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Comparative Clinical Study Evaluating Serum Vitamin D levels in Women with Polycystic Ovary (PCOS) And Normal Fertile Women

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Abstract— ***Background:*** Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder in women of reproductive age with a prevalence of up to 10%. ***Aim:*** The aim of this study was to evaluate vitamin D levels in PCOS women compared to normal fertile women and the relation between vitamin D and fasting insulin hormone levels in PCOS women. ***Materials and Methods*:** A prospective case-control study was conducted on 80 subjects who were classified into two groups: *group (I) cases* included 40 infertile women diagnosed with PCOS and *group (II) control* included 40 normal fertile women. Demographic and clinical characteristics of all the patients were recorded. ***Results*:** No significant differences were noticed between groups regarding age, body mass index, sun exposure, however, cases group had lower gravidity. The results showed that LH level was significantly higher in PCOS group compared to the control one, while the opposite trend was observed in FSH levels. The fasting insulin hormone level was higher in PCOS group compared to control. PCOS group had a significantly lower 25 (OH) D level in comparison with the control group. In the PCOS group, 25 (OH) D level was negatively correlated with both fasting insulin level and body mass index. ***Conclusion*:** Women with PCOS had a significantly lower serum 25 (OH) D level compared to normal fertile women. Insulin resistance was prevalent in PCOS patients and there was a significant inverse correlation between vitamin D level and both fasting insulin hormone and BMI in these patients.

Keywords: 25 (OH) D, Fertile Women, PCOS, Polycystic Ovarysyndrome, Vitamin D.

Introduction

Polycystic ovary syndrome is the commonest endocrine disorder among women in reproductive age with a worldwide prevalence of 5–20% [1]. This disorder is manifested by ovulatory dysfunction, hyper and rogenism in addition to polycystic ovarian morphology [2]. Also, several metabolic disturbances are associated with PCOS such as insulin resistance, compensatory hyperinsulinemia, dyslipidemia and obesity and these consequently increase the risk for type 2 diabetes mellitus, metabolic syndrome and cardiovascular diseases [3]. The exact etiology of PCOS remains debatable and existing treatments had a moderate effect in controlling its symptoms and preventing its complications [2].

Vitamin D is a fat-soluble vitamin that is naturally synthesized in the body through the photochemical conversion of cholesterol to 7-dehydrocholesterol in the skin under sunlight or obtained from the diet [4]. Serum 25 (OH) D is the main circulating form of vitamin D and it is used as the major indicator of vitamin D status [5]. Vitamin D has vital functions in the body such as regulating bone metabolism and maintaining calcium homeostasis in addition to its recently proved role in cell proliferation, differentiation, immune regulation, and neurogenesis [6]. Growing evidence advocate a vital role of vitamin D in female reproductive diseases, vitamin D receptors (VDRs) were identified in some female reproductive tract organs such as the ovary, uterus, and the placenta and some studies

reported that females with null vitamin D receptors were infertile and had folliculogenesis impairment [7,8].

Several studies reported that vitamin D deficiency is common among women with PCOS and confirmed the association between low levels vitamin D and PCOS manifestations including insulin resistance, hyperandrogenism and infertility [9,10,11]. Vitamin D regulates many genes that are vital for the metabolism of glucose and lipids, so its deficiency may be the missing link between insulin resistance and PCOS [3]. Also, the abnormalities that occurred in calcium homeostasis and PTH levels which resulted from vitamin D deficiency may be responsible for the arrested follicular development and menstrual dysfunction in women with PCOS [2]. In addition, vitamin D regulated steroidogenesis and IGFBP-1 production in cultured human ovarian cells and there is a proven interrelation between vitamin D and IGF-1 [12,13]. On the other hand, vitamin D supplementation to PCOS patients led to beneficial effects on follicles maturation and regulation of the menstrual cycle [14,15]. The objective of this study is to evaluate vitamin D levels in women with PCOS compared to normal fertile women and to study whether levels of vitamin D in women with PCOS are related to fasting insulin concentration.

Methods

This prospective case-control study was performed during the period from July 2019 to January 2020 under the registration no.:9114991.All participants were enrolled in this study after informed written consent. The study protocol and all procedures were approved by the ethical committee of the department of Obstetrics & Gynecology at Minia College of medicine. All Participants had signed a written informed consent after they have been made aware of the purpose of the study.

