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Research Article

Comparison of vitamin D levels in obese and non obese patients with polycystic ovarian syndrome in a South Indian population

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ABSTRACT

Polycystic ovary syndrome (PCOS) is the most common metabolic abnormality occurring in young women of reproductive age. Low vitamin D levels were found to be associated with the development of obesity and insulin resistance in young women with PCOS. The study was conducted as a prospective observational study involving 121 women with PCOS. The diagnosis of PCOS cases were based on the revised Rotterdam consensus criteria. Vitamin D levels were compared in the obese and non obese PCOS groups and also with the controls. In the PCOS group, sixty subjects were obese with BMI of ≥25 kg/m^2 and forty seven subjects were found to be non obese. In the control group, sixteen subjects were obese and sixty five subjects were non obese. The mean vitamin D level in the PCOS group was 15.45±7.88 ng/ml and in the control group was 12.83±5.76ng/ml. The mean vitamin D levels in the obese and non obese group with PCOS were 16.11±8.9ng/ml and 14.61±6.1ng/ml respectively. Majority of the patients and controls had vitamin D deficiency and there was no difference in the vitamin D levels in PCOS group and controls as well as obese and non obese groups.

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

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common metabolic abnormality occurring in about 10% of young women of reproductive age.[1,2] In 1935, Stein and Leventhal described the association of polycystic ovaries to amenorrhea, infertility and obesity and over the last few decades, diagnostic criteria of PCOS has been defined by several professional groups[3,4] which are based on expert opinions rather than evidence based.

Vitamin D is a key regulator of serum calcium metabolism and has an important role in the maintenance of bone health. It has been found that vitamin D has important roles in extra skeletal health as well.[5] Vitamin D has pleotropic effects and its deficiency has been associated with the pathogenesis of cancer, immune system disorders, diabetes mellitus, cardiovascular diseases etc.[6] This has attracted the attention of many researchers and several trials have been conducted in this field. Several cross sectional and prospective studies have observed the negative association between vitamin D levels and insulin resistance. Low Vitamin D levels were found to be associated with the development of obesity and insulin resistance in young women with PCOS.[7,8]

The current study was aimed to compare the vitamin D levels in obese and non obese PCOS patients.

Diagnostic criteria

Polycystic ovary syndrome (PCOS) is a diagnosis of exclusion, with other androgen excess and ovulatory

dysfunction disorders to be ruled out. There are three principal features of the syndrome, including hyper androgenism, ovulatory dysfunction, and polycystic ovarian morphology. The diagnostic criteria used for PCOS are based on expert opinions with low evidence support. Polycystic ovarian syndrome has heterogeneous signs and symptoms and several agencies have proposed different diagnostic criteria. However, all these recommendations suggest excluding other conditions which can mimic PCOS before confirming the diagnosis.[3,4,9] There are arguments that, including poly cystic ovaries found in ultrasound as one of the diagnostic criteria might spuriously increase the prevalence of PCOS among ovulating women.[10]

NIH consensus criteria

Menstrual irregularity due to oligo or anovulation Evidence of hyper androgenism, whether clinical or biochemical Exclusion of other caused of hyper androgenism and menstrual irregularity, such as congenital adrenal hyperplasia, androgen secreting tumors, and hyper prolactinemia.

Rotterdam criteria[11]

In the revised criteria, two out of three of the following are required to make the diagnosis.

- Oligo and /or anovulation
- Clinical and/or biochemical signs of hyper androgenism
- Demonstration of polycystic ovaries by ultrasound
- Other etiologies like congenital adrenal hyperplasia, androgen secreting tumors, Cushing's syndrome etc must be excluded.

Androgen Excess Society (AES) Criteria[12]

AES proposed that, PCOS should be diagnosed when patient demonstrates both:

- Hirsutism and/or hyper androgenemia
- Oligo-anovulation and/or polycystic ovaries
- Exclusion of other etiologies of androgen excess and anovulaton is necessary.

Presence of hyper androgenism is mandatory in NIH and AES criteria. The Rotterdam criteria introduced two new phenotypes which are a) Poly cystic ovaries and hyper androgenism without chronic anovulation, b) Polycystic ovaries and chronic anovulation without hyper androgenism.[11,12] AES criteria also introduced an additional phenotype of hyper androgenism, ovulatory cycles and polycystic ovaries.[12] These several overlapping PCOS phenotypes are shown in figure 1.

