Original Research Article

Relationship between vitamin D₃ deficiency and polycystic ovarian syndrome

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ABSTRACT

Background: Vitamin D_3 (VD_3), a seco-steroid that is synthesized in skin and sequentially metabolized in liver and kidneys in humans, has been well-known for its function in maintaining calcium and phosphorus homeostasis and promoting bone mineralization. Polycystic ovary syndrome (PCOS) is a common cause of ovarian dysfunction in women with anovulation. Aim of this study is to show and evaluate VD_3 level in women who are suffering from polycystic ovarian syndrome.

Methods: This study was conducted on 200 women; group A: (study group) 100 infertile women who were suffering from PCOS and group B: (control group) 100 patients were selected with other cause of infertility than PCOS. US examination, hormonal profile (FSH, LH, AMH, TSH and prolactin level) and laboratory assay of serum VD3 level (postmenstrual) were done for every patient to evaluate relationship between VD_3 deficiency and PCOS patients.

Results: There was a significant relationship between group A compared to group B as regards irregular menstrual cycle, clinical hyperandrogenism, LH/FSH ratio and AMH. There was no significant difference between both groups as regards TSH, prolactin and VD_3 level. VD was deficient in both groups as it was lower than normal level. There was a negative significant correlation between VD_3 level and both hyperandrogenism and AMH.

Conclusions: There was VD_3 deficiency in PCO patients and infertile cases due to another factor, and negative significant correlation between VD_3 level and clinical hyperandrogenism, LH/FSH ratio, menstrual cycle and AMH.

Keywords: VD_3, PCOS, Infertility

INTRODUCTION

Vitamin D3, (VD_3) a secosteroid that is generated in skin and subsequently processed in the liver and kidneys of humans, is well-known for its role in calcium and phosphorus homeostasis and bone mineralization.[1]

PCOS is a common reason for ovarian dysfunction in females with anovulation. The main symptoms are characterized by chronic anovulation, hyperandrogenism, and/or the presence of polycystic ovary (PCO) morphology from ultrasound investigation.[2]

Clinical manifestation of this disorder is associated with various degrees of gonadotropic and metabolic abnormalities determined by the interaction of multiple genetic and environmental factors.[2] In recent years, there has been a growing interest in studying the association of VD deficiency and infertility. It has been postulated that vitamin D receptors (VDR) are found in human tissues such as male and female reproductive organs and play a major role in facilitating the biological activity of VD. VD deficiency has been advocated as a possible cause of infertility in many studies conducted in the past several years.[3]

Low 25(OH) Vit D levels might exacerbate the symptoms of PCOS, such as insulin resistance, ovulatory, menstrual irregularities, infertility, hyperandrogenism, obesity and elevate the risk of cardiovascular diseases.[4]

Many observational studies recommend a possible role of VD in an inverse relation between VD status and metabolic disturbances in PCOS, but it is still hard to draw a definite conclusion in the causal relationship due to inconsistent findings from various individual studies and from a recent meta-analysis report of a systematic review.[4]

The aim of this study was to show and evaluate VD_3 level in women who are suffering from polycystic ovarian syndrome.

METHODS

This case control study was conducted on 200 women who are attending outpatient and inpatient clinics of obstetrics and gynecology department, Tanta university hospital. The study conducted from January 2019 to December 2019. The study was approved from the ethics committee of faculty of medicine, Tanta University.

Informed written consent was taken from all participants before recruitment in the study, and after explaining the purpose and procedures of the study.

The patients were divided into two equal groups: group A: (study group) 100 infertile women who were suffering from PCOS (diagnosed according to Rotterdam criteria 2017). Group B: (control group) 100 patients were selected with other cause of infertility than PCOS.

The exclusion criteria were patients suffering from (Metabolic bone disease-abnormal liver function-impaired kidney function), patients receiving medication known to affect calcium and vitamin D metabolism (antiepileptic agents, glucocorticoids, antiestrogens, weight loss drugs, antiretroviral drugs), patients who refuse to participate in the study.

All cases were subjected to the following: full history taking with special emphasis on menstrual , obstetric and past history, general examination including calculation of the body mass index (BMI), assessment of signs of hyperandrogenism (according to modified Ferriman-Gallwey scale, a score of 8 to 15 indicates mild hirsutism, and a score greater than 15 indicates moderate or severe hirsutism), clinical examination, ultrasound examination using Samsung H60 Korean manufacturer which is an electronic sector transducer with a frequency of 5-8 MHz, hormonal profile of the patients including FSH, LH, AMH, TSH and prolactin at 3rd day of the menstrual cycle, Laboratory assay of serum VD_3 level which was done for every patient after stoppage of menstrual blood and diagnostic laparoscopy was done after stoppage of menstrual blood to confirm diagnosis.

