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Saumya Prasad
Obstetrics & Gynaecology, Maulana Azad Medical College & Lok Nayak Hospital, Delhi University, New Delhi, India

Pratima Mittal
Vardhman Mahavir Medical College & Safdarjung Hospital, I P University, New Delhi, India

Rekha Bharti
Vardhman Mahavir Medical College & Safdarjung Hospital, I P University, New Delhi, India

Jyotsna Suri
Vardhman Mahavir Medical College & Safdarjung Hospital, I P University, New Delhi, India

Corresponding Author:
Saumya Prasad
Obstetrics & Gynaecology, Maulana Azad Medical College & Lok Nayak Hospital, Delhi University, New Delhi, India

Correlation of vitamin D and Parathyroid hormone with insulin resistance in PCOS women

Saumya Prasad, Pratima Mittal, Rekha Bharti and Jyotsna Suri

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Abstract
Objectives: To investigate the relation of 25, hydroxyvitamin D concentration and parathyroid hormone with insulin resistance in PCOS women.
Methods: A cross-sectional study was conducted on 50 PCOS (Rotterdam's criteria) women. Concentrations of 25, hydroxyvitamin D and PTH were measured along with serum levels of fasting sugar and insulin. The homeostasis model assessment index was used as the insulin resistance index.
Results: Total prevalence of vitamin D deficiency (<20ng/ml) was found to be 84% while increased parathyroid hormone level was observed in 64%. There was significant negative correlation between vitamin D deficiency and HOMA-IR (r=-0.67, p<0.01). Positive association was found between increased PTH levels (normal levels: 13.9- 38.3pg/ml) and HOMA-IR.
Conclusion: Vitamin D deficiency and high parathyroid levels are associated with glucose intolerance in PCOS women. Strong correlation between vitamin D deficiency and insulin resistance in PCOS women may suggest that normalization of vitamin D levels may correct insulin resistance.

Keywords: PCOS, Vitamin D, Parathyroid hormone, insulin resistance, HOMA-IR

1. Introduction
Polycystic ovary syndrome (PCOS) is the most common endocrine disorder presenting in 15% to 18% in women of reproductive age [1].
PCOS was first recognized by Stein and Leventhal in 1935 and hence was originally also referred as Stein-Leventhal syndrome. They found an association between polycystic ovaries, signs of hirsutism and amenorrhea [2].
As per the European and American societies for Reproduction & Embryology, the frequently described Rotterdam's criteria for the diagnosis of PCOS includes the presence of two or more factors out of three i.e. chronic anovulation, clinical or biochemical signs of hyperandrogenism and ultrasonographic evidence of polycystic ovaries [3].
Excess adipose tissue in obese women with PCOS leads to insulin resistance. Obesity results in reduced levels of adiponectin, in association with elevated circulating levels of free fatty acids, favours a state of insulin resistance. Insulin resistance in lean women who have PCOS appears to be secondary to abnormalities in postreceptor insulin signalling. The compensatory hyperinsulinemia, favours the ovarian production of testosterone leading to hyperandrogenism.
There is increasing evidence that vitamin D metabolism affects insulin and glucose metabolism. Decreased level of vitamin D metabolites and increased PTH concentration has been shown to be associated with insulin resistance [4]. The active form of vitamin D, 1, 25-dihydroxyvitamin D (1,25OHD) directly enhances insulin action for glucose transport by stimulating the expression of insulin receptors, as the vitamin D response element is present in the promoter region of the insulin receptor gene [5]. Increased insulin receptor expression or suppression of pro-inflammatory cytokines are believed to mediate insulin resistance [6].
To the best of our knowledge, this is the first study done on Indian population in which calcitropic hormones were studied in a sizable sample of PCOS along with their effect on insulin resistance and clinical features of the syndrome.

2. Materials and Methods
It was a cross-sectional study done at a tertiary hospital over a period of eighteen months. Sample size was calculated by taking 15% prevalence of PCOS with 10% as the absolute margin of error and 95% confidence limit.