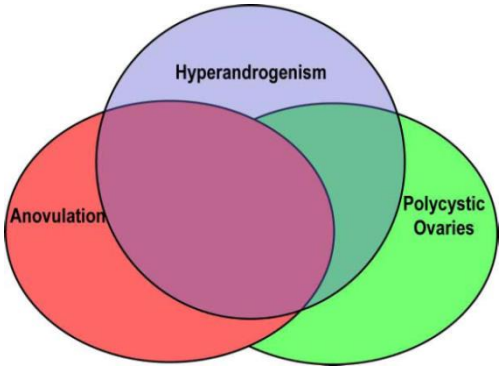

Figure 1: The overlapping phenotypes of PCOS when defined by various diagnostic criteria.

Ultrasound assessment of the polycystic ovary[11]

The PCO should have at least one of the following: either 12 or more follicles measuring 2-9 mm in diameter and increased ovarian volume (>10 ml). If there is evidence of a dominant follicle (>10 mm) or a corpus luteum, the scan should be repeated during the next cycle .Only one ovary fitting this definition or a single occurrence of one of the above criteria is sufficient to define the PCO.

A woman having PCO in the absence of an ovulatory disorder or hyper androgenism (''asymptomatic PCO'') should not be considered as having PCOS, until more is known about this situation. In addition to its role in the definition of PCO, ultrasound is helpful to predict fertility outcome in patients with PCOS (response to ovulogens, risk for ovarian hyper stimulation syndrome (OHSS), decision for in vitro maturation of oocytes). Whenever possible, the trans vaginal approach should be preferred, particularly in obese patients. Regularly menstruating women should be scanned in the early follicular phase (days 3-5). Oligo-/amenorrhoeic women should be scanned either at random or between days 3-5 after a progestogen withdrawal bleed. Follicle number should be estimated both in longitudinal, transverse and antero posterior cross-sections of the ovaries.

Etiopathogenesis of PCOS

The pathogenesis of PCOS is complex with more than one mechanism involved. Hostile intrauterine environment and low birth weight may predispose to the development of early adrenarche, PCOS and Metabolic Syndrome later in life in keeping with Barker hypothesis.[13,14] A primary abnormality in folliculogenesis may have a role in the pathogenesis of PCOS. The polycystic ovaries accumulate multiple small antral follicles and some of these prematurely acquire LH receptors and become responsive to LH. There is increase in granulosa cell proliferation in preantral PCOS follicles. These changes may result in anovulation.[15] The increased visceral fat with enhanced lipolytic activity increases free fatty acid which induces insulin resistance in skeletal muscle. With the new diagnostic criteria proposed, there

may be an increase in the diagnosis of PCOS based on ovarian morphology on ultrasound findings. However, it should be kept in mind that, ultrasound appearance of polycystic ovaries without PCOS is a common age dependent finding among ovulatory women without any metabolic abnormalities of PCOS.[16]

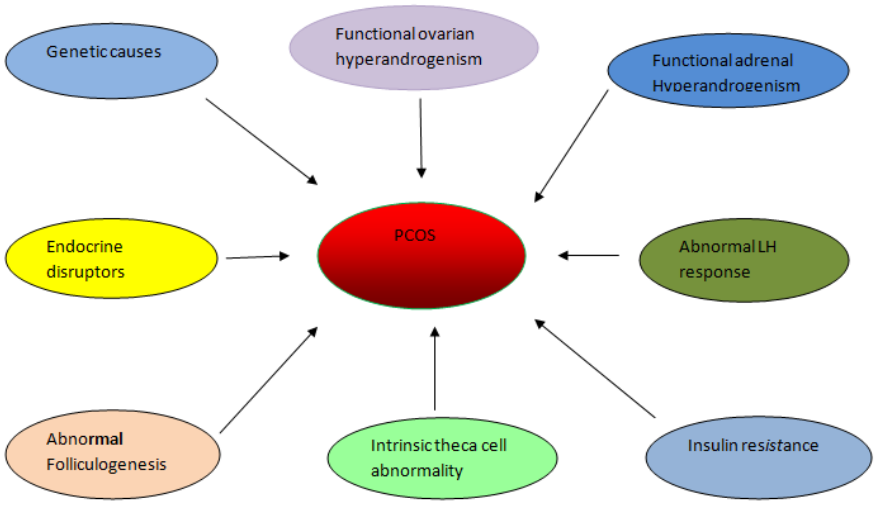

Figure 2: Mechanisms involved in the pathogenesis of PCOS.

