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Vitamin D levels in PCOS women and correlation with metabolic parameters

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Abstract
Background: PCOS is the common endocrine disorder with reproductive and metabolic dysfunction, which may get adversely affected in association with hypovitaminosis D. we studied vitamin D levels in PCOS women and correlation with metabolic parameters.
Materials and Methods: In this cross-sectional study, we enrolled 108 PCOS women, after excluding women, who were on insulin sensitisers, hormone therapy, vitamin D. Detailed history, physical examination findings were noted. Fasting blood sample was analysed for hormonal, biochemical Parameres and OGTT was done as per the standard protocol. Study subjects were categorized based on vitamin D levels into vitamin D deficiency (<20ng/ml), insufficiency (20-30ng/ml), sufficiency (>30ng/ml) groups and were compared for clinical and metabolic parameters using appropriate statistical tests and $p< 0.05$ was considered statistically significant.
Results: study population had a mean age of 24.99±5.07 years with a mean BMI of 28.1±4.67kg/m2. Hypovitaminosis D was found in 85.2% (deficiency in 62.96%, insufficiency in 22.2%) and normal vitamin D levels in 14.8% of the PCOS women. Impaired fasting glucose was found in10.2%, IGT in 15.7% and type2 diabetes in 4.63% women. Triglycerides, LDL-C were significantly higher and HDL-C were lower in women with hypovitaminosis D, with a significant negative correlation with triglycerides and no correlation with other metabolic parameters.
Conclusion: vitamin D deficiency is very common in PCOS women and may exacerbate the metabolic disturbances.

Keywords: Metabolic dysfunction, dyslipidaemia, prediabetes, reproductive dysfunction, obesity

Introduction
PCOS is the most common endocrine disorder affecting 5-10% of women in the reproductive age [1]. It is characterized by hyperandrogenism, chronic anovulation and polycystic ovarian morphology on ultrasonography. Insulin resistance plays an important role in its pathophysiology with clustering of metabolic disturbances and cardiovascular risk factors such as obesity, type 2 diabetes, hypertension and dyslipidemia. PCOS is a heterogenous condition with varying severity of reproductive and metabolic abnormalities with long term health consequences.
Vitamin D plays an essential role in the maintenance of calcium homeostasis and skeletal health. However, there is a growing interest in the past few years to understand its role in cellular metabolism, intra cellular signaling, immunomodulation and maintenance of extra skeletal health, including the reproductive health. Vitamin D deficiency has been reported to be very common across all age groups in India [2]. It has been observed that obese individuals are at higher risk for having hypovitaminosis D and the association between hypovitaminosis D and obesity in PCOS women has been well documented [3, 4, 5].
Evidence suggests that, vitamin D deficiency is associated with insulin resistance and may play a role in the pathogenesis of type 2 diabetes, either affecting insulin sensitivity or β cell function or both [6, 7]. The causative role of insulin resistance in hypertension and dyslipidemia apart from dysglycemia is well-known and has been associated with PCOS and hypovitaminosis D. Consequently, hypovitaminosis D in PCOS women may negatively impact the metabolism further exacerbating the metabolic abnormalities. Hence in this study we attempted to study the vitamin D levels in PCOS women and also to find any correlation with metabolic parameters.

Materials and Methods

Study subjects

In this cross-sectional study, a total of one hundred and eight (n=108) consecutive PCOS women, who were attending endocrinology and gynecology out-patient clinic of tertiary care hospital, aged between 18-30 years, were enrolled after taking written informed consent from each subject. Prior institutional ethical committee approval was obtained. Diagnosis of PCOS was made according to Rotterdam criteria [8], after exclusion of other etiologies like hypothyroidism, hyperprolactinemia, Cushing's syndrome, congenital adrenal hyperplasia, adrenal tumors and drug related disorders. We also excluded PCOS women who were on insulin sensitizers, O.C pills, Vitamin D supplementation, and use of any drug which influences vitamin D, glucose and lipid metabolism (phenytoin, phenobarbital, glucocorticoids). PCOS women were categorized into three groups for comparison, based on vitamin D levels: vit D deficiency (<20 ng/ml), vit D insufficiency (20-30ng/ml), vit. Dsufficiency or normal (>30ng/ml). Hypovitaminosis D refers to both deficiency and insufficiency. Subjects were categorised into normal weight, overweight and obese with a BMI of 18.5-24.9, 25-29.9 and >30 kg/m^2 respectively.