Ethical clearance was obtained from the hospital ethical committee. Women between 20-40 years, attending the Gynaecology OPD and willing to comply with the study protocol, participated in the study. 50 PCOS women diagnosed by the Rotterdam criteria were included. Rotterdam's criteria is defines as presence of atleast two of the three features; anovulation, clinical or biochemical signs of hirsutism or features of polycystic ovaries on pelvic ultrasonography. Hirsutism was classified using modified Ferrimon-Galleway score. On ultrasonography, presence of polycystic ovaries were defined by wither a volume of at least 10ml or more than 12 follicles in at least one ovary. Women with ongoing pregnancy, elevated calcium or prolactin levels, kidney or liver disease, thyroid disorder, or currently using vitamin D supplements were excluded from the study. Ultrasonography was done during the early follicular phase, by using Toshiba Ultrasound Diagnostic System model SSA-220A with trans-abdominal probe of 3.75 MHz frequency and vaginal probe of 6 MHz frequency. Number of 2-8mm in diameter follicles in each ovary was counted and their mean was calculated. Ovarian volume was estimated according to the formula ½ (A X B X C), where A is the longitudinal diameter, B the antero-posterior diameter and C, the transverse diameter of the ovary. Blood sample was withdrawn afer 8 to 9 hours of overnight fasting between days 2 to 4 of menstrual cycle during a spontaneous bleeding episode or progestin- induced menstrual cycle. Serum 25 (OH) D levels and PTH concentration was measured by electro immunoassay (ROCHE Cobas e 411). Serum Insulin (fasting) was be measured using electro immunoassay (ROCHE Cobas e 411). Insulin resistance was estimated using the homeostatic model assessment- insulin resistance (HOMA-IR). HOMA-IR was calculated as the product of the fasting plasma insulin value in µU/ml and the fasting plasma glucose value in mg/dl, divided by 405. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD .Normality of data was tested by Kolmogorov-Smirnov test. Pearson correlation coefficient was used to find out association of various parameters with Vitamin D3 and PTH. A p value of <0.05 was considered statistically significant.

3. Results

Fifty PCOS women participated in the study. The mean age of the women was 25 years and the median of BMI was 23.19kg/m2. Majority of the women had irregular cycle, hirsutism (mFG score>=7) and acne.

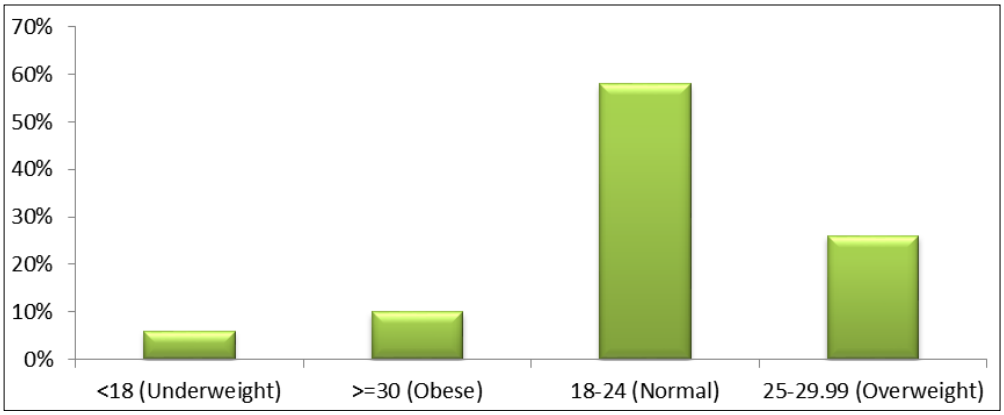

Fig 1: Distribution according to BMI among PCOS women

Median of serum LH was 12.2 IU/ml.72% had irregular menstrual cycle while acne and hirsutism were present in 52% and 80% of women respectively.

Impaired fasting glucose (90-12mg/dl) was present in 70% of women. The mean fasting serum insulin and fasting serum glucose was 32muU/ml and 95.5 mg/dl. The range for HOMA-IR was 2.13-14.88 with a median of 6.98.

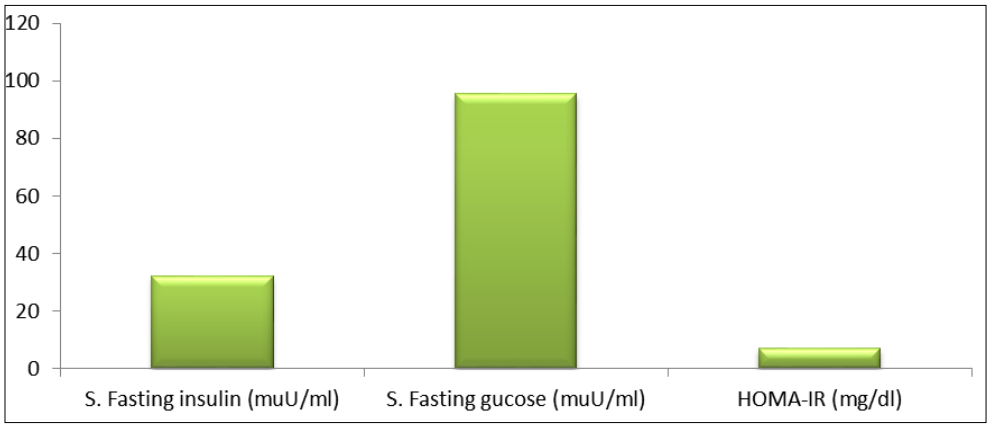

Fig 2: Distribution according to insulin resistance

Only 3 women with PCOS had vitamin D in the normal expected range (30ng/ml). Hypovitaminosis D [25(OH)D<20ng/ml] was present in 84 % of women with a median level of 25(OH)D was 6.5ng/ml. Hyperparathyroidism

was present in 64 % of women; with a median of 42.45pg/ml. Among these women, 79 % of women with hypovitaminosis D and 13 % of women without hypovitaminosis D had irregular menstrual cycles. Significant association was observed between vitamin D deficiency and menstrual irregularities (p=0.001). While no significant association was found between hyperparathyroidism and menstrual irregularities (p=0.88).