Vitamin D

Vitamin D is one of the oldest hormones which are a 9, 10-seco steroid. It has 2 forms, vitamin D2 and vitamin D3. Vitamin D2 is derived from plant sterol ergosterol and vitamin D3 is a 28 carbon cholesterol derivative [5, 17]. Vitamin D must be converted to its active form calcitriol to be biologically active.[18] The major source of vitamin D for humans is from sunlight. The sunlight exposure should be typically between 10 am to 3 pm in all seasons.[19] It is estimated that adults exposed to sunlight in bathing suit that causes skin pigmentation 24 hours later is equivalent to ingesting about 20,000 IU of vitamin D.[5]

The other natural source of vitamin D3 is oily fish, cod liver oil, and that of vitamin D2 is plant sources like sun exposed mushrooms etc. In humans, vitamin D2 is not as bioactive as vitamin D3.[17] Few countries have fortified milk, dairy products as well as orange juice with vitamin D.[20]

Recently, it has become clear that vitamin D has many effects apart from its traditional role in calcium metabolism and bone health. In fact, in early 1900s Finsen noted curative effects of sunlight on several skin disorders like lupus vulgaris and he received Nobel prize in 1903 for his observations.[5] In 1980s, the first insights in to the non calcium, non skeletal effects of vitamin D was reported. A decade later, several investigators reported that cultured cells from skin, colon, prostate, breast, lung and brain had capability to produce calcitriol.[21,22] About 3% of human genome are regulated by vitamin D receptor gene including the genes crucial for glucose and fat metabolism as well as blood pressure regulation.[23]

Most of the tissues in body express Vitamin D receptor (VDR) and hence, to have enough vitamin D to satisfy all cellular requirements and for the optimal health, human body requires a blood level of vitamin D above 30 ng/ml.[24] Endocrine society defines vitamin D deficiency as levels below 20 ng/ml and vitamin D insufficiency as D levels of 21-29 ng/ml.[25] It is estimated that for every 100 IU of vitamin D ingested, blood level of vitamin D increases by 1 ng/ml and hence to achieve a blood level of above 30 ng/ml, one require to ingest 3000 IU of vitamin D a day.[5,26,27]

Obesity and insulin resistance are found to be associated with low 25-hydroxy vitamin D levels. Being a fat soluble vitamin, vitamin D is sequestrated in to the fat of obese people and serum levels may be low. In addition, the limited mobility as well as sun exposure seen in obese people can also contribute to low vitamin D levels. Many cross sectional and prospective studies have observed the negative association between Vitamin D levels and Insulin resistance. Several studies supports that vitamin D plays a role in glucose homeostasis and showed an inverse relationship between vitamin D and insulin resistance, fasting insulin, HbA1c as well as the risk of developing type 2 diabetes.[28-30] Vitamin D may have an indirect effect on glucose homeostasis by maintaining normo calcemia intracellularly. In addition to this, there may be a direct effect on insulin production, secretion and insulin sensitivity by increasing insulin receptor transcription and by translocation of glucose transporters to the cell membrane of insulin sensitive cells.[31]

Even though India is a vast tropical country extending from 8.4 degrees N latitude to 37.6 degrees N latitude and majority of the population lives in areas with abundant sunlight, vitamin D deficiency is very common in India from north to south across all ages and both sexes.[32,33] Studies by Harinarayan et al confirms that 76% of women in reproductive age and 70% of women in post menopausal age have vitamin D deficiency in south India.[34] A recent study done among school children and adolescents in Delhi, the prevalence of vitamin D deficiency was found to be 10.8% with no difference between the upper and lower socioeconomic groups.[33]

Association of Vitamin D with PCOS

There is evidence that vitamin D might be a causal factor in the pathogenesis of PCOS, however, the exact role remains unknown.[7,35] Vitamin D supplementation may have a favorable effect in the glucose metabolism in women with PCOS.[36] There are conflicting reports on the association of Vitamin D receptor polymorphisms and insulin resistance in women with PCOS.[37,38] It is possible that, vitamin D Receptor (VDR) may be involved in the pathogenesis of PCOS by exerting their effect on luteinizing hormone, sex hormone binding globulin levels and testosterone.[38,39] Vitamin D deficiency raises Para Thyroid Hormone levels which is independently associated with PCOS, anovulatory infertility and increased androgens.[40]