The study included a total of 80 subjects who were classified into two groups: group (I) cases which included 40 infertile women diagnosed with PCOS and group (II) control which included 40 normal fertile women. The diagnosis of PCOS in cases group was based on the presence of at least two of the Rotterdam criteria that includes the following: the presence of oligomenorrhea and/or amenorrhea, hyperandrogenism and/or hirsutism in addition to polycystic ovarian morphology. For the control group, all fertile women how had a spontaneous pregnancy and delivered a normal healthy baby without congenital malformations were included. Exclusion criteria for the two groups were women with endocrinopathies, those who had taken any medication influencing the metabolism of bone, vitamin D or calcium for at least 2 months before the inclusion of study and women who had renal or liver function impairment.

All included women were subjected to the following: thorough history taking including personal, present, menstrual, obstetric, past and family histories, style. Low sun exposure was considered to spend less than 30 minutes outside during the day. also, general examination in terms of weight, height, body mass index, blood pressure, the presence or absence of galactorrhea, chest, heart and abdominal examination. Gynaecological examination was done to evaluate the uterus and ovaries. Regarding sonographic evaluation, transvaginal ultrasonography was performed using Toshiba SAA 270 AUS machine with 7.5 MHZ vaginal transducer to evaluate the uterus and ovaries and to confirm the diagnosis of PCOS. Also, the ovarian volume, the stromal thickness and the number and arrangement of follicles were evaluated. In addition, some laboratory investigations were done including basal LH, FSH hormone levels.

●Insulin hormone and 25 (OH) vitamin D assays:

Venous blood sample (4 ml) was taken from all included women after 12 hours overnight fasting and serum was separated by centrifugation and then stored at -40 C^{o}.

Serum insulin assay was done by the method of quantitative determination of insulin levels in human serum by a Microplate Enzyme Immunoassay, Colorimetric using AccuBind ELISA Microwells, supplied by MonobindInc, Lake Forest, CA 92630, USA. Also, 25 OH Vitamin D assay was done by the method of quantitative determination of 25 OH Vitamin D concentration in human serum by a Microplate Enzyme Immunoassay, Colorimetric using AccuBind ELISA Microwells, supplied by MonobindInc, Lake Forest, CA 92630, USA.

●Statistical analysis.

Data were statistically analyzed using SPSS program (Statistical Package for Social Sciences, version 20, IBM, NY, USA) [16]. Descriptive statistics were expressed for numerical data as mean ± standard deviation (SD) and range, while for categorical data as number and percentage. For quantitative data, independent sample T-test and One-way ANOVA test were used for the comparisons. While for qualitative data, Chi-square test or Fisher exact were used when appropriate. Person correlation coefficient was used to get the correlations between variables. A Probability value of less than 0.05 was considered significant and of less than 0.01 was considered as highly significant.

Results:

A total of 40 women with PCOS (group, I) and 40 normal fertile women (group, II) were included in this study. The present results showed that there were no significant differences between groups regarding age ($p=0.624$), body mass index ($p=0.680$), daily sun exposure ($p=0.616$) however, cases group had significantly lower gravidity (85% of cases were P0+(0:2), $p<0.01$) (Table, 1). In cases group, there are 22 cases (55.0%) had a primary type of infertility while, 18 cases had a secondary type and the duration of infertility was 1-3 years in about two-thirds of cases (62.5%) and it was 4-9 years in the rest of cases.

The majority of cases group (39 cases, 97.5%) had irregular menstrual pattern (80.0% had oligomenorrhea and 17.5% had amenorrhea) versus only 2 cases (5.0%) in the control group who hadoligomenorrhea ($p<0.01$). The results of the ultrasound findings showed that PCOS group had significantly higher both right and left antral follicle count compared to control group ($p<0.01$) (Table, 2). As regards the previous treatment of cases group, 37 cases (92.5%) were treated with Clomid, 18 cases (45.0%) had hormonal treatment (Synthetic progesterone, Cyproterone + Ethinyl Estradiol), 12 cases (30.0%) had drilling and 5 cases (12.5%) had ICSI.

The results revealed that LH level was significantly higher in PCOS group compared to control one (11.37 vs. 4.04 IU/L, $p<0.01$). While in contrary, FSH level was significantly lower in PCOS group compared to control (4.68 vs. 7.51 IU/L, $p<0.01$). The fasting insulin level was significantly elevated in PCOS group compared to control (12.64 ± 3.94 vs. 7.49 ± 2.41 IU/ml, $p<0.01$). Regarding the results of 25 (OH) D, PCOS group had a significantly lower 25 (OH) D level compared to control group (15.5 ± 5.16 vs. 23.5 ± 5.0 ng/ml, $p<0.01$). Cases group had 11 cases (27.5%) with vitamin D deficiency versus no cases in control group while, 32 cases (80.0%) had vitamin D sufficiency incontrol group versus only 4 cases (10.0%) in cases group ($p<0.01$) (Table. 3).

