

Original Research Article

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Correlation of vitamin D levels with polycystic ovary syndrome: A ~~case~~ case-control study

Abstract

Objective: To compare vitamin D status in, women with PCOS & fertile women without PCOS and its subsequent evaluation.

Introduction: PCOS is an endocrine disorder of women in reproductive age, characterised by obesity, hyperandrogenemia and insulin resistance. Women with PCOS tend to be overweight and have ~~an~~ increased risk of ~~development-developing~~ of Type II Diabetes and cardiovascular disease. ~~Exact-The exact~~ Etiology of PCOS ~~still-remains~~ an enigmatic dilemma however various studies conducted ~~til-to~~ date include diet and lifestyle modification as the key factor to promote health, BMI, reduced hyperinsulinemia and reduce the risk of development of PCOS.

~~Main-The main~~ aim of our study was to compare vitamin D status in women with PCOS, with fertile women in Uttarakhand.

Methodology: ~~The~~ conducted study was ~~eross-cross-~~cross-sectional, involving the enrolment of 100 women comprising of 50 women with PCOS and 50 fertile women without PCOS. The serum 25-hydroxy vitamin D and other metabolic markers were measured. Vitamin D deficiency was defined as serum 25 (OH) D concentrations less than 20 ng/ml.

Comment [FK1]: Where the study was conducted

Result: Serum 25-hydroxyvitamin D was significantly lower in women with PCOS compared to fertile controls ($p < 0.0001$), and the prevalence rates of 25(OH) D deficiency and insufficiency were higher in women with PCOS than ~~in-~~fertile women ($p < 0.0001$). The prevalence of 25 (OH) D deficiencies in PCOS women was significantly higher. Serum 25 (OH) D concentrations was significantly negatively correlated with body mass index (BMI), waist-to-hip ratio (WHR), fasting insulin, total cholesterol and low-density lipoprotein cholesterol (LDL-C), ($P < 0.05$). In comparison, serum 25 (OH) D concentrations were significantly positively correlated with high-density lipoprotein cholesterol (HDL-C) ($P < 0.05$). Increased BMI and WHR, high levels of fasting insulin, total cholesterol, and LDL-C were regarded as risk factors, but ~~a~~ high level of HDL-C was considered to be protective factor of vitamin D deficiency in PCOS women.

Conclusion: The study demonstrated that women with PCOS have a significantly lower 25(OH) D compared to fertile controls. A compromised vitamin D status in PCOS women is associated with a higher prevalence and metabolic risk of PCOS in women.

Introduction

PCOS is an endocrine disorder of women in reproductive age and is the main cause of anovulatory infertility (1). The prevalence of PCOS range from 9 to 18% (2,3). [A](#)

1 Characteristic feature of PCOS is the presence of polycystic ovaries and menstrual
2 dysfunction leading to infertility along with biochemical abnormality. PCOS manifests
3 clinically as hirsutism, Hyperandrogenism, and acne (4). The most prevalent characteristics
4 of PCOS ~~is-are~~ Obesity, Hyperandrogenemia, and insulin resistance (5). The prevalence of
5 PCOS will rise in near future (6). The potential impact will be negatively on population
6 growth and cardiovascular morbidity and mortality, and consequently, it will lead to major
7 public health concerns. The development of PCOS is influenced by Vitamin D and hormonal
8 modulation influences insulin metabolism and fertility regulation (7,8). Several studies have
9 reported low levels of vitamin D in women with PCOS, with an average of 25-hydroxy
10 vitamin D (25OHD) levels between 11 and 31 ng/ml,(7,9,10,8,11-17) with the majority
11 having values <20 ng/ml (67–85%).(9,18,19,8,13,14) The functioning of all systems of the
12 body is disrupted by vitamin D deficiency, which increases the risk of chronic disease
13 including physical diseases such as cancer, cardiovascular, autoimmune and infectious
14 diseases; and psychological disorders such as depression and chronic pain (20). Vitamin D3
15 is obtained from the diet or synthesised endogenously through sunlight—induced
16 photochemical conversion of cholesterol in the skin and subsequently hydroxylation in the
17 liver and kidney. In the skin, 7-dehydrocholesterol undergoes ultraviolet photolysis to form
18 vitamin D3. Vitamin D3 then undergoes two successive hydroxylations, the first of which
19 takes place in the liver and is catalysed by vitamin D-25 hydroxylase to form 25OHD. The
20 second hydroxylation step is regulated by parathyroid hormone (PTH) and mediated by 25-
21 hydroxyvitamin D3 1 α -hydroxylase and occurs predominately in the kidney. This second
22 hydroxylation produces the final active metabolite of vitamin D3, which is 1,25-dihydroxy
23 vitamin D3. 1, 25-dihydroxyvitaminD3 circulates bound to vitamin D-binding protein until it
24 reaches its target tissue where it binds to vitamin D receptors to initiate its effect.

