrogenism and polycystic ovaries in 6-10% women in their reproductive age [1]. PCOS is associated with insulin resistance (IR), hyperinsulinemia, dyslipidemia and central obesity, all of which are risk factors for metabolic syndrome, type 2 diabetes mellitus, and cardiovascular disease [2]. Women with PCOS have glucose tolerance disorder in 30–40%, insulin resistance in 60–80%, and type 2 diabetes in 10% in their thirties or forties [3]. Obesity is common in PCOS, and over 50% of women affected are overweight. Obesity is associated with insulin resistance, impaired glucose tolerance and dyslipidemia in PCOS women [4]. Dyslipidemia is also common in PCOS and includes high levels of total cholesterol, low density lipoprotein (LDL) and triglyceride (TG) and low high density lipoprotein (HDL). Lipid disorders are seen in about 65–81% of these women [4]. Metabolic syndrome, which involves abnormalities in the metabolism of sugar, fat, protein, and maintenance of blood pressure, is an important complication of PCOS.

Current evidence suggests that insulin resistance (IR) has a central role in the pathogenesis of PCOS, contributing to both metabolic and reproductive disturbances [5]. In part, IR might be due to obesity.

However, a substantial number of lean women affected by PCOS have IR as well, independent of obesity [6].

Recently, vitamin D deficiency has been proposed as the possible missing link between IR and PCOS. This assumption is supported by the finding that the active vitamin D–vitamin D receptor (VDR) complex regulates over 300 genes, including genes that are important for glucose and lipid metabolism as well as blood pressure regulation [7]. Moreover, there is an association between poor vitamin D status and IR in patients with type 2 diabetes mellitus [8]. Increased prevalence of vitamin D deficiency has been observed in South Asian Countries which include India, Pakistan, Bangladesh, and Sri Lanka [9].

Several studies have documented that vitamin D supplementation in vitamin D deficient PCOS patient improves their metabolic profile. Studies regarding Vitamin D status in patients with PCOS show an inverse correlation between Vitamin D levels and metabolic risk factors, e.g. insulin resistance, BMI, waist-to-hip-ratio, triglycerides, total testosterone and a positive correlation with insulin sensitivity [10-12]. Clinical trials with either Vitamin D supplementation or administration of Vitamin D3 analogues show positive effects on insulin secretion, lipid profile, menstrual cycle and follicular development and a decrease of fasting and stimulated glucose and C peptide levels [11, 13, 14]. Taking these findings in consideration we have undertaken this study to find out a simple adjuvant treatment for PCOS. The aim of our study was to evaluate the effect of vitamin D supplementation on the metabolic profile of women with Polycystic Ovary Syndrome.

## METHODS

The longitudinal study was carried out in the Department of Reproductive Endocrinology and Infertility, Bangabandhu Sheikh Mujib Medical University, Dhaka from January 2019 to December 2019.Diagnosed cases of PCOS with metabolic syndrome who were also vitamin D deficient were included in the study. PCOS was diagnosed if at least two of the Rotterdam PCOS criteria following criteria were present: oligo menorrhea/ anovulation (defined as delayed menses >35 days or <8 spontaneous hemorrhagic episodes/year), hyperandrogenism (hirsutism using modified Ferriman-Gallway score of >8) and polycystic ovarian morphology on ultrasonography. Metabolic syndrome (MetS) was defined as the presence of any three of the following five factors for a diagnosis of MetS: i) waist circumference >80 cm, ii) hypertriglyceridemia >150 mg/dl or drug treatment for elevated TG, iii) high-density lipoprotein <50mg/dl, iv) blood pressure (BP) >130/85 mmHg or drug treatment for elevated BP, v) fasting plasma glucose >5.6mmol/L or drug treatment for elevated glucose (the modified National Cholesterol Education Program Adult Treatment Panel III, NCEP ATP III). Those who had serum vitamin D levels less than 20 ng/ml were considered to have vitamin D deficiency. The age range was 18-45 years. The exclusion criteria were pregnant or lactating, use of drugs affecting metabolic parameters such as metformin, oral contraceptive pills (OCPs), corticosteroid in the previous 3 months, vitamin D and calcium, and multivitamin in the previous 6 months, chronic diseases such as hypothyroidism or hyperthyroidism, liver disease, osteopenia, osteoporosis, renal failure, cirrhosis, pancreatitis, nephrotic syndrome and malignancy, secondary causes of hyperandrogenism such as Cushing's syndrome, congenital adrenal hyperplasia, acromegaly and androgen secreting tumors. The sample size was 77calculated with power 0.80 and alpha 0.05.