The fasting insulin hormone level was negatively correlated with 25 (OH) D level in the PCOS group ($r=0.48$, $p<0.01$), (Table, 5 & fig.1). Cases with vitamin D deficiency (<12 ng/ml) had higher fasting insulin hormone level (15.5 ± 3.79 IU/ml), cases with vitamin D insufficiency (12-20 ng/ml) had moderate fasting insulin hormone level (12.07 ± 3.36 IU/ml) while, cases with vitamin D sufficiency (20-50 ng/ml) had the lowest level of fasting insulin hormone (8.15 ± 1.55 IU/ml) with a significant difference among all (Table, 4). Also, the results showed a significant negative correlation between 25 (OH) D level and body mass index in PCOS patients ($r=-0.50$, $p<0.01$), (fig. 2).However, no obvious correlation was noticed between 25 (OH) D level and all of LH, FSH and, age (Table, 5).

Discussion:

The results of this study illustrated that PCOS patients had a significantly lower 25 (OH) D level compared to normal fertile women (15.5 ± 5.16 vs. 23.5 ± 5.0 ng/ml, $p<0.01$), 11 cases in PCOS group had vitamin D deficiency versus no cases in the control group while, 32 cases (80.0%) had vitamin D sufficiency in control group versus only 4 cases (10.0%) in PCOS group ($p<0.01$). These findings are in line with some earlier and recent studies, Eftekhar*et al.*[17] found that PCOS women had a significantly lower vitamin D level compared to normal controls (20.6±9.2 vs. 29.1±5.50 ng/ml,$p<0.001$). Also, Krul-Poel*et al.*[4]found that serum 25(OH)D was significantly decreased in PCOwomen compared to fertile ones (49.0 vs. 64.5 nmol/l). Also, Wehr*et al.* [8] and Li *et al.*[10] reported that vitamin D deficiency was highly prevalent in PCOS women. In addition, Thomson *et al.*[19] stated that the prevalence of vitamin D deficiency in women with PCOS is about 67-85%.

The relation between vitamin D and fertility may be explained by that vitamin D has been found across several tissues of the female reproductive system (i.e. ovarian, decidua, placenta and endometrium cells) and that it is strongly related to the production of estrogen and progesterone in ovary and placental cells [12,20]. In addition to that, vitamin D can lower the levels of Mullerian hormone "which reflects abnormal folliculogenesis" and increases serum anti-inflammatory soluble receptor for advanced glycation end-products in PCOS women [21,22]. On the other hand, some studies reported that vitamin D levels did not differ significantly between women with and without PCOS [23,24].

The fasting insulin level was significantly elevated in PCOS group compared to control group (12.64 ± 3.94 vs. 7.49 ± 2.41 IU/ml, $p<0.01$). Many studies reported similar results [8, 19, 25]. It has been reported that insulin resistance and the compensatory hyperinsulinemia affects about 65-85% of women with PCOS and they play a critical role in the syndrome's pathogenesis [26,27].

The present results revealed that there was a significant inverse correlation between vitamin D level and fasting insulin hormone in PCOS patients ($r=0.48$, $p<0.01$), cases with vitamin D deficiency had the highest fasting insulin hormone level (15.5 ± 3.79 IU/ml) while, cases with sufficient vitamin D level had the lowest level of fasting insulin hormone (8.15 ± 1.55 IU/ml). These findings agreed with many studies which reported that low serum 25 (OH) D level is significantly associated with higher insulin levels in women with PCOS [1,4]. Also, a significant inverse correlation between serum vitamin D and insulin resistance was found in many observational studies [12, 28]. Furthermore, Krul-Poel*et al.*[3] found that serum 25(OH)D could be considered as a significant predictor for insulin resistance in PCOS women. Vitamin D affects glucose metabolism, a directeffect of vitamin D on insulin secretion may be mediated by activation of VDRs in the pancreatic beta-cell with the addition of the presence of 1α-hydroxylase to locally produce $1,25(OH)_2D$ [29]. In addition, vitamin D deficiency may cause an increase in systemic inflammation which plays a key role in insulin resistancepathogenesis [30]. Furthermore, vitamin D may activate the transcription of the human insulin receptor gene as the promoter of this gene has a vitamin D responsive element [31]. Additionally, as insulin secretion from β cells is a calcium-dependent process, vitamin D regulates extracellular and intracellular calcium and consequently affects this process [1,32]. Also, some recent studies confirmed a positive correlation between vitamin D and IGF-1 levels [1,33].

