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Impact of Vitamin-D Supplementation in PCOS and Non PCOS Patients

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Abstract

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder affecting women in reproductive age group. Vitamin D is thought to influence the development of PCOS through gene transcription. A level of 20ng/ml to 50ng/ml is considered adequate for healthy people. Several studies have reported low level of vitamin D in women with PCOS, with average 25-hydroxy vitamin (25-OHD) levels between 11 and 31ng/ml with majority having values less than 20ng/ml (67 to 85%). impact of vitamin-D supplementation in PCOS and non PCOS patients. An observational, cross-section, analytical study, conducted in the department of Gynecology and Obstetrics, OPD, Birsa Munda GMC Shahdol for 24 months (1st January 2022-1st January 2023) in 60 cases and 30 control. The patients satisfying the inclusion criteria were enrolled in the study following informed written consent. History of the enrolled patients was taken in details with special emphasis on menstrual history, history of excessive weight gain, excessive hair growth and acne. PCOS patients ranged from the ages 18-39 years with a mean (±sd) ae of 27.13±5.59 years. Menstrual irregularities were more common in PCOS women with a mean menstrual cycle per year 5.63±0.78. FBS and Insulin resistance were common in PCOS group with a mean value of 89.03±14.70 gm/dl and 18.15±8.82 IU/ml, respectively. Acne and hirsutism were significantly higher in PCOS women. BMI was more in PCOS group as compared to the Non PCOS group. Mean BMI in PCOS group was 26.89±4.19 kg/m^2. WHR was also found to be more in PCOS women. Mean ratio was 0.91±0.11. The prevalence of Vitamin D deficiency among PCOS women attending the hospital was found to be 11.4%. The risk of deficiency or insufficiency of Vitamin D was 4.75 times more among the patients with PCOS as compared to the patients without PCOS. Vitamin D deficiency was more prevalent among obese women. 57.1% of obese women were deficient in Vitamin D levels. Vitamin D was more prevalent among patients with WHR >0.81. PCOS patients are more likely to develop low vitamin D levels as compared to those without it. As obese PCOS patients are at a greater risk of Vitamin D deficiency and its later morbidity, they should be followed up more frequently. Obese PCOS women should be advised about weight reduction by lifestyle changes and dietary modification with the inclusion of high protein calcium and vitamin D rich diet and exclusion of fried and oily food items. A reasonable regime of exercise should be advised to all PCOS patients especially those with more than normal BMI, in order to increase insulin sensitivity. Vitamin D supplements may be considered in treatment of PCOS women having altered vitamin D levels. Insulin sensitizer may be considered in patients with insulin resistance.

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Key Words
Polycystic ovarian syndrome, vitamin-D, BMI

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INTRODUCTION

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder affecting women in reproductive age group. It was discovered by and named as Stein-Leventhal Syndrome. It is characterized by the presence of chronic history of oligomenorrhoea or anovulation, hyperandrogenism (clinically-hirsutism or acne: biochemical-elevated androgen) and presence of polycystic changes in ovary, along with features of obesity and insulin resistance[1,2].

PCOS is a multifactorial disease with polygenic mode of inheritance. The prevalence of PCOS varies from 5-10% in the reproductive age group[3,4,5] and may present up-18% of this population[6].

Vitamin D is a fat soluble vitamin obtained from diet and can be synthesized endogenously from cholesterol through sunlight induced photochemical reaction. The reaction occurs in the skin and cholesterol is converted to 7- dehydrocholesterol. This metabolite undergoes two successive hydroxylation in the liver and kidney, respectively, to form the final active metabolite which is 1,25 -dihydroxycholecalciferol or vitamin D3[7-17].

A recently identified and potentially important addition to this group of pathophysiology in PCOS is low level of vitamin D in PCOS women. A number of studies have demonstrated association between vitamin D level and various PCOS symptoms including insulin resistance, infertility and hirsutism[18-22].

Deficiency of Vitamin D disrupts the function of body and can result in increased risk of chronic inflammatory disease, cancer, cardiovascular, autoimmune, infectious diseases, depression and chronic pain[23]. Vitamin D is thought to influence the development of PCOS through gene transcription. A level of 20ng/ml to 50ng/ml is considered adequate for healthy people. Several studies have reported low level of vitamin D in women with PCOS, with average 25-hydroxyvitamin (25-OHD) levels between 11 and 31ng/ml(18-20,24, 26-31) with majority having values<20ng/ml (67-85%)[19-21].