Vitamin D deficiency was significantly associated with obesity and overweight; $p<0.005$. There was negative correlation of vitamin D levels with BMI; r=-0.55,$p<0.00$ while no such association was seen with hyperparathyroidism (r=0.142, p=0.326). There was significant association between vitamin D deficiency and serum fasting insulin and insulin resistance among PCOS women; $p<0.05$ and $p<0.05$ respectively.

Table 1: Correlation of Vitamin D levels and PTH levels with obesity

Author	Clinical symptoms	Year	Vitamin D deficiency	Hyperparathyroidism
Parikh *et al*. [101]	BMI	2004	r= -0.4, $p<0.01$	r=0.42,$p<0.05$
Panidis *et al*. [12]	BMI	2005	r= -0.19,p= 0.03	r=0.20,$p<0.01$
Yildizhan *et al*. [98]	BMI	2009	r= -0.95,$p<0.05$	NR
Ott *et al*. [83]	BMI	2012	NR	r=0.347,p=0.001
Ghadimi *et al*. [77]	BMI	2014	Correlated negatively p=0.491	NR
Wehr *et al*. [99]	WTHR	2009	r=-0.31,p=0.023	
	BMI		Negatively correlated,P=0.001	
Present study	BMI	2014	r=-0.55,p=0.58	r=0.142,p=0.913
	WTHR		r=-0.52,p=0.03	r=-0.02,p=0.234

There was significant negative correlation with vitamin D levels and fasting sugar, fasting insulin and HOMA IR; r=-0.31, p=0.03, r=-0.74, $p<0.001$, r=-0.67, $p<0.01$ respectively. Association with hyperparathyroidism and insulin resistance was not found to be significant (r=0.51, p=0.51).