VD_3 level measurement[5]

Specimen collection and handling: whole blood specimen was collected by puncture of antecubital vein then 2 ml blood was withdrawn by usual plastic syringe then blood sample was kept in plain test tube. Separation of the serum by centrifugation at a speed of 4000 rpm was done. Then all serum samples were refrigerated at -20°C up to whole specimens were collected for chemiluminescent immunoassay (CLIA) (iFlash-25-OH VD kits) on YHLO CLIA iFlash 1800 device. Hemolyzed samples rejected.

The primary outcome was relationship between VD_3 deficiency and PCOS patients and the secondary outcome were relation between VD_3 level and: (hyperandrogenic manifestations/FSH ratio, menstrual irregularities, ovarian reserve (AMH) in PCOS patients).

Statistical analysis

Statistical analysis was done by SPSS v25 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as mean, standard deviation (SD) and range and were compared between the two groups utilizing unpaired Student's t-test. Categorical variables were presented as frequency and percentage and were analysed utilizing the Chi-square test or Fisher's exact test when appropriate. Pearson or Spearman coefficient correlation (r) was used to estimate the degree of correlation between two variables. $P<0.05$ was considered statistically significant.

RESULTS

Regarding Patients' characteristics in both studied groups, there were non-significant relationships between both groups as regard age, BMI, gravidity and duration of infertility while there was a significant difference between both groups as regard the irregularity of menstrual cycle with and a significant difference between both groups as regard the clinical hyperandrogenism (Table 1).

Regarding laboratory investigations in both groups, significant increase in group A than B as regards LH/FSH ratio and AMH but no significant difference between both groups as regards TSH and prolactin (Table 2).

Regarding VD3 level, there was non-significant difference between both groups (Table 3).

Regarding VD_3 level in correlation with other parameters, there were a negative significant correlation with hyperandrogenism and AMH while there were insignificant correlations with both LH/FSH ratio and menstrual cycle (Table 4).

Table 1: Patients' characteristics in both studied groups, (n=100).

Characteristics		Group A	Group B	Test	P value
Age (years)	Mean±SD	25.1±2.56	25.65±4.15	T=1.128	0.260
	Range	20-30	19-32		

Characteristics		Group A	Group B	Test	P value
BMI (kg/m²)	Mean±SD	29.91±5.11	29.24±3.54	T=1.091	0.277
	Range	23.7-45.9	22.2-37.1		
Gravidity	0	31 (31%)	36 (36%)	X²=0.7613	0.755
	1	31 (31%)	29 (29%)		
	2	38 (38%)	35 (35%)		
Duration of infertility (years)	Mean±SD	2.21±0.89	2.1±0.61	T=1.038	0.301
	Range	1-4	1-3		
Menstrual cycle	Regular	20 (20%)	96 (96%)	X²=16.977	<0.001
	Irregular	80 (80%)	4 (4%)		
Clinical hyperandrogenism	No cases	44 (44%)	93 (93%)	X²=0.000	<0.001
	Mild cases	43 (43%)	7 (7%)		
	Moderate cases	4 (4%)	0		
	Severe cases	9 (9%)	0		

Table 2: Laboratory investigations in both groups, (n=100).

Variables		Group A	Group B	T	P value
LH/FSH ratio	Mean±SD	1.27±0.27	0.55±0.10	24.941	<0.001
	Range	0.6-1.75	0.37-0.79		
AMH (ng/ml)	Mean±SD	6.36±3.01	2.89±1.17	10.748	<0.001
	Range	1.1-11.8	1-5.2		
TSH (IU/ml)	Mean±SD	2.09±0.95	1.99±0.77	0.957	0.442
	Range	0.88-5.2	0.96-3.6		
Prolactin (ng/ml)	Mean±SD	18.81±7.10	17.31±7.44	0.319	0.146
	Range	0.5-33.4	9-35		

Table 3: VD₃ level in both groups.

Variables		Group A	Group B	T	P value
VD₃ level (ng/ml)	Mean±SD	13.63±3.54	14.17±3.72	1.052	0.297
	Range	8.13-24.4	6.14-24.9		

Table 4: Correlation between VD₃ level and other parameters.

Variables	VD₃ level	
	R	P value
Hyperandrogenism	-0.150	0.034
LH/FSH ratio	-0.126	0.075
Menstrual cycle	0.021	0.768
AMH	-0.164	0.021

DISCUSSION

There was an insignificant difference as regards VD₃ level between both groups (p=0.297). Vitamin D was deficient in both groups.