Aims: Impact of vitamin-D supplementation in PCOS and non PCOS patients.

MATERIALS AND METHODS

Study Design: An observational, cross-section, analytical study.

Study Settings: Study will be conducted in the department of Gynecology and Obstetrics, OPD, Birsa Munda GMC Shahdol.

Study Population: Women attending Gynaecology OPD are taken randomly. Those diagnosed with PCOS are taken as cases.

Study Period: 24 months (1st January 2022-1st January 2023)

Sample Size: 60 cases and 30 control

The mean (mean±s.d.) level of Vitamin-D of the patients with PCOS (n=80) and without PCOS (n=80) were for 31.0±10.6 ng/ml and 23.12±11.2 ng/ml respectively. The pooled s.d. was s=10.90 and M1-M2= 7.88. Therefore, DSD = 7.88 / 10.90=0.72. From the sample size Table, to detect an effect size of 0.72 there was a need of 30 study subjects per group with 80% power at 5% level of significance. Thus there was a need of 30 study subjects per group with power 80% power. The number of patients in each group was in the ratio 2:1. Thus, the patients with PCOS were 60 and without PCOS were 30. So the required sample size for the study was 90.

Sampling Techniques: Patients of the two groups were selected with the help of computer generated random numbers by the process of randomization.

Inclusion Criteria of Cases: Patients between the age group of 15-45 years will be selected as cases according to Rotterdam criteria i.e. presence of any two of the following three criteria:

- History of chronic oligo/anovulation i.e six or less spontaneous cycles per year.
- Clinical or Biochemical evidence of hyperandrogenemia.
- Clinically it was ascertained by acne or hirsutism.
- Hirsutism being taken into account when Ferriman score- Appendix 1)
- Biochemically hyperandrogenemia was quantified as raised Total Testosterone or DHEAS levels.
- Ultrasound findings showing polycystic ovaries with twelve or more follicles, peripherally arranged, 2-9mm in diameter and/or one or both the ovaries having a volume of 10cc or more.

Exclusion Criteria of Cases: The exclusion criteria will include patients on

- Oral contraceptive pills
- Oral hypoglyceamic agents or insulin
- Smokers
- Patients with congenital adrenal hyperplasia, cushing's disease, thyroid disorder, hyperprolactinemia.

Inclusion Criteria of Control: Women in the age group of 15-45 years with

- 8 or more spontaneous cycles in a year

- No clinical or biochemical evidences of hyperandrogenemia
- Normal ultrasound findings

Exclusion Criteria of Control: The exclusion criteria will include women on

- oral contraceptive pills
- smokers
- Patients with congenital adrenal hyperplasia, cushing's disease, thyroid disorders, hyper-prolactinoma.

Methodology:

- Each subject was explained the details of study and an informed written consent were taken.
- Study proforma was filled for each subject
- History of the enrolled patients was taken in detail with special emphasis on Menstrual History, History of excessive weight gain, excessive hair loss/baldness, increased acne or facial oiliness, excessive hair growth.
- General physical examination for enrolled subject will be done including measurement of the following.
- Weight (in kg measured by simple weighing scale in the OPD)
- Height (in cm measured via stadiometer in the OPD)
- Waist circumference (in cm using simple meter tape at the level of umbilicus)
- Hip circumference (in cm using simple meter tape at the level of iliac crest)
- **Waist:** hip ratio was calculated
- **Blood Pressure :** Systolic/Diastolic in mm Hg (using Sphygmomanometer)
- Assessment of Hirsutism by Ferriman Gallwey score.(30)
- Clinical assessment of acne, acanthosis nigricans.

Calculating the B.M.I of the Patients by the Formula:

- B.M.I = Weight in kg/ (height in meter)^2
- According to the guidelines released jointly by the Health Ministry, the Diabetes Foundation of India (DFI), the All-India Institute of Medical Science (AIIMS), Indian Council of Medical Research (ICMR), the National Institute of Nutrition (NIN) and 20 other health organizations.