25 It has been very controversial regarding the difference between vitamin D levels
26 between PCOS women and healthy women, and the relationship between vitamin D and
27 metabolic factors in PCOS women. Certain studies have shown that PCOS women had lower
28 serum 25 (OH) D concentrations than healthy women, and vitamin D deficiency.

29 Vitamin D deficiency and PCOS are associated with metabolic disorders, but little is
30 known about vitamin D status in women with PCOS in Dehra Dun, Uttarakhand. Therefore,
31 this study aims to investigate vitamin D status and analyse the relationship between vitamin
32 D deficiency and metabolic risk factors in women with PCOS.

34 **Methodology**

35 It was an observational, ~~case-case~~ control study conducted from July 2019 to January 2020.
36 The sample size was n= 100 out of which 50 were control and 50 patients belonged to the
37 PCOS group. All women fulfilling the inclusion criteria were included after informed
38 consent. Non-probability sampling technique was used for ~~the purpose of~~ data collection. All
39 the young women of age (18-40), and those with polycystic ovary syndrome for more than or
40 equal to ~~one-one~~ year duration were included. PCOS women can be diagnosed by two of the
41 three criteria;—: Oligoovulation or anovulation, clinical or biochemical evidence of
42 hyperandrogenism, and polycystic ovaries (12 follicles of size 5-7mm). Vitamin D deficiency
43 was defined as 25- hydroxyvitamin D [25OHD] level < 20 ng/ml. Women with thyroid
44 disease, congenital adrenal hyperplasia or autoimmune diseases were excluded. The protocol
45 was approved by the Institutional Ethical ~~committee~~ Committee of the hospital.

46 **Statistical Analysis**

47 Data in this study was analyzed using SPSS version 19.0. The continuous variables are
48 presented as mean \pm SD, which were performed by Student's t-test or variance analysis. The

1 | categorical parameters are displayed as numbers (%), which were analyzed by [the](#) chi-square
2 | test. Linear regression analysis was used to analyze the correlation of 25 (OH) D
3 | concentrations with metabolic parameters. Post-stratification was done by applying Chi-
4 | square test. $P \leq 0.05$ was taken as significant.

5

6 | **Result**

7 | The numerical range for age in our study was from 18 to 45 years with mean age of control
8 | 24.02 ± 4.3 and PCOS group 23.16 ± 5.0 years, mean duration of PCO was 2.5 ± 1.2 years and
9 | mean BMI for control 24.48 ± 5.72 and PCOS 25.90 ± 5.16 . Overall, 29(38.16%) control and
10 | 47(61.84%) PCOS group of women had vitamin D deficiency which was statistically
11 | significant ($p=0.0001$).-(Table1). When [the](#) outcome variable was stratified with respect to
12 | age, BMI, [waist-waist](#)-hip ratio, systolic and diastolic blood pressure, it showed no significant
13 | difference as p-values were 0.3577, 0.1942, 0.4663, 0.1547, and 0.2098.752 respectively.
14 | Table 2 shows the clinical and biochemical profiles of the subjects. Women with PCOS
15 | showed increased serum levels of FSH, LH, TSH, and T3 compared with matched controls,
16 | but they showed no differences in the levels of T4. There was [a](#) marked difference in Vitamin
17 | D levels or prevalence of vitamin D deficiency (< 20 ng/ mL) (Table 2). In addition, we
18 | found correlations between serum vitamin D level and clinical or metabolic profiles in both
19 | PCOS patients and controls (Table 2). Vitamin D insufficiency was observed in the majority
20 | of the subjects (61.84% of patients and 38.16% of the controls Table 2).