The study was approved by the Institutional Review Board and informed written consent was taken from the participants after full explanation of the study procedure. The amount of terminal hair growth was assessed using a modified Ferriman-Gallway method in which the upper lip, chin, chest, upper and lower abdomen, thighs, upper and lower back and upper arms was scored from 0 to 4. The presence of acne and acanthosis nigricans was also noted. Anthropometric measurements including height in cm, weight in kg, waist circumference (WC) in cm was measured in standing position. WC was measured midway between the lower rib margin and the upper margin of the iliac crest at the end of a gentle exhalation. The BMI was calculated by dividing the weight (in kg) by the height (in $m^2$) to assess obesity. Systolic and diastolic blood pressure was measured twice in one visit with a sphygmomanometer. Vitamin D level was measured in the Department of Biochemistry and Molecular Biology by Chemiluminiscence method. Fasting venous blood (after 8 - 14 hours overnight fasting) was drawn for fasting plasma glucose (FPG) and lipid profile. The plasma glucose was estimated by glucose-oxidase method by automated analyzer: Dimension RxL Max and total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) was measured by Trinder reaction method. Low-density lipoprotein cholesterol (LDL-C) was calculated with the use of the Fried Ewald formula: LDL-C = TC - HDL-C – (TG/5).

This population was administered standard therapy of oral vitamin D $(OH)_2$ 40000 IU weekly for seven weeks followed by maintenance therapy of oral vitamin D $(OH)_2$ 2000 IU daily. Follow up vitamin D level was done at pre fixed schedule 3 months after initiation of vitamin D supplementation to analyze the change that is achieved. Pre and post treatment effect of vitamin D on metabolic profile was assessed. The side effects and the spontaneous pregnancies were also recorded. The end point of the study was the changes in different parameter of metabolic syndrome in PCOS namely- WC, BP, FPG, TG and HDL.

Statistical analysis was carried out by using the Statistical Package for Social Sciences version 22.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Frequency and percentage was calculated for categorical variables. The mean values were calculated for continuous variables. The quantitative observations were indicated by frequencies and percentages. Paired t-test was used for continuous variables. P values <0.05 was considered as statistically significant.

## RESULTS

Among 77 selected patients, 2 participants became pregnant and another 2 moved overseas. So, 73 participants completed the study and were available for analysis. The baseline demographic and clinical characteristics of the study participants are summarized in table 1. The mean age was 26.4±4.4 years.

**Table 1: Baseline demographic and clinical characteristics of the study participants(n=73)**

| Parameters | ber of patients | Percentage |
|---|---|---|
| **Age (years)** | | |
| ≤20 | 4 | 5.2 |
| 21-30 | 62 | 80.5 |
| 31-40 | 11 | 14.3 |
| **Occupation** | | |
| Housewife | 66 | 85.7 |
| Others | 11 | 14.3 |
| **Residence** | | |
| Rural | 25 | 32.5 |
| Urban | 52 | 67.5 |
| **Menstrual disturbance** | | |
| Amenorrhea | 7 | 9.1 |
| Oligo menorrhea | 70 | 90.9 |
| **Hirsutism** | 13 | 16.9 |
| **Acne** | 9 | 11.7 |
| **Acanthosis nigricans** | 6 | 7.8 |

Table 2 shows that mean serum vitamin D was found 11.5±4.0 ng/ml before treatment and 36.8±10.7 ng/ml after treatment, which indicate that serum vitamin D level was significantly increased after treatment of vitamin D supplementation.

**Table 2: Serum vitamin D (n=73) levels at baseline and after treatment**

| | **Before treatment (n=73)** | ***After treatment (n=73)** | **Changes (before vs after treatment)** | **P value** |
|---|---|---|---|---|
| | **Mean±SD** | **Mean±SD** | **Mean±SD** | |
| Serum vitamin D (ng/ml) | 11.5±4.0 | 36.8±10.7 | 25.38±9.98 | $0.001^{s}$ |
| Range (min-max) | 4.2-19.6 | 21.0-68.0 | 7.8-(53.6) | |

s= significant

Table 3 shows the changes in the features of metabolic syndrome: waist circumference, blood pressure, fasting glucose level decreased but the decrease was not statistically significant after treatment of vitamin D supplement. However, triglycerides level decreased and HDL level increased significantly after vitamin D supplement.