BMI Limit for India:

- <18.4-Underweight
- 18.5-22.9-Normal
- 23-24.9-Overweight
- >25-Obese

Statistical Methods: Statistical Analysis was performed with help of Epi Info (TM) 3.5.3. EPI INFO is a trademark of the Centers for Disease Control and Prevention (CDC). Using this software, basic cross-tabulation, inferences and associations were performed. χ2 test was used to test the association of different study variables with the study groups. Corrected chi-square (χ2) test was used for any cell frequency found to be less than zero. Z-test (Standard Normal Deviate) was used to test the significant difference between two proportions. t-test was used to compare the means. Odds ratio with 95% confidence interval was calculated to assess the risk. $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSIONS

There are 60(66.7%) patients were having PCOS and rest 30(33.7%) were not having PCOS. Median age in pcos group is 26yrs and non-pcos group is 27.5yrs. there are

There was significant association between level of Vitamin D and patients of the two groups (p=0.018). All the patients with Vitamin-D deficiency had the PCOS. The prevalence of Vitamin-D deficiency among the patients with PCOS was 11.7%. t-test showed that the mean level of Vitamin D of the patients with PCOS was significantly lower than that of the patients without PCOS. (t_{88} = 2.78., $p<0.001$).

There was significant association between deficiency or insufficiency of Vitamin D and patients of the two groups (p=0.025). The risk of deficiency or insufficiency of Vitamin D was 4.75 times more among the patients with PCOS as compared to the patients without PCOS and the risk was significant [OR-4.75 (1.09, 20.57)., p=0.025].

There was significant association between level of Vitamin D and BMI of the patients (p=0.02). Vitamin-D deficiency was more prevalent among the patients with obesity. there was significant association between level of Vitamin D and WHR of the patients (p=0.003). Vitamin-D deficiency was more prevalent among the patients with WHR>0.81.

we studied 90 newly diagnosed cases of PCOS and compared them with 30 Non-PCOS women, who were taken as control.

A total of 60 PCOS patients were selected for study. Out of the 60 subjects, 7 (11.7%) were <20 years of age, 34 (56.7%) were between 21-30 years of age and 19(31.7%) were above 30 years of age. The mean age (mean±s.d) of the patients was 27.13±5.59 with a range of 18-39 years. The mean age of the control group was 28.36±5.69 with a range of 19-40 years. This

Table 1: Comparison of mean of different base parameters of the patients of the two groups.

Base Parameters	With PCOS (n=60)	Without PCOS (n=30)	t_{88}-test	p-value
Age (years)	27.13±5.59	28.37±5.60	0.98	0.33
Age at Menarche (years)	11.38±1.24	11.83±1.37	1.56	0.12
Duration of Menstrual Cycle (days)	4.03±1.09	4.93±1.24	3.51	<0.001*
Menstrual Cycles per year	5.63±0.78	8.50±0.76	16.45	<0.001*
FG Score	11.80±5.09	3.90±1.19	8.36	<0.001*
BMI (kg/m^2)	26.89±4.19	23.07±2.57	5.33	<0.001*
Waist-Hip Ratio	0.91±0.11	0.73±0.13	6.51	<0.001*
FBS (gm/dl)	89.03±14.70	88.97±14.17	0.02	0.98
PPBS (gm/dl)	110.50±22.36	107.93±16.05	0.55	0.57
Fasting Insulin (IU/ml)	18.15±8.82	9.03±4.56	5.30	<0.001*
HOMA	4.00±2.04	2.00±1.10	4.98	<0.001*
LH-FSH Ratio	1.00±0.88	1.70±0.63	3.85	<0.001*
Testosterone (ng/ml)	6.65±36.31	0.74±0.63	0.88	0.37
DHEAS (mcg/dl)	184.45±105.07	153.98±56.79	1.47	0.14
TSH(mU/l)	2.63±5.2	2.66±1.16	0.85	0.39
Prolactin (ng/ml)	15.48±7.01	13.58±5.59	1.28	0.21
17 OHP	0.66±0.06	NA	NA	NA

shows that even though PCOS is a disorder of reproductive age group, majority of the patients were <30 years of age.

These findings are similar to the prospective study performed by Knochenhauer[4] in south eastern United States, in which they studied 369 reproductive age group women and determined the mean age to be 29.4±7.1 in whites and 31.1±7.8 years in black women respectively.

Similar study performed by Azziz[34] also showed a mean age of 29.1±7.2 years in 400 women they evaluated for PCOS.

In this study it was found that religion had no significant association with the disease.