There is some suggestion that the combination of vitamin D deficiency, together with dietary calcium insufficiency may contribute to the menstrual abnormalities in PCOS.[41] In a study of fifty seven women with PCOS, Wehr et al showed that vitamin D treatment might improve glucose metabolism and menstrual frequency in PCOS women.[36]

Li et al demonstrated that ,Vitamin D deficiency is highly prevalent in women with PCOS in Scotland, and their study supported the evidence that vitamin D deficiency is associated with multiple metabolic risk factors in PCOS women.[42] Hahn et al investigated the effect of vitamin D on metabolic parameters and Insulin resistance in 120 untreated PCOS patients and confirmed that in PCOS women, low vitamin D levels are associated with obesity and insulin resistance but not with PCOS per se.[7]

An Italian study comprising of 90 untreated PCOS patients showed that in obese/overweight PCOS, vitamin D levels were significantly lower, and leptin to adiponectin ratio which is a biomarker of insulin resistance and low grade inflammation in PCOS, was significantly higher in obese/overweight patients compared to lean PCOS.[43]

Yildizhan investigated the correlation between serum vitamin D concentrations and metabolic parameters in 120 obese and non-obese women with polycystic ovary syndrome and found that the mean Vitamin D levels were 56.31% lower in the obese PCOS patients. There was also an association of increased HOMA-IR, Body Mass Index (BMI), Waist to Hip Ratio (WHR), triglycerides, total testosterone, and DHEAS with decreased Vitamin D concentrations in the obese PCOS patients. They concluded that, low serum vitamin D concentrations result from the presence of obesity and insulin resistance, but, the dependency between PCOS and hypo vitaminosis D is questionable.[8] With this background, we wished to assess the vitamin D levels in obese and non obese patients with PCOS.

METHODS

The study was conducted as a prospective observational study involving 121 women with PCOS attending Gynaecology outpatient clinic at Amrita Community Health Centre, Njarakkal, Ernakulam, Kerala State, India over a period of 2 years from August 2010 to August 2012 were selected after applying the inclusion and exclusion criteria. The study was conducted as per written consent of the participants.

Subjects

121 women with PCOS were selected for the study based on the inclusion criteria. The diagnosis of PCOS cases were based on the revised Rotterdam consensus criteria. Based on the available information on the prevalence rate of PCOS and with 95% confidence and 20% allowable error, the minimum sample size was estimated at 120. Based on the available information on the vitamin D level in obese and non obese women and with 95% confidence and 80% power, the minimum sample size estimated was about 10 in each group. However, we were able to do the vitamin D levels in 108 patients in total. 81 age matched controls, who were the staffs and students of AIMS with regular menstrual periods and without hyper androgenism or history of polycystic ovary syndrome were selected and vitamin D levels were estimated.

Inclusion Criteria

1. Diagnosis of PCOS based on revised Rotterdam criteria
2. Age from Menarche to 45 yrs.

Exclusion Criteria

1. Current pregnancy or nursing
2. Conditions known to affect vitamin D deficiency like renal disease, liver disease, gastro intestinal problems, malnutrition
3. Patients on calcium and vitamin D supplementation

Methodology

On the first OPD visit, a detailed history was taken including the age, presenting complaints with duration, detailed menstrual history, past medical history and

family history. The defining criteria for menstrual irregularities were as follows.

- Regular cycles – Menstrual cycles varying in length between 22 to 35 days.
- Oligomenorrhoea – Infrequent, irregularly timed episodes of menstrual bleeding usually occurring at intervals >35 days to < 180 days.
- Polymenorrhoea – frequent episodes of menstrual bleeding occurring usually at ≤21 days.
- Secondary amenorrhoea – Absence of menstrual bleeding for a period of ≥ 180 days in a woman who has menstruated before.
- Irregular cycles – Menstrual cycles whose average duration has been between 22-41 days but at least 2 cycles in a year has been < 22 days or > 41 days.
- Primary Infertility – Inability to conceive even after 1 year of regular, unprotected sexual intercourse in a woman who has never conceived before.
- Secondary Infertility – Inability to conceive in a woman who has had a prior conception.

