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Original Article

Biochemistry Section

Hypovitaminosis D and Associated Cardiometabolic Risk in Women with PCOS

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ABSTRACT

Introduction: Women with Polycystic Ovary Syndrome (PCOS) frequently suffer from metabolic disturbances like insulin resistance, hypertension and atherogenic dyslipidemia. Accumulating evidences suggest that Vitamin D deficiency is common in PCOS and may be associated with metabolic and endocrinal dysfunctions in PCOS. Thus women with PCOS may be at elevated risk of cardiovascular disease.

Aim: Present study aims to evaluate Vitamin D status and to assess its association with metabolic and endocrinal dysregulations in women with PCOS, which might help in early identification and prevention of future symptomatic cardiac disease.

Materials and Methods: A total of 44 women with PCOS, diagnosed by Rotterdam criteria and 45 healthy control without PCOS, were evaluated for Vitamin D and cardiometabolic risk factors, including fasting plasma glucose, insulin resistance, dyslipidemia, hs-CRP. That apart, several endocrinal parameters of hyperandrogenism were also examined. Several correlation studies were determined to establish the role of Vitamin D as a cardiometabolic risk factor in PCOS.

Results: Results were expressed as mean±SD and were statistically analysed using SPSS software version 16, unpaired student's t-test and Pearson's correlation coefficient. We found lower levels of Vitamin D, which was statistically significant as compared to healthy controls. Hyperinsulinemia, rise in insulin resistance and marked dyslipidemia was observed in the present study. Another relevant finding was significant correlation of Vitamin D with insulin and Homeostatic Model of Assessment-Insulin Resistance Index (HOMA-IR).

Conclusion: Hypovitaminosis D was prevalent in PCOS. This was related to metabolic and hormonal disorders in PCOS. Possibly this combined with impaired fasting glucose, IR and dyslipidemia, could account for Cardio vascular risks in PCOS. Further prospective observational studies and randomized control trials are required to explore the above hypothesis.

Keywords: Dyslipidemia, Insulin resistance, Polycystic ovary syndrome, Vitamin D

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a highly prevalent endocrinal disorder among women of reproductive age group, which is characterized by anovulation, oligomenorrhea or amenorrhea, hyperandrogenism and infertility [1]. Insulin resistance (IR) and compensatory hyperinsulinemia appear to play a major role in etiopathogenesis of PCOS and might lead to a number of co-morbidities like Metabolic Syndrome (MS) [2]. MS refers to a clustering of at least three of the following medical conditions: central obesity, elevated blood pressure, elevated fasting plasma, high triglycerides, and low High-Density Lipoprotein (HDL) levels. MS is associated with the risk of developing atherosclerotic Cardiovascular Disease (CVD) and type 2 Diabetes Mellitus [3]. PCOS and MS are two distinct but inter-related entities as MS is more common in females with PCOS in presence of IR and visceral obesity [4]. Several studies have highlighted the risk of cardiovascular co-morbidities, such as diabetes, hypertension and dyslipidemia, in PCOS cases [3,4]. Thus they may represent largest group of young women at higher risk for possible development of early onset of cardiovascular disease, diagnosed many years before the onset of symptoms [5].

Vitamin D (Vit D) is known for its primary role in bone and mineral homeostasis. However recent evidence demonstrates its beneficial role in a spectrum of pathologic process including Diabetes Mellitus (DM), Cardiovascular Disease (CVD), cancer and immune disorders [6,7]. With increasing data of low level of Vit D prevalence in general population across India and with growing urbanization, Vit D insufficiency is emerging as an unrecognized risk factor for CVD [8,9]. Moreover, presence of Vit D receptors in vascular smooth muscle and endothelium might support the above hypothesis. There are reports of association of Vit D with hyperandrogenism, which predominates in PCOS [10]. that apart, recent clinical studies have established association of low Vit D status with metabolic disturbances in PCOS [11]. This clearly hypothesizes a link between hypovitaminosis D and metabolic syndrome, prevailing in PCOS, with elevated cardiovascular mortality.

In an attempt to improve global cardiovascular disease prediction, significant efforts have been focused on recognition of these cardio-metabolic risks, which requires high level of awareness along with early and regular screening. So considering the above points the present study was planned to evaluate serum Vitamin D along with other metabolic parameters in PCOS, which provides evidence for treatment as well as for prevention of future symptomatic CVD in PCOS. Various correlations were also studied to establish the role of Vitamin D as a new risk factor for CVD PCOS.