Among PCOS cases studied, 37 (61.7%) were married and 23 (38.3%) were unmarried. Whereas in the control group 17 (56.7%) were married and 13 (43.3%) were unmarried. There was no significant association between the marital statuses of the two groups. Marital status did not have any effect on the outcome of the disease.

In a study conducted by Ramanand[38] on Indian PCOS patients, of the 120 patients studied, 47 were married and 73 were unmarried. Marital status was not seen to play any role in the disease outcome.

Menstrual irregularities and hyperandrogenemia were more common among PCOS women in the present study. Menstrual cycle per year among Women with PCOS had a mean of 5.63±0.78 cycles per year. Hirsutism and acne were also found more in PCOS women[37]. (61.7%) PCOS women had acne and the mean serum testosterone levels were 6.65±36.31 ng/ml. These findings were similar to the studies conducted by Gambineri[35], A.Majumdar[36] and Giallauria[37].

In my study BMI was seen to have a significant association with PCOS. It was noted that 1(1.7%) was underweight, 4(6.7%) was normal, 23 (38.3%) was overweight and 32 (53.3%) was obese among the PCOS women. The mean BMI of PCOS women was 26.89±4.19. Compared to the control group 1 (3.3%), 19 (63.3%), 3 (10%), 7 (23.3%) belonged to the underweight, normal, overweight and obese category respectively. The mean BMI of the control group was 23.07±2.57.

Studies carried out by Fruzetti[39], Dimanti Kandarakis[40] suggested that obesity is more prevalent in women suffering from PCOS, similar to my study.

The main aim of my study was to show abnormal vitamin D levels in PCOS women as compared to the non PCOS group. It was found that all the patients with Vitamin-D deficiency had the PCOS. The prevalence of Vitamin-D deficiency among the patients with PCOS was 11.7%. *t*-test showed that the mean level of Vitamin D of the patients with PCOS was significantly lower than that of the patients without PCOS. (t_{88} = 2.78., p<0.001).

Among the PCOS women 7 (11.7%) were deficient in Vitamin D, 50 (83.3%) had insufficient level and 3(5%) had optimal levels. The mean levels of vitamin D was 12.57±4.06 ng/ml with a median and range of 12.01ng/ml and 5.40-24.30ng/ml respectively.

Among the control group 24 (80%) had insufficient levels and 6 (20%) had optimal levels of vitamin D. They had a mean of 15.25±4.78 ng/ml and a range of 8.25-25.40ng/ml.

The risk of deficiency or insufficiency of Vitamin D was 4.75 times more among the patients with PCOS as compared to the patients without PCOS and the risk was significant [OR-4.75 (1.09, 20.57)., p=0.025].

A study conducted by Li[24] reported a lower level of vitamin D in women with PCOS compared with women without PCOS (11ng/mlin PCOS group vs 17ng/ml in control group).

A recent study conducted by Wehr[25] also reported lower levels in women with PCOS (n=85) compared to control group (n=145) 25.7ng/ml vs 32ng/ml, respectively, similar to my study.

However, unlike my study, a study conducted by Mahmoudi[26] comparing women with PCOS (n=85) to control group (n=115) with similar age (30years) and BMI (27kg/m^2), found that women with PCOS had

significantly higher vitamin D levels (29.3ng/ml in PCOS vs 19.4 in control group)

Thus there is inconsistency in literature about whether vitamin D levels are similar between women with and without PCOS.

In the present study it was also found that vitamin D levels were lower in PCOS patients more so in the obese group. Among the obese PCOS patient 4 (10.63%) had deficient levels, 35 (89.7%) had insufficient levels and none had optimal levels. Whereas among the overweight PCOS patients 2 (7.7%) had deficient levels, 22 (84.6%) had insufficient levels and 2 (7.7%) had optimal levels.

CONCLUSION

PCOS patients are more likely to develop low vitamin D levels as compared to those without it. As obese PCOS patients are at a greater risk of Vitamin D deficiency and its later morbidity, they should be followed up more frequently. Obese PCOS women should be advised about weight reduction by lifestyle changes and dietary modification with the inclusion of high protein calcium and vitamin D rich diet and exclusion of fried and oily food items.

A reasonable regime of exercise should be advised to all PCOS patients especially those with more than normal BMI, in order to increase insulin sensitivity. Vitamin D supplements may be considered in treatment of PCOS women having altered vitamin D levels. Insulin sensitizer may be considered in patients with insulin resistance.

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