Informed consent was obtained from all the patients. Anthropometric measurements like weight (in kg), height (in meters), BMI (body mass index), waist to hip ratio (WHR) were measured. Waist circumference was taken midway between the lowest rib margin and iliac crest. Hip circumference was taken over the widest part of the gluteal region.

Anthropometric measurements were made by the help of trained physician assistants using World Health Organization (WHO) techniques.[45] Height (in meter) was measured bare foot to within 0.5 cm. Weight (kilograms) was measured to within 100 gm in light clothes using analog scale.

Body Mass Index (BMI) is defined as the weight in kilograms divided by the square of the height in meters (kg/m^2). Obesity was defined as a BMI ≥25 kg/m^2 and non-obese as BMI < 25 kg/m^2. This was based on the consensus statement that the cut-offs for overweight and obesity need to be revised for Asian Indians.[46]

Unmarried patients were referred to radiologist for a Trans abdominal pelvic ultrasound in the follicular phase and married women were referred to gynecologist for a trans vaginal ultrasound to assess the ovarian size and morphology. An ovary was diagnosed as being polycystic if the ovarian volume was >10 cc or if it contained ≥ 12 follicles.[11]

For assessing Vitamin D levels, 5 ml of venous blood was collected and centrifuged and serum was stored at -20 degrees in our research lab freezer until analysis was performed as a single batch in November 2012. It is well known that, vitamin D remains stable up to 72 hours in room temperature and up to 10 years if stored in – 20 degrees[8]. 25-OH-Vitamin D level was estimated a Roche-Elysis Cobas total Vitamin –D kit.

Controls were selected from age matched female doctors, nursing staff, para medical staff and medical and para medical students of Amrita Institute of Medical Sciences who had regular menstrual periods, who were non pregnant and not lactating. Those who had chronic illness and who were taking vitamin D preparations were excluded. Anthropometry measurements including height, weight, and waist circumference were done using the above mentioned methods. 5 ml of venous blood was collected, centrifuged and stored in – 20 degree till analysis of Vitamin D was done.

Vitamin D levels were compared in the obese and non obese PCOS groups and also with the controls.

Statistical Analysis

Statistical analysis was done using IBM SPSS Statistics 20 Windows (SPSS Inc., Chicago, USA). For all the continuous variables, the results are given in Mean ± SD and for categorical variables, as percentage. To compare the means of continuous variables between two groups, which follow normal distribution, Student's independent samples t test was performed. To compare the averages of continuous variables between two groups, which do not follow normal distribution, Mann Whitney U test was performed. A p-value <0.05 was considered statistically significant. All tests of statistical significance were two tailed.

RESULTS

There were totally 121 and 81 subjects in the PCOS and control groups respectively. Vitamin D levels were estimated in 107 subjects in the PCOS group and in all the controls .The mean age of subjects (Figure 3) in the study group was 24.78 years (range 12-41 years) in the PCOS group and 25.86 years in the control group (range 18-46 years).

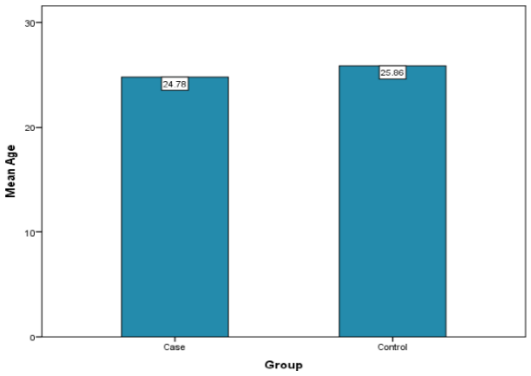

Figure 3: The mean age of cases and controls.

In the PCOS group, sixty subjects were obese with BMI of ≥25 kg/m2 and forty seven subjects were found to be non obese. In the control group, sixteen subjects were obese and sixty five subjects were non obese.

The mean vitamin D level in the PCOS group was 15.45 ± 7.88 ng/ml and in the control group was 12.83 ± 5.76ng/ml. Only 5 persons in the PCOS group had vitamin D level of > 30 ng/ml. The maximum value was 40.21 ng/ml. The mean vitamin D levels in the obese and non obese group with PCOS were 16.11±8.9ng/ml and 14.61±6.1ng/ml respectively (table 1).

