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RESEARCH ARTICLE

THE ROLE OF VITAMIN D IN POLYCYSTIC OVARY SYNDROME AND ITS METABOLIC DYSREGULATIONS: A CASE CONTROL STUDY

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting the women of reproductive age. Vitamin D deficiency may have a role in etiopathogenesis of PCOS and its metabolic and endocrine dysregulations. Various studies have shown conflicting results regarding role of vitamin D in PCOS. Therefore, the aim of this study was to find out vitamin D status in PCOS and its association with various metabolic dysregulations.

Methods: This single center prospective case control study included 100 females with PCOS and 100 controls. Participates were evaluated for vitamin D status. Correlation of vitamin D with metabolic dysregulations in PCOS was then done.

Results: Vitamin D deficiency was seen in 102 (51%) participants. Vitamin D levels were lower in PCOS group compared to control group (20.9 ± 10.2 vs 27.0 ± 15.6, P value 0.001). Prevalence of Vitamin D deficiency was also more in PCOS group compared to control group (59% vs 43 %, P value 0.024).Vitamin D levels were negatively correlated with BMI of PCOS subjects. However, there was no other significant association between Vitamin D and other metabolic parameters in PCOS subjects.

Conclusion: This study highlights that there is high prevalence of vitamin D deficiency among women with PCOS and suggests the inverse association between vitamin D and BMI. The findings of our study have potentially important public health implications as the vitamin D supplementation can ameliorate insulin resistance which is the main cause for PCOS.

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common female endocrine disorder, affecting up to 18% of women of reproductive age (March *et al*., 2010). It is characterized by the presence of polycystic ovaries, menstrual dysfunction, infertility and hyperandrogenism (Dunaif, 1997). It is associated with an increased incidence of cardiovascular disease (CVD) risk factors, like increased prevalence of subclinical atherosclerosis, type 2 diabetes, dyslipidemia, insulin resistance and impaired glucose tolerance (Talbott *et al*., 2004; Alexander *et al*., 2009). Vitamin D regulates the expression of 229 genes in more than 30 different tissues of the body (Holick *et al*., 2007; Ramagopalan *et al*., 2010). So, the deficiency of this vitamin has varied manifestations.

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Besides its role in calcium and bone metabolism, it deficiency cause a wide range of skeletal and extra-skeletal effects, with impact on glucose homeostasis, cardiovascular disease, cancer, autoimmune diseases and psychological disorders (Holick *et al*., 2007; Dobnig *et al*., 2008; Freedman *et al*., 2007; Rasheed *et al*., 2013). Vitamin D decreases insulin resistances by enhancing insulin synthesis, increasing insulin receptor expression and suppressing proinflammatory cytokines (Teegarden *et al*., 2009). Metabolic and endocrine dysfunctions in women may be mediated by insulin resistance. It has been shown that the insulin resistance has a central role in the pathogenesis of PCOS and 50–80% of PCOS patients suffer from insulin resistance syndrome (De Ugarte *et al*., 2005). Considering this association between Vitamin D, Insulin resistance and PCOS, many studies have been done on vitamin D status in PCOS and its association with various metabolic parameters in PCOS. Evidence suggests that Vitamin D levels are similar in women with and without PCOS (Panidis *et al*., 2005; Li *et al*., 2011) however; some studies suggest lower levels (Wehr *et al*., 2011; Lerchbaum *et al*., 2012) in PCOS

group compared to control. In fact, there is one report which says that women with PCOS have significantly higher vitamin D levels compared to control women with similar age and BMI (Mahmoudi *et al*., 2010). Moreover, several studies have investigated an association between vitamin D status and metabolic dysregulations in PCOS. Low vitamin D levels in PCOS is thought to be related to metabolic risk factors such as insulin resistance, dyslipidemia, high blood pressure and high blood glucose (Wehr *et al*., 2009; Li *et al*., 2011). Vitamin D supplementation may have a beneficial effect on insulin resistance, blood glucose and triglycerides levels in PCOS (Selimoglu *et al*., 2010; Wehr *et al*., 2011). Jinn Ju et al. (2014) found no association between vitamin D and metabolic parameters. So, there is no consensus on Vitamin D status and its association with various metabolic abnormalities in Women with PCOS. Therefore, the objective of this study was to determine whether serum vitamin D levels were different in women with PCOS compared to women without PCOS and to determine whether vitamin D deficiency is associated with metabolic dysregulations in women with PCOS. This is a first study of its kind, where large number of participants were enrolled in a prospective case control study.