Study methods

A detailed history was recorded from all the participants including demographic details such as age, menstrual history, dietary and drug history. A thorough clinical examination was conducted and standard anthropometric data (height, weight, and waist circumference) were obtained from each subject. Blood pressure was measured twice with mercury sphygmomanometer after PCOS women had been seated for at least 15 min. The average of two measurements of systolic and diastolic blood pressure were used. The body mass index (BMI) is calculated by weight in kilograms divided by the square of height in meters. Waist circumference was measured in a standing position midway between the lower costal margin and the iliac crest.

Assays

Fasting venous blood samples were collected for hormonal assay, oral glucose tolerance test, lipid profile and measurement of vitamin D levels. Blood samples were obtained in the morning between 0800 and 0900 hours after an overnight fast during early follicular phase (day 2 to 5) of a spontaneous or progesterone induced menstrual cycle. All subjects underwent trans abdominal ultrasonography. Hormonal assays were done by Advia centaur Seimens Health care Diagnostics.25(OH) Vitamin D was measured using Chemiluminescence Immunoassay method using Total Vitamin D assay kits of Adviacentaur, and the coefficients of variation for all biochemical tests were <10% in our laboratory.

Plasma glucose levels were determined by the Glucose oxidase method on a glucose semi-auto analyzer. Total cholesterol was determined using the cholesterol esterase method on a semi-automated analyzer. HDL cholesterol was determined using cholesterol esterase method following selective precipitation of apo lipoprotein B containing lipoprotein with a polyanion solution. Triglycerides were determined enzymatically as glycerol on a Hitachi semi-automated chemistry analyzer after hydrolysis with lipase. All lipid assays had intra and inter assay variation of less than 3%. LDL cholesterol was calculated using Friedwald equation: LDL cholesterol = total cholesterol – (HDL + triglycerides/5).

Statistical analysis

Statistical analysis was carried out using R programming software version 3.0.All the values were expressed as Mean ± SD. Unpaired *t*-test and Chi-square test were used for comparative study of the data between the groups. To find the association between Vitamin D and other clinical parameters Pearson's correlation was used, and a two tailed p-value of <0.05 was considered to be statistically significant.

Results

A total of PCOS women had a mean age of24.99 ±5.07 years, with a mean BMI of 28.10±4.67kg/m2 and mean waist circumference of 89.77± 6.22 cm. 30.6% (n=33) of PCOS women were normal weight, whereas 36%(n=39) and 33.3%(n=36) were overweight and obese respectively. A total of 92 PCOS women(85.18%) had hypovitaminosis D(vitamin D levels <30ng/ml), among these 24 PCOS women (22.22%) had vitamin D insufficiency and deficiency was observed in 68 women(62.96%), where as normal vitamin D levels were found in 16 women (14.81%) as shown in figure-1.

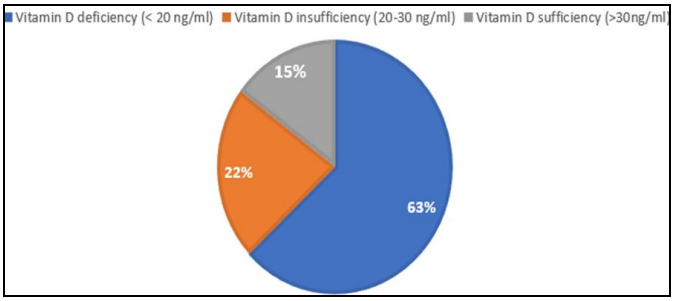

Fig 1: Vitamin D levels in PCOS women

Further analysis of Vitamin D levels in relation to BMI, found that vitamin D deficiency and insufficiency was observed among all the BMI categories, but found numerically more in over weight and obese PCOS women as shown in figure-2

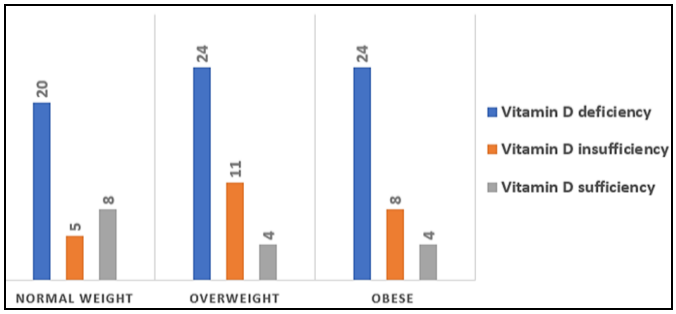

Fig 2: Vitamin D status among normal weight, overweight and obese women with PCOS

The comparison of clinical and biochemical parameters between the vitamin D deficient, insufficient and normal groups is presented in table-1. Fasting blood glucose and 1st hour and 2nd hour blood glucose levels were not significantly different among the vitamin D deficiency, insufficiency and sufficiency groups. However, triglyceridesand LDL cholesterol were significantly lowerand HDL cholesterol levels and vitamin D were significantly higher in vitamin Dsufficient group in comparison with insufficient and deficient group. Correlation of vitamin D levels with various clinical and biochemical parameters is presented in table-2. There was a significant negative correlation

of vitamin D with total cholesterol, triglycerides and waist circumference, and insignificantly with LDL cholesterol. Testosterone levels were significantly higher in insufficiency groupbut did not correlate with vitamin D levels. Impaired fasting glucose (IFG) was found in eleven PCOS women (10.2%), impaired glucose tolerance in seventeen women (15.7%) and type 2 diabetes in five women (4.63%).