MATERIALS AND METHODS

Proposed research work was carried out in Department of Biochemistry, Kalinga Institute of Medical Science, Odisha, India. This case control study is single center, prospective and conducted in a tertiary health centre over a period of eight months. Selection of cases was done on the basis of standard diagnostic criteria, as per Rotterdam [12]. Diagnosis of PCOS was made from the history of chronic oligomenorrhoea (cycle length>35days, or less than 9 cycle/year), amenorrhoea (cycle length>12weeks), infertility, hyperandrogenism (hirsutism with Ferriman-Gallwey(FG) score >/= 6, acne, alopecia and/or elevated androgen level) and with relevant ultrasonographic findings [12]. Patients with other similar clinical presentations like congenital adrenal hyperplasia, Cushing syndrome, androgen secreting tumours and hyperprolactinemia were excluded from the study group by specific laboratory analysis. Following exclusion criteria were kept in consideration: Women with prior history of glucose intolerance (including

gestational DM or NIDDM), hypertension, thyroid dysfunction, angina, myocardial infarction, coronary arterial disease, any other vascular disease, renal disease, liver disease, brain ischemia, inflammatory disease and recent infection. The study participants did not take any medication known to affect endocrine parameters and biochemical profile for at least three months prior to the study. None of them had been treated with oral contraceptive pills or anti-androgen drugs in the last year. After carefully considering inclusion and exclusion criteria, 44 young women, within age group 18-35 years, diagnosed to have PCOS were enrolled in this study after giving informed consent. Forty five age, BMI matched healthy individuals, selected from para-medical staff were selected as controls. They had normal menstrual cycle with no evidence of hyperandrogenism. They were not receiving any medication and were not diabetic.

Standard anthropometric data (height, weight, waist and hip circumference), systolic and diastolic blood pressure were recorded from both study group and controls. Hirsutism was quantified with modified F-G score. Blood samples were collected after overnight fast preferably in early follicular phase of menstrual cycle (2^{nd} or 3^{rd} day) from both cases and controls. Fasting blood samples were analysed for Vitamin D, high sensitive-C Reactive Protein (hs-CRP), Fasting plasma glucose (FPG), Fasting serum insulin, HOMA-IR (Homeostasis Model of Assessment: fasting plasma insulin in μ U/ml × fasting plasma glucose in mmol/L divided by 22.5) [13], hormones like Total Testosterone (TT), Follicle-Stimulating Hormone and Luteinizing Hormone ratio (FSH/LH) and lipid profile {Total Cholesterol (TC), Triglycerides (TG), High Density Lipoprotein(HDL), Very Low Density Lipoprotein(VLDL)}. Serum 25(OH) D is the most abundant circulatory precursor of active Vit D and is most widely accepted indicator of Vit D status. This was done by electrochemiluminescent (ECL, e411 Cobas) on Roche ELECSYS, which is a fully automated, random access system for immunoassay analysis with increased sensitivity and superior analytical performance. Level of 25(OH) D 30 ng/ml is considered to be sufficient. Levels 20-29ng/ml is insufficient, but levels less than that is deficiency and < 12ng/ml is considered as severe deficiency [6]. Hormones like serum insulin, TT and LH/FSH ratio were also done by e411 Cobas of Roche ELECSYS using ECL technology. Serum fasting glucose, lipid profile, and hs-CRP were estimated in fully automated analyser (COBAS INTEGRA 400 plus by Roche) using respective kits.

STATISTICAL ANALYSIS

Results were expressed as mean±SD and were statistically analysed using software SPSS version 16 and MS excel. Student unpaired t-test was used to analyse difference between the two groups. Relationships between the variables were evaluated using Pearson's correlation coefficient. A p-value < 0.05 was considered to be statistically significant.

RESULTS

[Table/Fig-1] shows distribution of PCOS patients based on their 25 (OH) D status which observed, 7 cases (16%) with insufficiency, 28 cases (64%) with deficiency and 9 cases (20%) with severe deficiency of Vit D. [Table/Fig-2] depicts the comparison of different anthropometric and biochemical parameters between PCOS cases and healthy controls, which was as follow: Vit D levels were significantly lower in PCOS cases (p<0.05) as compared to healthy controls (15.31±2.11ng/ml vs 28.3±3.5ng/ml). In addition, marked dyslipidemia was observed in PCOS cases. Moreover a significant higher level of hs-CRP was noted in study cases. [Table/Fig-3] revealed a statistically significant (p<0.001) rise in fasting serum insulin, HOMA-IR, TT and LH/FSH ratio in PCOS cases. [Table/Fig-4] shows the correlation of 25(OH) D with other biochemical and hormonal parameters in PCOS patients. We found significant negative correlation between Vit D and HOMA-IR (r = - 0.213, p<0.05), hyperinsulinemia (r = - 0.173, p<0.05). Significant positive correlation was documented between Vit D and HDL cholesterol (r = 0.312, p<0.05). Current study could not find association of Vit D with hyperandrogenism (TT) and BMI.