Also, the present results showed a significant inverse correlation between vitamin D level and body mass index in PCOS patients ($r=-0.50$, $p<0.01$). Similarly,Krul-Poel*et al.*[4] found that PCOS women with BMI > 25 kg/m^2 had a significantly lower 25 (OH) D level. Also, some studies reported the negative correlation between the serum vitamin D level and both BMI, body fat, waist circumference, and metabolic disorders in PCOS patients [9,19,34,35].

Several intervention trials examined the effects of vitamin D supplementation on metabolic parameters and clinical parameters including fertility in PCOS women. These studies differed in study design, population, dosing regimens, as well as study outcomes [12,28]. A

significant inverse association was found between serum 25 (OH)D and insulin resistance in the included observational studies, which is in line with our results.

A study reported that in PCOS patients with vitamin D deficiency, a 2-month treatment with 1500 mg calcium on a daily basis and 50,000 units of vitamin D on a weekly basis improved menstrual cycles in 7 out of 9 cases [23]. In a largest study with an RCT design among 104 obese, vitamin D deficient PCOS women did reveal a positive effect of weekly 50.000 IU vitamin D plus calcium 1000mg/day on insulin resistance [36]. The strength of this study was that it was a randomized, controlled design, and consisted of control and PCOS patients. We assessed BMI, sun exposure to find the correlation between vitamin D deficiency and obesity and exclude any variability in vitamin D levels due to sun exposure. In addition, the narrow age range of the present population controlled the factor that vitamin D levels are affected by age.

Finally, this study has some limitations, of these, the relatively small sample size in addition to factors related to blood sampling and laboratory work such as the higher cost of kits used, the kits are not easily available, and the procedures required a higher level of accuracy and professionality.

Conclusion

In conclusion, the results illustrated that woman with PCOS had a significantly lower serum 25 (OH) D level compared to normal fertile women. Also, insulin resistance was prevalent in PCOS patients and there was a significant inverse correlation between vitamin D level and both fasting insulin hormone and BMI in these patients. These results suggest a possible role of vitamin D supplementations in the management of PCOS.Further large-scale randomized controlled trials are warranted to explore the underlying mechanisms.More studies with a larger sample size are required to confirm the correlation between vitamin D and BMI in PCOS patients and explain the cause of this correlation.

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Conflict of interest: None.

Ethical considerations

The study protocol and all procedures were approved by the ethical committee of the department of Obstetrics & Gynecology at Minia College of medicine. All Participants had signed a written informed consent after they have been made aware of the purpose of the study.

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Table (1): Baseline characteristics between groups.

Variable		Groups Group (I) Cases (n=40)	Group (II) Control (n=40)	*P.* Value
Age (year)		27.8 ± 5.2 (19-39)	28.4 ± 3.8 (22-37)	0.62^{NS}
Weight (kg)		74.8 ± 9.3 (60-92)	72.9 ± 6.8 (60-90)	0.32^{NS}
Height (cm)		165.1 ± 4.7 (157-178)	162.8 ± 5.9 (136-170)	0.05^{NS}
Body mass index (kg/m^2)		27.4 ± 3.0 (22-35)	27.2 ± 2.4 (22-33)	0.68^{NS}
Gravidity	**P0+(0:2)**	34 (85.0%)	0	**<0.01****
	P1+(0:1)	4 (10.0%)	3 (12.0%)	
	P2+(0:2)	2 (5.0%)	12 (30.0%)	
	P3+(1:2)	0	12 (30.0%)	
	P4+(0:2)	0	7 (17.5%)	
	P5+(0:2)	0	5 (12.5%)	
	P6+0	0	1 (2.5%)	
Daily sunlight exposure	**Yes**	12 (30%)	10 (25%)	0.61^{NS}
	No	28 (70%)	30 (75%)	

†Quantitative data were presented as mean ± SD (range). Qualitative data were presented as No. (%) , T-test and Chi-square test were used. *NS : Not significant ** Significant (P≤ 0.01)

Variable		Groups Group (I) Cases (n=40)	Group (II) Control (n=40)	P.value (Sig.)
Normal ovaries	**No**	40 (100.0%)	1 (2.5%)	**<0.01****
	Yes	0	39 (97.5%)	

Antral follicle (right)	**Count**		14.6 ± 2.7 (8-19)	2.4 ± 0.50 (2-4)	**<0.01****
	Size	**2-7 mm**	0	9 (22.5%)	**<0.01****
		2-8 mm	8 (20.0%)	24 (60.0%)	
		2-9 mm	32 (80.0%)	7 (17.5%)	
Antral follicle (left)	**Count**		12.62 ± 2.46 (3-18)	2.51 ± 0.63 (2-4)	**<0.01****
	Size	**2-6 mm**	1 (2.5%)	0	0.42^{NS}
		2-7 mm	5 (12.5%)	2 (5.0%)	
		2-8 mm	12 (30.0%)	14 (35.0%)	
		2-9 mm	22 (55.0%)	24 (60.0%)	

Table (2): Ultrasound findings between groups.