Table 1: Comparison of demographic and biochemical parameters among vitamin D deficient, insufficient and sufficient groups.

parameter	Vitamin D deficiency group(<20ng/ml) mean±SD n=68	Vitamin D insufficiency group(20-30ng/ml) mean±SD n=24	Vitamin D sufficiency group(>30ng/ml) mean±SD n=16	P value
Age (years)	24.66±4.94	26.33±5.50	24.38±4.92	0.335
BMI(kg/m2)	27.98±4.60	28.93±4.72	27.35±5.01	0.550
Waist circumference(WC)(cm)	92.94 ±6.28	89.71±6.36	89.04 ±6.01	0.078
SBP(mm of Hg)	107.97 ±6.30	109.17 ±6.43	108.19 ±6.26	0.728
DBP(mm of Hg)	78.13 ±4.31	78.54 ±4.50	78.88 ±3.44	0.790
FBS(mg/dl)	92.44 ±15.06	91.88 ±10.88	86.56 ±8.89	0.292
Ist hour plasma glucose after OGTT(mg/dl)	163.07±45.88	159.54±45.76	144.75±43.59	0.354
2nd hour plasma glucose after OGTT(mg/dl)	124.09±30.67	128.00±42.43	107.69±37.56	0.149
TSH(mIU/L)	3.32 ±1.00	3.24 ±1.07	2.93 ±1.09	0.403
Total cholesterol (TC) (mg/dl)	162.72 ±23.85	155.83 ±27.63	147.56 ±17.47	0.062
Triglycerides (mg/dl)	132.39 ±45.63	110.12 ±38.27	95.47 ±8.05	0.002
HDL-C(mg/dl)	40.12 ±5.99	38.08 ±8.29	45.64 ±4.01	0.001
LDL-C(mg/dl)	98.75 ±22.82	96.86 ±23.90	82.56 ±16.88	0.036
Testosterone (ng/ml)	46.05 ±16.84	57.82 ±21.27	46.26 ±17.61	0.022
HOMA-IR	3.26 ±0.88	3.61 ±1.32	3.23 ±1.14	0.344
Vitamin D(ng/ml)	10.66±4.95	25.07±3.01	33.38±3.34	<0.001

Table 2: Correlation of vitamin D with various clinical and biochemical parameters

parameter	r value	P value
Age	0.11	0.27
BMI	0.04	0.69
WC	-0.22	0.02
SBP	0.06	0.56
DBP	0.10	0.32
TSH	-0.05	0.63
FBS	-0.09	0.38
1st hour glucose	-0.09	0.36
2nd hour glucose	-0.13	0.18
HOMA-IR	0.04	0.68
TC	-0.23	0.02
TG	-0.25	0.01
HDL	0.14	0.14
LDL	-0.16	0.11
Testosterone	0.13	0.19

Discussion

PCOS is a complex heterogenous disorder with long term implications on reproductive and metabolic health. Many studies have shown higher prevalence of varying severity of Vitamin D deficiency among PCOS women [9, 10]. Research in the recent past, has given insights not only in our understanding on the causative role of vitamin D deficiency in the pathogenesis of PCOS, but also in our understanding of pleiotropic role of vitamin D in reproductive as well as metabolic health [10-12].

In our study, 85% of PCOS women had hypovitaminosis D, and majority of them(63%) had vitamin D deficiency with vitamin D levels < 20ng/ml. This is similar to the studies by Hahn *et al.* [4] and, Yildizhan *et al.* [3] who have reported low levels of vitamin D in women with PCOS, with average 25-hydroxy vitamin D levels between 11 and 31ng/ml with the majority having values <20 ng/ml. In a cross-sectional study, Krul-Poel *et al.* [13]. found significantly lower vitamin D concentrations in PCOS women compared to fertile controls. In contrast, Lakshman LR *et al.* from South India reported low vitamin D levels in both PCOS and control women with mean vitamin D levels15.45±7.88ng/ml and 12.83±5.76ng/ml respectively [14]. In another study, prevalence of vitamin D deficiency was equally common among Korean PCOS women and controls [15].