Table 1. Baseline characteristics of PCOS patients and matched controls

Variable	PCOS (n=100)	Controls (n=100)	P Value	Remarks
Age	28.7±7.3	29.3±7.0	0.593	NS
BMI	22.3±3.3	21.9±3.1	0.451	NS
Insulin uIU/mL	7.9±4.2	7.1±3.8	0.153	NS
HOMA-IR	2.2 ±1.7	1.9 ±1.5	0.265	NS
Blood Glucose mg/dL	83.3 ±15.7	80.7 ±14.2	0.240	NS
Triglycerides mg/dL	101.7 ±31.4	99.4 ±30.2	0.603	NS
Total Cholesterol mg/dL	163.4 ±46.2	165.9 ±45.9	0.691	NS
HDL mg/dL	43.8 ±9.2	44.7 ±8.8	0.491	NS
LDL mg/dL	103.3 ±20.8	100.9 ±17.2	0.372	NS

Values are presented as mean±SD. BMI: Body mass index, HOMA-IR: Homeostatic model assessment for insulin resistance, HDL: high-density lipoprotein, LDL: low-density lipoprotein, NS: Not significant.

Table 2. Comparison of vitamin D levels between two groups

	PCOS(n=100)	Controls(n=100)	P Value	Remarks
Vitamin D Levels (ng/mL)	20.97±10.2	27.04±15.6	0.001	S

Values are presented as mean±SD, S: Significant.

Table 3. Comparison of Vitamin D Deficiency between two groups

	PCOS(n=100)	Controls(n=100)	P Value	Remarks
Vitamin D Deficiency (<20 ng/mL)	59(59.0%)	43(43.0%)	0.024	S

Values are presented as n (%), S: Significant.

Table 4. Correlation of Vitamin D levels with metabolic parameters in PCOS patients

Variable	R	P Value	Remarks
Age	- 0.067	0.510	NS
BMI	- 0.222	0.027	S
Insulin uIU/mL	0.105	0.297	NS
HOMA-IR	0.115	0.255	NS
Blood Glucose mg/dL	0.056	0.580	NS
Triglycerides mg/dL	0.012	0.906	NS
Total Cholesterol mg/dL	0.019	0.850	NS
HDL mg/dL	0.177	0.790	NS
LDL mg/dL	0.013	0.896	NS

Abbreviations; BMI: Body mass index, HOMA-IR: Homeostatic model assessment for insulin resistance, HDL: high-density lipoprotein, LDL: low-density lipoprotein, NS: Not significant, S: Significant.

MATERIALS AND METHODS

This prospective single center case control study was conducted in the department of medicine SKIMS medical college & hospitals, Srinagar, India over a period of two years from December 2014 to December 2016. The study was approved by clinical research and ethics committee of institute.100females with PCOS and 100 controls were included in the study. PCOS was diagnosed on the basis of Rotterdam criteria. This criterion consists oligo/anovulation, clinical/biochemical hyperandrogenism and polycystic ovaries on ultrasound. 100 women matched with cases based on age (± 2Yr) and body mass index (± 1 kg/m^2) were taken as controls. Controls were not having any element of Rotterdam criteria. Inclusion criteria for the study were females aged 18-40 years. Participants with other endocrine disorders like congenital adrenal hyperplasia, thyroid disorders, androgen-secreting tumors, Cushing's syndrome and hyperprolactinemia were excluded as were the participants with history of calcium and vitamin D intake in preceding three months. All participates provided a signed informed consent. Data regarding the age, body mass index (BMI), vitamin D levels, fasting blood glucose, insulin levels, insulin resistance, triglycerides, total cholesterol, high density lipoprotein and low-density lipoprotein were collected from participants. Fasting blood sample was taken for blood chemistry. Body mass index (BMI) was calculated as = kg/m^2. The insulin resistance was calculated by homeostasis model assessment (HOMA) as: [Fasting Insulin (uIU/mL) × Fasting Glucose (mg/dL.)]/405. Vitamin D deficiency was indicated as ≤ 20 ng/ml.