Table 1: Vitamin D levels in obese and non obese subjects in the PCOS and control groups.

Group	Obese (BMI ≥25)			Non Obese (BMI<25)			P value
	No	Mean Vitamin D	SD	No	Mean Vitamin D	SD	
PCOS N: 121	60	16.11	8.9	47	14.61	6.16	0.309
Control N: 81	16	14.18	4.76	65	12.50	5.96	0.297

Among the controls, obese subjects had a mean total vitamin D level of 14.18±4.76ng/ml whereas; non obese subjects had mean vitamin D level of 12.50±5.96 ng/ml (table 1). In both groups, vitamin D levels were found to be higher in obese group compared to non obese group, but the difference was not statistically significant.

Control subjects

Among eighty one control subjects, sixteen patients were found to be obese and 65 subjects were non obese. The mean weight, waist circumference, hip circumference as well as ICO were significantly elevated in the obese group compared to the non obese controls (table 2).

Table 2: Characteristics of obese and non obese controls.

Variable	Obese (BMI≥ 25) [16]	Non Obese (BMI < 25) [65]	P value
	Mean ±SD	Mean± SD	
Age	31.88±7.12	24.38±6.06	<0.001
Height (cm)	1.54±0.046	1.57±0.067	0.185
Weight (kg)	67.06±7.75	50.91±6.77	<0.001
WC (cm)	92.06±11.59	74.54±8.18	<0.001
HC (cm)	99.38±5.65	85.97±8.75	<0.001

HC: Hip circumference
WC: Waist circumference

Table 3: Race specific waist circumference cut offs.

Country/Ethnic group	Waist circumference cutoff	
	Male	Female
Europoids. In the USA, the ATP 111 values (102 cm in male; 88 cm female) are likely to continue to be used for clinical purposes.	≥ 94 cm	≥ 80 cm
South Asians Based on a Chinese, Malay, and Asian-Indian population	≥ 90 cm	≥ 80 cm
Chinese	≥ 90 cm	≥ 80 cm
Japanese	≥ 90 cm	≥ 80 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data available	
Sub-Saharan Africans	Use European data until more specific data are available.	
Eastern Mediterranean population and Middle east (ARAB) populations	Use South Asian recommendations until more specific data available	

DISCUSSION

Polycystic ovary syndrome is a common endocrine disorder among women in their reproductive years and it is associated with several metabolic abnormalities. In the younger years, PCOS is associated with menstrual and fertility issues, whereas later in life, it is a risk factor for Type 2 Diabetes mellitus and cardiac disease.

The vitamin D levels were found to be low in majority of the PCOS subjects with only five persons having a vitamin D level more than 30 ng/dl. The mean vitamin D level in the PCOS group was 15.45±7.88 ng/ml. However, this was not different in the control group which had a mean vitamin D level of 12.83±5.76 ng/ml. Surprisingly, control group had lower vitamin D levels compared to the PCOS group. This could probably be explained by the fact that, the controls were hospital workers who work indoors most of the day and were not exposed adequately to sunlight. Majority of the patients in PCOS group were unemployed women as well as students who probably were exposed to more sunlight. However, there is no reason to think that diet contributed to this difference in vitamin D levels.

On comparison of vitamin D levels in the obese and non obese PCOS patients, it was found that, obese persons had more vitamin D levels than non obese persons (table 1). This was different from previous studies which showed higher vitamin D levels in non obese persons.[7,8,43] In our group, all the five persons who had vitamin D

levels more than 30 ng/ml were obese and this would have contributed to the overall difference in the vitamin D levels in Obese and non obese persons. These vitamin D sufficient individuals denied any intake of vitamin D preparations. However, as the vitamin D prescription pattern has changed in India, it is possible that they might have received some vitamin D. The results in the control group was somewhat similar where vitamin D levels were seen to be elevated in the obese group compared to the non obese group though this was not statistically significant. This need to be further studied in a larger group. The overall low Vitamin D levels in this study in both patients as well as controls may reflect the underlying vitamin D deficiency in the general public in Indian population as previously described.[32-34]

CONCLUSION

Majority of the patients and controls had vitamin D deficiency and there was no difference in the vitamin D levels in PCOS group and controls as well as obese and non obese groups. This may reflect the vitamin D deficiency status of the community. Vitamin D deficiency should be looked upon as a serious problem among the south Indian population, which demands immediate attention.

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