**Table 3: Changes in metabolic syndrome parameters from baseline to after treatment (n=73)**

| **Metabolic syndrome** | **Before treatment (n=73)** | ***After treatment (n=73)** | **Changes (before vs after treatment)** | **P value** |
|---|---|---|---|---|
| | **Mean±SD** | **Mean±SD** | **Mean±SD** | |
| Waist circumference (cm) | 93.9±8.6 | 93.4±8.2 | -0.16±0.73 | $0.057^{ns}$ |
| SBP (mmHg) | 117.6±12.4 | 117.5±11.9 | -0.22±1.00 | $0.066^{ns}$ |
| DBP (mmHg) | 80.9±7.6 | 80.8±7.8 | -0.21±0.91 | $0.058^{ns}$ |
| Fasting glucose (mmol/L) | 5.77±1.02 | 5.74±0.99 | -0.01±0.03 | $0.101^{ns}$ |
| Triglycerides (mg/dl) | 180.7±62.3 | 149.5±43.7 | -30.37±39.16 | $0.001^{s}$ |
| HDL (mg/dl) | 38.2±11.3 | 47.1±10.3 | 9.74±9.92 | $0.001^{s}$ |

s= significant, ns= not significant
P value reached from paired t-test

**Table 4: Changes in related anthropometric and metabolic parameters from baseline to after treatment (n=73)**

| Parameters | Before treatment (n=73) Mean±SD | *After treatment (n=73) Mean±SD | P value |
|---|---|---|---|
| Body mass index (BMI) $kg/m^2$ | 26.6±2.2 | 26.5±2.2 | $0.083^{ns}$ |
| Total cholesterol (mg/dl) Range (min-max) | 192.9±37.0 117.0-320.0 | 182.0±35.0 86.0-250.0 | $0.001^{s}$ |
| LDL (mg/dl) Range (min-max) | 114.5±29.7 41.0-182.0 | 110.3±32.6 41.0-180.0 | $0.042^{s}$ |

## DISCUSSION

PCOS is the most frequent endocrine disorder among women of reproductive age and vitamin D deficiency is a general problem in PCOS patients [15]. The debate continues regarding whether vitamin D concentrations are correlated with PCOS risk and whether vitamin D supplementation is an effective therapy for PCOS. There are intriguing reports suggesting that vitamin D deficiency is more prevalent among women with PCOS [16].

PCOS women have higher values of parameters of hyperglycemia and dyslipidemia as well as obesity indices [17]. Because the current treatment of PCOS is still suboptimal and the metabolic diseases are common causes of morbidity and mortality all over the world, we aimed in our study to investigate the effect of vitamin D on the metabolic profile namely WC, BP, FPG, TG and HDL level in the polycystic ovary syndrome patients.

In our study it was observed that mean serum vitamin D was significantly increased after supplementation (11.5±4.0 ng/ml vs. 36.8±10.7ng/ml). These results are in agreement with the observation of some studies [15, 18-19]. Study conducted by Ardabili *et al*., [15] showed that the mean vitamin significantly increased from baseline (6.9±2.8 vs. 23.4±6.1ng/ml). This lower level of Vitamin D at baseline may be caused by reduced sun exposure due to prevalent social and religious practice. Vitamin D deficiency in women with PCOS is probably due to the obesity of patients with this pathology [20]. Obesity causes decrease vitamin D flow with trapping of vitamin D in adipose tissue [21] and lack of sun exposure due to physical inactivity and limited social participation due to hirsutism with PCOS [22]. Racial differences and its influence on VDR polymorphism may be also a probable factor [23] behind differences in baseline vitamin D levels in different studies.

Regarding observation of triglyceride level, it was 180.7±62.3 mg/dl before and 148.1±46.2 mg/dl after treatment which indicate that TG level was significantly decreased after vitamin D supplementation. The level of HDL was significantly improved after vitamin D treatment (38.2±11.3 mg/dl vs. 47.1±10.3 mg/dl). The results of our study were similar to the other study by Kotsa *et al*., [24] where they showed that triglyceride level significantly decreased and HDL significantly increased after receiving of alfacalcidol for 3 months. Supporting our results, another study [11] demonstrated a significant decrease in triglycerides after 12 weeks. Improvements of HDL was also observed by Gupta *et al*., [18].