In agreement with our results, Rahsepar et al included 60 PCOS women (20-40 years old) and 90 healthy women as control group in this case-control study. It was found that the mean of serum 25(OH)D was lower in the PCOS group (10.76±4.17) than in the control group (12.07±6.26) but this difference was not statistically significant (p=0.125).[6] Also, Davis et al showed that a higher proportion of VD deficiency was observed among the PCO cases although it did not reach statistical significance (21.2% verses 13.6%, p=0.13).[7]

This was in disagreement with Wehr et al showed that the serum VD level in women with PCOS (n=545) was lower than that of the control group (n=145), being 25.7 and 32 ng/ml, respectively.[8] This may be contributed to the lower serum VD level in our control group, and this may be due to ethnic group or geographical factors or different lifestyle.

Moreover, Eftekhar et al study showed that a lower serum VD level in the PCOS patients than in control patients (p<0.001).[9] This may be contributed to ethnic group or geographical factors or different lifestyle.

Moreover, Li et al showed that the serum VD level in women with PCOS was lower than that of the control group.[10] This may be contributed to the lower serum VD level in our control group, and this may be due to ethnic group or geographical factors or different lifestyle.

Also, Mahmoudi et al found that women with PCOS had a significantly lower serum VD level than the control women, with the similar age and BMI.[11] This may be contributed to the lower serum VD level in our control group, and this may be due to ethnic group or geographical factors or different lifestyle. Also, the control was healthy women not infertile women.

This was in agreement with Eftekhar et al study.[9] They showed that AMH was significantly higher in PCO patients. Also, Bhide et al showed that women with PCO morphology had significantly higher AMH levels than women in the control group.[12] The prevalence of PCOS increased from 21% in the low-AMH (<4 ng/ml) group to 37% in the moderate-AMH (4-11 ng/ml) group and 80% in the high-AMH (>11 ng/ml) group.

This agreement with Hashemi et al found no significant difference in TSH between PCO and control groups.[13] In disagreement with our results, Benetti-Pinto et al who found that thyroid function was normal in 149 women, and 19 had subclinical hypothyroidism in young PCO women.[14] This difference may be due to exclusion of patients who had associated another cause of infertility beside PCOD in our study.

In disagreement with our results, Tagliaferri et al found that TSH median values were significantly higher in PCOS patients than in controls.[15] Subclinical hypothyroidism was found in 14% of PCOS subjects and in 1% of controls. This difference may be due to exclusion of patients who had associated another cause of infertility beside PCOD in our study. Another explanation, they compared PCO with healthy control. Also, Kachoie et al showed that high TSH was found in 50% of women in reproductive age diagnosed with PCOS.[16] This difference may be due to exclusion of patients who had associated another cause of infertility beside PCOD in our study.

In agreement with our results, Hashemi et al found no significant difference in prolactin between PCO and control groups.[13] In disagreement with our results, Kachoie et al descriptive analytical study was performed on PCOS patients.[16] The mean prolactin serum level was 18.56±11.53 ng/l (range: 18.56-69.81 ng/l). It was significantly different from the normal level. This difference may be due to exclusion of patients who had associated another cause of infertility beside PCOD in our study. Also, Benetti-Pinto et al found that prolactin levels were significantly higher in the women with subclinical hypothyroidism of PCO women.[14] This difference may be due to exclusion of patients who had associated another cause of infertility beside PCOD in our study.

There was a negative significant correlation between VD_3 level and hyperandrogenism (r=-0.150, p=0.034). There was a negative significant correlation between VD_3 level and AMH (r=-0.164, p=0.021). There were insignificant correlations between VD_3 level and both LH/FSH ratio and menstrual cycle (r=-0.126 and 0.021 respectively, p=0.075 and 0.768 respectively). In agreement with our results, Rashad et al showed that VD_3 level was negatively correlated with free testosterone.[17] In contrast to our results, Arslan et al demonstrated that AMH levels were not correlated with 25(OH)D levels in PCO group.[18] This may be contributed to different ethnic group or geographical factors or different lifestyle.

In disagreement with our results, Kozakowski et al found that VD in PCOS women with abdominal obesity was correlated with LH/FSH ratio (LH/FSH). This may be contributed to different ethnic group or geographical factors or different lifestyle.[19] Further studies are needed to reveal the role of VD deficiency or supplementation on the efficacy of management of PCO disease.

Limitation

We excluded patients who had associated another cause of infertility beside PCOS. Single centre study.

CONCLUSION

There was VD_3 deficiency in PCO patients and infertile cases due to another factor, and negative significant correlation between VD_3 level and clinical hyperandrogenism, LH/FSH ratio, menstrual cycle and AMH.