Sl no.	Vit D Level (ng/ml)	No. of cases	Percentage
1	20 -29	7	16
2	12 -20	28	64
3	< 12	9	20

[Table/Fig-1]: Distribution of PCOS patients as per Vitamin D status.

Sl no.	Parameters	Control (n=45)	PCOS (n=44)	p-value
1	BMI (Kg/m)	23.17 ±2.35	24.35 ±2.87	NS
2	FG Score	0.14 ±0.21	12.13 ±2.44	< 0.001
3	FPG (mg/dl)	82.51 ±3.1	89.2 ±8.67	< 0.001
4	hs CRP (mg/l)	2.72±1.78	4.21 ±3.5	< 0.05
5	Total Cholestral(mg/dl)	140.27 ±15.10	185.51 ±26.31	< 0.001
6	TG (mg/dl)	115.09 ±24.46	144.12 ±53.4	< 0.001
7	LDL (mg/dl)	67.78 ±15.20	93.78 ±23.17	NS
8	HDL (mg/dl)	49.8 ±4.84	43.71 ±5.72	NS
9	VLDL (mg/dl)	22.96 ±4.91	28.62 ±10.14	NS
10	25(OH) D (mg/dl)	28.3 ±3.5	15.31 ±2.11	< 0.05

[Table/Fig-2]: Comparison of clinical and biochemical parameters in control and cases.

SL No	Parameter	Control (n=45)	PCOS (n=44)	p-value
1	Serum insulin (μlU/ml)	8.03 ±3.16	14.71 ±7.18	< 0.001
2	HOMA-IR	1.25 ±0.73	3.35 ±1.17	< 0.001
3	Serum TT (ng/ml)	0.43 ±0.12	1.26 ±0.73	< 0.001
4	Serum LH/FSH	1.04 ±0.61	2.31 ±0.85	< 0.001

[Table/Fig-3]: Comparison of endocrinal parameters in control and PCOS cases.

25(OH) D in PCOS		
Parameters	r Value	p
HOMA-IR	- 0.213	<0.05
Insulin	- 0.173	<0.05
HDL	0.312	<0.05
TT	- 0.07	0.55
FPG	- 0.56	0.52
BMI	- 0.63	0.50

[Table/Fig-4]: Correlation 0f 25(OH) D with biochemical and hormonal parameters in PCOS cases.

DISCUSSION

PCOS has been a subject of research and debate over past six decades. IR accompanied by compensatory hyperinsulinemia plays a vital role in PCOS cases by increasing ovarian androgen production and by decreasing sex hormone binding globulin concentration. Accumulating evidences suggest that Vitamin D deficiency is emerging as a new risk factor for CVD [14-16]. Although Vit D deficiency is often clinically unrecognizable, it is associated with IR, menstrual irregularities, hirsutism, hyperandrogenism, obesity and elevated cardiovascular risk factors, besides the classical diseases such as rickets, osteomalacia and osteoporosis [17]. Our study observed, 7 PCOS cases (16%) with Vit D insufficiency, 28 cases (64%) with deficiency and 9 cases (20%) with severe deficiency. So we demonstrated that women with PCOS are often Vit D deficient. This proportion is lower in other studies, like 26.7% in PCOS patients in Germany [10], 2.9% in Austria [11]. Vit D levels were observed to be significantly lower in PCOS cases (p<0.05) as compared to healthy controls (15.31±2.11ng/ml vs 28.3±3.5ng/ml). This was similar to many accumulating evidences [10,18,19], which reported of lower levels of 25(OH) D in women with PCOS