Our study also found that total cholesterol (192.9±37.0 vs.182.0±35.0 mg/dl) and LDL cholesterol (114.5±29.7 mg/dl vs.110.3±32.6 mg/dl) decreased significantly. Dastorani *et al*., [25] found significant decrease in total and LDL-cholesterol levels in infertile women with PCOS after vitamin D supplementation.

All the studies with similar findings were on PCOS women with metabolic syndrome. However there was one study by Kubiak *et al*., [26] which found that vitamin D supplementation did not improve lipid profile parameter in vitamin D deficient population. Kubiak *et al*., [26] did the double blind randomized trial on male subjects with mean age around 50 years. Genetic factor may play a role for the outcome.

The causal relationship between dyslipidemia and hypovitaminosis D remains unclear. However recent studies suggested that the active vitamin D metabolite acting like a potent hormone that binds to VDRs and regulates transcription of several genes, is also associated with metabolic syndrome and its components (i. e. high TG and low HDL) [27].

On evaluation of waist circumference, this study found no significant impact of vitamin D on waist circumference (93.9±8.6 cm before treatment and 93.9±8.5 cm after treatment). Similar study conducted by Wehr *et al*., [11] did not find any change in waist–hip circumference after supplementation of vitamin D.

In our study a small non-significant drop was observed in both systolic and diastolic blood pressure. Vitamin D acts as a potent endocrine suppressor in renin biosynthesis. So vitamin D deficiency upregulate the renin-angiotensin-aldosterone system (RAAS), resulting in hypertension [28]. These non-significant blood pressure lowering effect also observed in a RCT by Raja-Khan *et al*., [19]. Rashad *et al*., [17] found significant improvement of both systolic and diastolic

blood pressure. They added calcium supplementation along with vitamin D which may influence this result.

There was a little improvement in fasting plasma glucose after the supplementation of vitamin D. But the fall of blood glucose was not statistically significant. This finding was in conformity with the studies Raja-Khan *et al*., [19], Dastorani *et al*., [25], Ardabili *et al*., [15] and Trummer *et al*., [29], but contradictory to other studies Rashad *et al*., [17] and Gupta *et al*., [18]. These later studies revealed that there was significant improvement of fasting plasma glucose after vitamin D supplementation. This improvement may be due to increased dose of vitamin D (60,000 IU/ week for 12 weeks). Accumulating evidence suggests that vitamin D deficiency triggers the development of insulin resistance or decrease in insulin secretion or both thus potentiating Type 2 DM [28].

In our study BMI was assessed; but there was no significant improvement of BMI after supplementation in comparison to that before supplementation (26.6±2.2 kg/$m^2$ vs. 26.5±2.2 kg/$m^2$). Raja-Khan *et al*., [19] and Ardabili *et al*., [15] found similar results. On the other hand Wehr *et al*., [11] and Yildizahan *et al*., [12] found an inverse correlation between BMI and vitamin D level. In obese PCOS, higher proportion of vitamin D is sequestered in adipose tissues; hence bioavailability of vitamin D is lowered [30].

In summary, vitamin D supplementation increased vitamin D level, improved all parameters of lipid profile - triglyceride, HDL, cholesterol and LDL, but did not alter levels of Waist Circumference, Blood Pressure or Fasting Plasma Glucose.

The limitations of the study include absence of comparison group, small sample size from a single centre, absence of randomization. Further larger studies with randomized control trial design are recommended.

The most urgent problem with the current management of PCOS is that many doctors focus on the short-term cosmetic and reproductive consequences, while cardio-metabolic risks are not often considered. All the women with PCOS should be screened for the presence of metabolic syndrome, since the frequently found derangements at young age imply an elevated risk for the development of diabetes mellitus and cardiovascular disease later in life. Vitamin D supplementation may be a cheap, easily accessible and safe measure to improve metabolic syndrome and to provide comprehensive management of PCOS women.

## CONCLUSION

This study concludes that vitamin D supplementation has significant effect on metabolic syndrome parameters such as serum triglyceride and high density lipoprotein (HDL) but no significant effect on waist circumference, blood pressure or fasting plasma glucose. Vitamin D supplementation could be a promising treatment of PCOS and its associated morbidity when vitamin D deficiency is present.

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