Obesity is a risk factor for hypovitaminosis D. Vitamin D being fat soluble vitamin, is sequestered in the adipose tissue and hence its bioavailability is decreased in obesity [16].

Obese subjects may spend less time outdoors, with inadequate exposer to sunlight, that can lead to insufficient vitamin D biosynthesis in skin. Studiesby Li *et al.* [17] and Wehr *et al.* [5] showed that PCOS women with hypovitaminosis D had significantly higher weight and BMI, showing an inverse relationship between the vitamin D levels and BMI Similarly, Kumar A *et al.* [18] also reported higher prevalence of vitamin D deficiency among women with higher BMI. In this study 69% PCOS women were overweight and obese and we found higher prevalence of vitamin D deficiency among all the BMI categories, though numerically more in overweight and obese PCOS women. This observation might be due to high prevalence of low vitamin D levels in thegeneral population. Dawood AS *et al.* reported low levels of vitamin D in lean PCOS women [19].

Metabolic disturbances are well recognized features of PCOS even at a young age. Insulin resistance is the key pathophysiology in PCOS, hence disturbances in glucose and lipid metabolism are consistent with those found in insulin resistant state. There is conflicting data on the relationship of vitamin D levels with metabolic abnormalities in these women. In our study fasting plasma glucose and 1st hour and 2nd hour post oral glucose tolerance test was insignificantly higher in vitamin D deficient group in comparison with sufficient group. HOMA-IR was increased in 86% of the PCOS women with no significant difference among the different levels of vitamin D groups. We found no significant correlation of vitamin D with HOMA-IR and other glycemic parameters. These findings in our study are strikingly different compared to studies by Patra *et al.* [20] and Wehr *et al.* [5] where they found significantly higher HOMA-IR, fasting insulin in vitamin D deficient PCOS women than sufficient women. In fact, in the Indian study by Patra *et al.*, insulin resistance was most severe in the sub group with vitamin D deficiency. Kumar A *et al.* [18] in their study found no

significant difference in HOMA-IR and other glycemic and metabolic parameters between deficient and sufficient groups and also found no correlation with vitamin D levels, which is consistent with our study. Evidence suggest that PCOS women are at increased risk of developing prediabetes and diabetes [21-23]. Obesity has been shown to negatively impact the glucose metabolism independently and synergistically with insulin resistance [24]. Hypovitaminosis D may accelerate the development of diabetes in obese individuals [25]. In the present study IFG, IGT and type 2 diabetes was found in 10.2%, 15.7% and 4.6% of PCOS women respectively. Ashraf GM *et al.* [26] found, higher prevalence of glucose intolerance and diabetes with IFG in 3.57%, IGT in 29.2% and DM in 8.9% young PCOS women.

Dyslipidemia is common in PCOS with a reported prevalence upto70% [27]. The presence of interrelated risk factors in PCOS, such as insulin resistance, obesity and hyperandrogenemia can explain the increased prevalence but determining the individual risk factor and their intercalated effect on dyslipidemia is difficult[28].Various dyslipidemia patterns have been described in PCOS. Many studies have reported increased triglycerides with decreased HDL cholesterol in PCOS women, consistent with insulin resistant state. Few studies also observed an alteration in LDL-C in PCOS women, both quantitatively and qualitatively with increase in LDL-C and altered particle size [29-32].

In the present study with majority of PCOS women being overweight and obese, we found significantly increased triglyceride levels, LDL -C with lower HDL-C levels among hypovitaminosis D PCOS women in comparison with vitamin D sufficient PCOS women with a significant negative correlation of triglyceride levels with vitamin D levels. Our study findings are consistent with the earlier studies by Diamanti-Kandarakis *et al.* [28] and Valkenburg O *et al.* [30]. Kim JJ *et al.* [33] in their review on dyslipidemia in PCOS women, reported that substantially increased prevalence of dyslipidemia even in young non obese Korean PCOS women. Arecent meta-analysis on lipid abnormalities in PCOS women by Wild *et al.* [34] reported increased triglycerides, LDL-C, non HDL-C and lower HDL-C levels.

In our study waist circumference, total cholesterol and triglycerides showed an inverse correlation, however, none of the glycemic parameters have shown correlation with vitamin D levels. Which is different from the previous studies [13, 18, 35].

The observed difference in our study could be due to small sample size. The limitations of our study are small sample size, lack of estimating body fat mass.

Conclusion

Our study found higher prevalence of vitamin D deficiency not only among over weight, obese but also among normal weight PCOS women and showed an inverse relation with lipid parameters, hence may exacerbate the metabolic abnormalities. Further, properly designed larger studies with adequate sample size are required to confirm the findings.

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