21

22 | **Basic Characteristic of the Studied Groups**

23 | Table 1 illustrates the baseline characteristics of women in the two groups.

24

	Control N=50	PCOS Group N=50	P-value
Age(year)	24.02 ± 4.3	23.16 ± 5.0	0.3577
BMI	24.48 ± 5.72	25.90 ± 5.16	0.1942
Waist circumference	102.86 ± 15.35	94.58 ± 12.78	0.0042
Hip circumference	0.95 ± 0.06	0.94 ± 0.06	0.0031
Waist hip ratio	0.95 ± 0.06	0.94 ± 0.06	0.4663
Blood Pressure			
Systolic	122.02 ± 7.41	124.28 ± 8.3	0.1547
Diastolic	84.8 ± 5.79	83.2 ± 6.8	0.2098

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27 | **Clinical and Biochemical profiles of the subjects**

28 | Table 2: illustrates the clinical and biochemical profiles of women in the two groups.

29

Comment [FK2]: This is out of your inclusion criteria

Table 2: The Clinical and Biochemical profiles of women in the two groups.

	Control N=50	PCOS Group N=50	P-value
FSH	4.44±5.22	4.51±5.84	0.4586
LH	2.89±7.22	3.6±7.76	0.9231
TSH	1.76±2.19	1.79±2.56	0.1192
T ₃	81.0±89.26	84.2±89.12	0.2220
T ₄	5.98±6.21	5.98±7.63	0.0729
Triglyceride	130.31±17.89	124.13±29.25	0.2059
Total Cholesterol	166.08±25.05	151.29±30.76	0.0098
LDL	83.78±28.03	75.62±23.88	0.1207
Vitamin D ₃	21.09±18.07	11.91±10.57	0.0001

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Table 3: illustrate the Vitamin D Outcome in PCOS patients and Control group

Table 3: The Vitamin D Outcome in PCOS patients and Control group

Variable	Control N=50	Case N=50	p- value*
Vitamin D3	18.2 (6-66.5) 21.9±13.4	11.2 (5.23-31.2) 11.9 ±4.7	<0.0001
Sufficient (>=20.00)	21 (42)	3 (6)	1 (ref)
Low Vitamin D3 (<20.00)	29 (58)	47 (94)	11.3 (3.1-41.4)#

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Data expressed as Mean±Sd and Median (Min-Max) , f(%) . *Ranksum test, # Odd's ratio (95% CI)

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It was observed that the mean vitamin D3 level among cases was less as compared to controls, and it was found statistically significant. The prevalence of vitamin D deficiency was high in the study population (76%) however the odds of having the disease was 11 times more in Vitamin D deficient as compared to normal.

Comment [FK3]: Refer the table here?

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No significant difference was found when comparing other baseline characteristics between the two groups (P > 0.05).

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12

Vitamin D Status between PCOS Women and Controls

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The serum 25 (OH) D concentrations were significantly lower in PCOS women than in controls (11.91± 10.57 vs. 21.09 ± 18.07 ng/mL, P < 0.001). In addition, the serum 25 (OH) D concentration deficiencies were significantly high in women with PCOS than in controls

1 (61.84% vs. 38.16%, $P < 0.0001$). Furthermore, the prevalence of normal 25 (OH) D statuses
2 in women with PCOS was significantly lower than that in controls (12.5% vs. 87.5%, $P <$
3 | 0.0001). Table 2 shows the Clinical and Biochemical ~~profile~~-Profile of patients in two groups.
4 There were statistically significant differences in HDL and Abdomen girth among the two
5 groups ($P < 0.05$). No significant difference was found when comparing FSH, LH, TSH, T3,
6 | and T4, total cholesterol, LDL and triglycerides among ~~the~~ two groups ($P > 0.05$).
7

8 Discussion:

9 In women with PCOS, low vitamin D levels are associated with obesity, metabolic and
10 endocrine disturbances and vitamin D supplementation might improve menstrual frequency
11 and metabolic disturbances in those women.[21] Vitamin D deficiency is still considered a
12 problem of the past by health care professionals and the public. Populations at risk include
13 infants, children, pregnant and postmenopausal women.