*NS :Not significant ** Significant (P≤ 0.01)

Table (3): Laboratory findings between groups.

Variable		**Groups**		
		Group (I) Cases (n=40)	**Group (II) Control (n=40)**	***P.* Value**
LH (IU/L)		11.37 ± 2.34	4.04 ± 0.71	**<0.01****
FSH (IU/L)		4.68 ± 1.51	7.51 ± 0.98	**<0.01****
Fasting insulin hormone (IU/ml)		12.64 ± 3.94	7.49 ± 2.41	**<0.01****
25 (OH) D (ng/ml)		15.5 ± 5.16	23.5 ± 5.0	**<0.01****
25 (OH) D level	**Deficiency**	11 (27.5%)	0	**<0.01****
	Insufficient	25 (62.5%)	8 (20.0%)	
	Sufficiency	4 (10.0%)	32 (80.0%)	

†Abbreviations: LH , luteinizing hormone; FSH , Follicle-stimulating hormone; 25(OH) D, 25- hydroxyvitamin D.
** Significant (P≤ 0.01)

Variable	**Vitamin D level**			
	Deficiency (<12 ng/ml) (n=11)	**Insufficient (12-20 ng/ml) (n=25)**	**Sufficiency (20-50 ng/ml) (n=4)**	***P.* Value**
Fasting insulin hormone	15.5 [a] ± 3.79	12.07 [b] ± 3.36	8.15 [c] ± 1.55	**<0.01****

(IU/ml)

Table (4): Relation between 25 (OH) D and fasting insulin levels in cases group.

†One was ANOVA test was used to get the significance.,a, b, cMeans in the same row with different superscripts are significantly different. ** Significant (P≤ 0.01)

Table (5): Correlation between 25 (OH) D level and other variables in cases group.

Variable		Correlation coefficient *(r)*	*P*. Value
25 (OH) D	**Fasting insulin**	-0.48	**<0.01****
	Age	-0.21	0.191^{NS}
	BMI	-0.50	**<0.01****
	LH	-0.12	0.47^{NS}
	FSH	-0.05	0.76^{NS}

†*r*Person correlation coefficient.

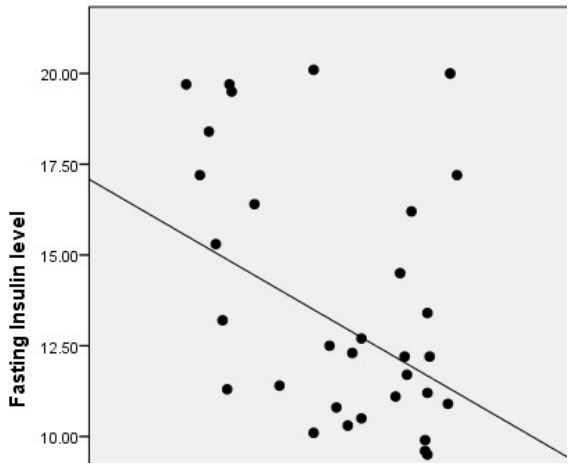

Figure (1): Correlation between 25 (OH) D and fasting insulin in cases group.

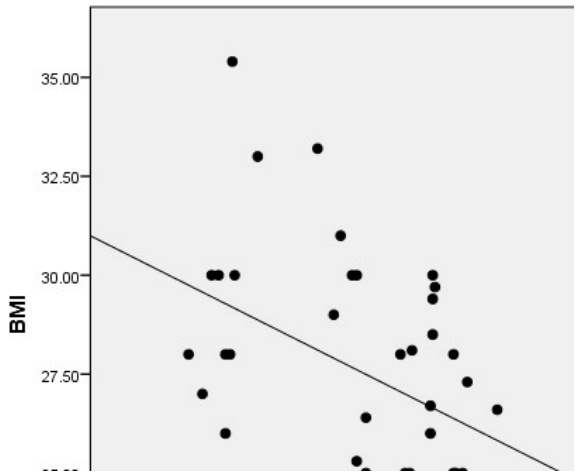

Figure (2): Correlation between 25 (OH) D and BMI in cases group.