with average levels between 11-31ng/ml with the majority having values <20ng/ml in 70-80% of cases. Limited studies have also examined higher levels of 25(OH) D in overweight/obese PCOS cases, which is likely to compensate for IR [20]. Yet some researchers have shown conflicting reports of apparently normal vit D levels in PCOS cases [21], which may be attributed to small sample size that could have limited the ability for correlation study and therefore conclusion, cannot be definitive. Many investigators claim a beneficial effect of Vit D supplementation on menstrual dysfunction [22]. This points toward relationship between Vit D and reproductive function. Furthermore, Pittas et al., analysed the role of Vit D on different cardiometabolic outcome where it was found to be the cause and aetiology [14]. So it is hypothesized to play a vital role in exacerbating symptoms of PCOS. Although growing evidences linking hypovitaminosis and CVD are consistent, the exact threshold at which risk of CVD increases, is still not clear. While the exact mechanism underlying low Vit D status remains unclear, gene transcription is thought to play a vital role in influencing the development of PCOS [23]. Marked rise in fasting serum insulin and HOMA-IR in PCOS cases [Table/Fig-3] in our study was in agreement with other studies showing the role of hyperinsulinemia in pathogenesis of PCOS [24]. A significant high level of serum TT in PCOS cases ($p<0.001$) may be due to excess ovarian production of androgen, which is central to the diagnosis of PCOS. In addition marked dyslipidemia was observed in PCOS cases [Table/Fig-2], which may be attributed to hyperinsulinemia stimulating synthesis and secraetion of VLDL in liver resulting in hypertriglyceredimia, which in turn enhances postprandial accumulation of lipoproteins with lowering of HDL cholesterol [25]. Present study found significantly higher level of hs-CRP in study participants as compared to controls, pointing towards a higher inflammatory response prevailing in PCOS. Recent studies have reported that CRP, one of the inflammatory markers, may account for prospective identification of young PCOS women prone to develop CVD in future [26]. Insulin has a physiologic inhibitory effect on acute phase protein synthesis in liver and hepatic IR is expected to lead to increased synthesis of hs-CRP [25,27].

One relevant finding of the present study was a significant negative correlation between Vit D and HOMA-IR ($r = -0.213$, $p<0.05$), hyperinsulinemia ($r = -0.173$, $p<0.05$). So low Vit D status is suspected to be a risk factor for impaired glucose tolerance, insulin resistance and type 2 DM. While the exact mechanism is not still clear, there are several research studies supporting the above relevant finding [10,11]. The potential mechanism by which Vit D can affect glucose metabolism could be the result of direct or indirect action of 25 (OH) D which are as follows: i) Direct stimulation of insulin release through the expression of Vit D receptor in pancreatic beta cells; ii) Enhancing insulin responsiveness for glucose transport; iii) Suppression of the release of pro-inflammatory cytokines that are believed to mediate IR [28]. But still it remains unclear whether Vit D and IR are casually interrelated or whether they constitute two independent characteristics in women with PCOS. Nevertheless a recent data suggested the beneficial role of Vit D in improving glucose metabolism and menstrual frequency, observed after supplementation [29]. Positive correlation was documented between Vit D and HDL cholesterol ($r = 0.312$, $p<0.05$), which was supporting the studies by Hahn et al., and Wehr et al., [10,11]. Multiple cellular and molecular mechanisms have been proposed to support the fact that Vit D receptor gene regulates 3% of human genome including genes that are crucial for glucose and lipid metabolism [6,30]. Current study could not find a significant correlation between Vit D and hyperandrogenism. On the contrary, there are conflicting reports justifying the above association [31]. Moreover several studies also suggested no change in testosterone level after therapeutic implementation of Vit D [29,32]. However, considering the inverse association of 25 (OH) D with metabolic disturbances in PCOS in the present study, regular screening is warranted. Consequently, whether treatment regimens directed towards lowering CVD risk factors should be more aggressive for those PCOS women with decreased Vit D levels, awaits further clinical experience. Given that millions are affected by PCOS, if substantiated by randomoized controlled studies, suggest more public implications.

LIMITATION

Our study is limited by the small sample size. In order to understand the casual relationship between Vit D and metabolic syndrome and cardiovascular risk factor, longitudinal studies are required. In order to provide high quality evidence, additional CVD risk markers like homocysteine, lipo-protein (a) and fibrinogen will be added in our future research work.

CONCLUSION

Present study demonstrated that Vitamin D deficiency is prevalent in women Polycystic Ovary Syndrome, with 60-70% of PCOS having serum 25(0H) D concentration <20ng/ml. Moreover, current evidence suggested an inverse association between Vitamin D status and metabolic disturbances in PCOS. Both combined together could account for cardio vascular risk in PCOS. Despite lack of well-conducted clinical trials, a positive association between Vit D deficiency and CVD seems to be true. So there may be place for Vit D supplementation in alleviating symptoms of PCOS as well as to avoid CVS risk factors. Future research and adequately powered randomized placebo controlled double blind studies of Vit D supplementation in women affected by PCOS is warranted to explore the effect. Till then regular screening of women at high risk of Vit D deficiency could be considered to reduce risk of cardiovascular disease in PCOS.

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