14 This study focuses on the serum levels of vitamin D and the prevalence of vitamin D
15 deficiency in patients with PCOS. Our study found significant differences in the absolute
16 level of serum vitamin D or prevalence of vitamin D deficiency between women with PCOS
17 | and ~~the~~ control group. Additionally, we found correlations between serum vitamin D and
18 hormonal or metabolic profiles in either PCOS patients or controls. Our findings suggest that
19 | there is ~~a~~ role of vitamin D in the pathogenesis of PCOS. Similar to our study Wehr et al. [20]
20 reported lower serum vitamin D levels in a large number of women with PCOS ($n = 545$)
21 compared to controls ($n = 145$) (25.7 vs. 32.0 ng/mL, respectively), a substantial number of
22 studies suggest that serum vitamin D levels are similar in women with and without PCOS
23 [12,17,30]. In previous studies, average serum vitamin D levels in women with PCOS were
24 reported to be between 11 ng/mL and 31 ng/mL, with the majority having mean values < 20
25 ng/mL [12,13,15-17,20,22,29, 31-33]. In our study, the mean 25-(OH) D3 level in women
26 with PCOS was also < 20 ng/mL (11.91 ± 10.57 ng/mL), and vitamin D deficiency (lower
27 than 20 ng/mL) was observed in 61.84% of patients. However, vitamin D deficiency is also
28 common in the control group, with 60% of adults having values lower than 20 ng/mL. The
29 control subjects in the current study also showed a high prevalence of vitamin D deficiency
30 (38.16%), with a mean level of 21.09 ng/ mL. Many studies have investigated an association
31 between vitamin D status and hormonal or metabolic features in PCOS. In women with
32 PCOS, a low vitamin D level is thought to be related to metabolic risk factors such as insulin
33 resistance, high total cholesterol, blood pressure, glucose, C-reactive protein, triglycerides,
34 and low high-density lipoprotein (HDL) cholesterol [14,17]. In addition, vitamin D
35 replacement therapy may have a beneficial effect on insulin resistance or fasting and on
36 stimulated glucose and triglycerides levels in women with PCOS [16, 33]. Furthermore,
37 several studies have identified relationships between low vitamin D status and measures of
38 hyperandrogenism such as SHBG, the degree of hirsutism, FAI, total T and
39 dehydroepiandrosterone sulphate [13, 14, 17, and 29]. Although our study found significant
40 differences in the absolute level of serum vitamin D or prevalence of vitamin D deficiency
41 between PCOS women and matched controls, the results need to be interpreted with caution.
42 First, vitamin D deficiency may be a universal phenomenon across PCOS patients and
43 controls. Second, inverse associations between obesity (BMI, body fat and waist
44 measurements) and serum vitamin D levels have been reported in many studies [12-14, 17,
45 | 22, and 29]. As vitamin D is ~~fat-fat~~-soluble, a higher proportion of vitamin D may be
46 sequestered in adipose tissue in obese individuals, which might lower serum levels. In our
47 study, patients and controls were matched by BMI, thus there were no differences in BMI,
48 WC, or body and visceral fat masses between the two groups. Third, a potential limitation of
49 the present study is the modest sample size in the PCOS group, which precludes drawing
50 strong conclusions. Finally, we did not evaluate the presence of other potential confounding

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1 factors, such as outdoor times or dietary patterns which could affect the serum vitamin D
2 | levels. In summary, we found a significant difference in the absolute level of serum vitamin
3 D or prevalence of vitamin D deficiency between women with PCOS and matched controls.
4 The women with PCOS are at 11.34% at risk of developing vitamin D deficiency.
5 Additionally, we did not find any correlation between serum vitamin D and hormonal or
6 metabolic profiles in either PCOS patients or controls. Although our findings suggest that the
7 role of vitamin D in the pathogenesis of PCOS is clear, vitamin D deficiency is a common
8 finding among PCOS patients and controls. Finally, the potential relationship between
9 vitamin D and PCOS requires further investigation, since vitamin D deficiency has been
10 | continuously proposed to increase the risk of insulin resistance and T2DM, which is also a
11 core pathophysiology of PCOS.
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Comment [FK7]: Same as ref 12

Comment [FK8]: This reference is the same as ref16