Statistical analysis

Statistical analysis was performed using SPSS 20. The difference in mean levels of vitamin D and metabolic parameters between PCOS and control subjects were

determined by independent t-test. Prevalence of vitamin D deficiency between cases and controls were done by Chi square test. The Pearson Correlation test was done to evaluate the relationship between metabolic parameters and vitamin D levels in PCOS group. Results were considered significant with a P-value of less than 0.05.

RESULTS

200 participants were taken into the study from outpatient clinics. The base line characteristics of participants in two groups were comparable (Tab 1). Vitamin D deficiency was seen in 102 (51%) participants. Vitamin D levels were lower in PCOS group compared to control group (20.9 ± 10.2 vs 27.0 ± 15.6). This was statistically significant with P value 0.001(Tab 2). Prevalence of Vitamin D deficiency was also more in PCOS group compared to control group.59%of PCOS participants were vitamin D deficient compared to 43% of control participants. This was again statistically significant with P value of 0.024 (Tab. 3). Vitamin D levels were negatively correlated with BMI of PCOS subjects. However, there was no other significant association between Vitamin D and other metabolic parameters in PCOS subjects (Tab 4).

DISCUSSION

Vitamin D deficiency is a global health issue and so is the PCOS in women of reproductive age. Insulin resistance has a central role in pathogenesis of PCOS and its metabolic disturbances (Kumar *et al*., 2015). Vitamin D may enhance insulin sensitivity (Teegarden *et al*., 2009), so its deficiency can promote and exacerbate clinical features of PCOS. Various studies have been done over years to find association between vitamin D and PCOS. However, these studies have shown conflicting results. Till date no clear relationship between vitamin D and PCOS have been found. Our study is the principal prospective case control study to determine whether serum vitamin D levels differ in women with PCOS and matched controls and determine whether vitamin D deficiency is associated metabolic dysregulations in women with PCOS. Wehr, *et al*. (2011) found lower vitamin D levels in women with PCOS compared to controls (25.7 vs. 32.0 ng/mL). Mazloomi *et al*. (2012) also reported lower vitamin D levels in PCOS group compared to control group (30 ± 2.99 nmol/L versus 43.7 ± 5.2 nmol/L).

Similarly, in study by Elida, *et al*. (Elida Sidabutar *et al*., 2016), vitamin D levels were significantly lower in women with PCOS compared to controls. However various other studies suggest that serum vitamin D levels are similar in women with and without PCOS (Panidis *et al*., 2005; Mahmoudi *et al*., 2008). Paninis *et al*. (2005) observed significant negative effect of vitamin D on increased body weight, but no association with PCOS was observed. Similarly Jinn Ju, *et al*. (Jin Ju Kim *et al*., 2014) found vitamin D levels(19.6 ± 6.6 vs. 20.1 ± 7.4, P =0.696) and prevalence of vitamin D deficiency does not differ between PCOS patients and controls (57.9% vs. 56.5%, P=0.880). In fact, Mahmoodi, *et al*. (2008) reported that women with PCOS have significantly higher vitamin D levels compared to control women with similar age and BMI (39.80 vs 29·3, P =0.035). Various studies have been done regarding association of vitamin D and metabolic parameters in PCOS and the results are conflicting. Some studies are showing association between vitamin D and metabolic parameters in PCOS while others are showing none. Li, *et al*. (2011) found that vitamin D and metabolic parameters in PCOS are significantly related while Jinn Ju, *et al*. (2014) found no association. Wehr, *et al*. (2009) also found significant inverse association between vitamin D and BMI. Our study showed significant differences in vitamin D levels between PCOS and control groups(20.9±10.2 vs 27.0 ± 15.6, P- 0.001) and the prevalence of vitamin D deficiency was also more in PCOS group compared to control group (59% vs 43%, P- 0.024). Vitamin D showed significant negative correlation with BMI.

Conclusion

This study highlights that there is high prevalence of vitamin D deficiency among women with PCOS and suggests the inverse association between vitamin D and BMI. The findings of our study have potentially important public health implications as the vitamin D supplementation can ameliorate insulin resistance which is the main cause for PCOS. However, because of the great diversity in results regarding role of vitamin D in PCOS no definite conclusion can be drawn. Further studies are needed to establish a cause-effect relationship between vitamin D, PCOS and its metabolic consequence and to evaluate the use of vitamin D3 supplementation in PCOS.

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