REFERENCES

1. Perez-Lopez FR. Vitamin D: the secosteroid hormone and human reproduction. Gynecol Endocrinol. 2007;23:13-24.
2. Thomson RL, Spedding S, Buckley JD. Vitamin D in the aetiology and management of polycystic ovary syndrome. Clin Endocrinol (Oxf). 2012;77:343-50.
3. Rainer D, Davis E, Peck J, Hansen K, Craig L. Vitamin D Deficiency and Time to Pregnancy in Women With Polycystic Ovary Syndrome. Fertil Steril. 2012;97:22-4.
4. Krul-Poel YH, Snackey C, Louwers Y, Lips P, Lambalk CB, Laven JS et al. The role of vitamin D in metabolic disturbances in polycystic ovary syndrome: a systematic review. Eur J Endocrinol. 2013;169:853-65.
5. Knox S, Harris J, Calton L, Wallace AM. A simple automated solid-phase extraction procedure for measurement of 25-hydroxy VD_3 and D2 by liquid chromatography-tandem mass spectrometry. Ann Clin Biochem. 2009;46:226-30.
6. Rahsepar M, Mahjoub S, Esmaelzadeh S, Kanafchian M, Ghasemi M. Evaluation of vitamin D status and its correlation with oxidative stress markers in women with polycystic ovary syndrome. Int J Reprod Biomed. 2017;15:345-50.
7. Davis EM, Peck JD, Hansen KR, Neas BR, Craig LB. Associations between vitamin D levels and polycystic ovary syndrome phenotypes. Minerva Endocrinol. 2019;44:176-84.
8. Wehr E, Trummer O, Giuliani A, Gruber HJ, Pieber TR, Obermayer-Pietsch B. Vitamin D-associated polymorphisms are related to insulin resistance and

vitamin D deficiency in polycystic ovary syndrome. Eur J Endocrinol. 2011;164:741-9.

9. Eftekhar M, Mirhashemi ES, Molaei B, Pourmasumi S. Is there any association between vitamin D levels and polycystic ovary syndrome (PCOS) phenotypes? Arch Endocrinol Metab. 2020;64:11-6.

10. Li HW, Brereton RE, Anderson RA, Wallace AM, Ho CK. Vitamin D deficiency is common and associated with metabolic risk factors in patients with polycystic ovary syndrome. Metabolism. 2011;60:1475-81.

11. Mahmoudi T, Gourabi H, Ashrafi M, Yazdi RS, Ezabadi Z. Calciotropic hormones, insulin resistance, and the polycystic ovary syndrome. Fertil Steril. 2010;93:1208-14.

12. Bhide P, Homburg R. Anti-Müllerian hormone and polycystic ovary syndrome. Best Pract Res Clin Obstet Gynaecol. 2016;37:38-45.

13. Hashemi AH, Mozdarani H, Naghavi A. Comparison of the Levels of LH and FSH, TSH, Prolactin, Progesterone and Estradiol Hormones between Iranian Infertile Women with Polycystic Ovary Syndrome and Healthy Women. Int J Med Sci Public Health. 2016;5:370-5.

14. Benetti-Pinto CL, Berini Piccolo VR, Garmes HM, Teatin Juliato CR. Subclinical hypothyroidism in young women with polycystic ovary syndrome: an analysis of clinical, hormonal, and metabolic parameters. Fertil Steril. 2013;99:588-92.

15. Tagliaferri V, Romualdi D, Guido M, Mancini A, De Cicco S, Di Florio C et al. The link between metabolic features and TSH levels in polycystic ovary syndrome is modulated by the body weight: an euglycaemic-hyperinsulinaemic clamp study. Eur J Endocrinol. 2016;175:433-41.

16. Kachoie A, Jahanipoor A, Ghahiri A. Evaluation of Serum Prolactin Levels in Patients with Polycystic Ovary Syndrome. Journal of Isfahan Medical School. 2012;30:1-6.

17. Rashad NM, Abd El-Fatah AH, Lashin ME-B, Abomandour HG, Allam RM. Impact of vitamin D supplementation on cardio-metabolic status and androgen profile in women with polycystic ovary syndrome: placebo-controlled clinical trial. Middle East Fertil Soc J. 2019;24:5.

18. Arslan E, Gorkem U, Togrul C. Is There a Relationship Between Vitamin D Deficiency Status and PCOS in Infertile Women? Geburtshilfe Frauenheilkd. 2019;79:723-30.

19. Kozakowski J, Kapuścińska R, Zgliczyński W. Associations of vitamin D concentration with metabolic and hormonal indices in women with polycystic ovary syndrome presenting abdominal and gynoidal type of obesity. Ginekol Pol. 2014;85:765-70.

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