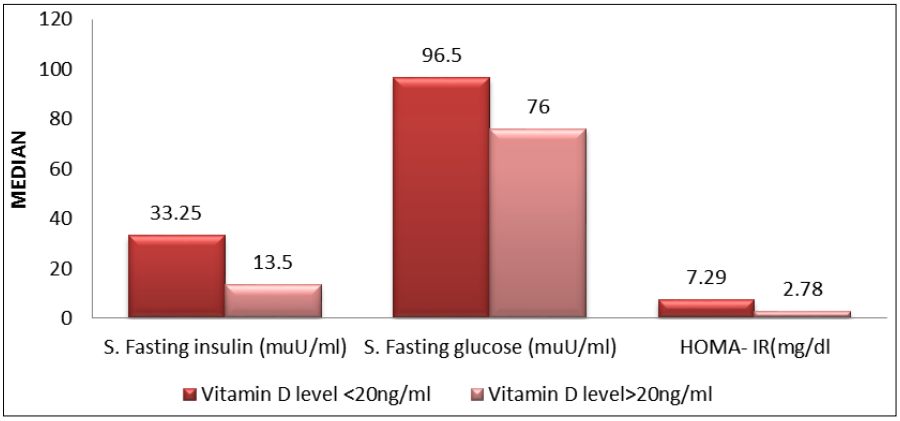

Fig 3: Association of vitamin D deficiency with IR in PCOS women

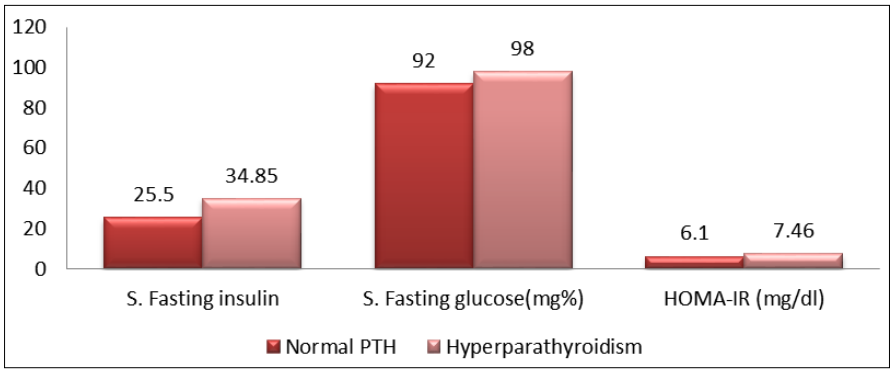

Fig 5: Association of PTH levels with IR

4. Discussion

Vitamin D is thought to influence the development of PCOS through gene transcription [7]. Vitamin D deficiency may exacerbate symptoms of PCOS, many observational studies have shown association of lower 25(OH)D levels with insulin resistance, menstrual irregularities, hirsutism, hyperandrogenism, obesity and increased cardiovascular risk factors [3]. In the present study, we found a significant association of hypovitaminosis D with menstrual disturbances in the study group, p=0.001. Vitamin D deficiency leads to an increase in PTH production.

Vitamin D deficiency increases PTH production, which is regulated through levels of serum calcium and vitamin D, and increased PTH is also independently associated with PCOS, anovulatory infertility and increased testosterone [8].

In our study, among the PCOS women, 72 % women had menstrual irregularities. Ozkan *et al*. (2010) reported that in PCOS women, the commonest reason for a gynaecological referral is menstrual irregularity [9]. Vitamin D receptors have been found on ovary, placenta and endometrium. Its deficiency

contributes to follicular arrest and menstrual dysfunction in women with PCOS [3]. Acne was seen in 86% of women in the study group, and hirsutism (mFG score ≥7) was seen in 94 % of women in the study group. Most studies have either reported an association of vitamin D levels with menstrual irregularities or have found beneficial effect of vitamin D supplementation in women PCOS with menstrual dysfunction.

Abnormalities in calcium homeostasis contribute in the pathogenesis of PCOS by causing arrest in follicular development. Pitkin *et al*. studied calcium metabolism during the menstrual cycle, and suggested that PTH is responsible for prolonged menstrual cycles [10]. In our study, no significant association was there between hyperparathyroidism and menstrual irregularities; p=0.88. However, Thys- Jacob S *et al*. reported higher mean of PTH level in women with PCOS with documented chronic anovulation [11]. Not many studies have being done to find out the correlation of increased parathyroid hormone level with menstrual irregularities. Hence, more research work is needed to find out this correlation.

Balen *et al*. (2005) has also reported acne in nearly one third of women with PCOS, and, vice a versa most of women with severe acne are diagnosed with PCOS [12]. The cause of acne in these women is due to androgen stimulated enlargement of the sebaceous glands [13].

In our study vitamin D levels and serum PTH level correlated negatively but the association was not significant (r=-0.041, p=0.77) among PCOS women. However, Panidis *et al*. found that vitamin D negatively correlated with Serum PTH among obese PCOS women; r = −0.142, p = 0.03 [8]. Similarly Ott *et al*. also found significant negative association between them; r=−0.664, $p<0.001$ among anovulatory PCOS women [17]. As there is paucity of studies to find the correlation between vitamin D and PTH level among PCOS women, more research is required for the same.

The various parameters assessed for insulin resistance in these women were fasting blood sugar, fasting serum insulin, and HOMA-IR (insulin resistance). Fasting insulin and HOMA IR was significantly higher among vitamin D deficient PCOS women compared to non PCOS women ($p<0.05$). However, we did not find any correlation of fasting glucose with vitamin D deficiency and hyperparathyroidism. Fasting insulin and HOMA IR were found to be significantly high in women with higher PTH concentration in PCOS women; $p<0.05$, p=0.003 respectively.

Similar to our observations, Hahn *et al*. and Yildizhan *et al.* so reported significant negative correlation between vitamin D and insulin resistance [18]. Wehr *et al*. (2009) found significant correlation with vitamin D deficiency with higher levels of HOMA IR. In the same manner, they also found negative correlation of vitamin D levels and fasting glucose and fasting insulin (both $p<0.001$) [16]. Similar to our results, Mahmoudi *et al*. reported significant correlation with PTH and fasting insulin and insulin resistance [14]. However, Panidis *et al*. studied PTH level in 291 PCOS women and 109 healthy women, and did not find any correlation of PTH with insulin resistance [8].

5. Conclusion

Due to the high proportion of women with vitamin D deficiency in PCOS, it is recommended that they should be made aware of importance of natural vitamin D synthesis with exposure to sunlight. Prospective studies are needed to address possible positive effect of vitamin D supplementation in PCOS women. The screening for PCOS should routinely include assessment of vitamin D and PTH levels for better management of PCOS women and ameliorate the health burden distinctly associated with this prevalent disorder.

Author's contribution

SP contributed to the design of the study, data collection, data analysis, data interpretation, and writing and revising the manuscript. PM and RB contributed to data analysis, data interpretation, and revising the manuscript. JS contributed in data interpretation and revising the manuscript.

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Conflicts of interest: None

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