Assessment of Serum Vitamin D Levels in Women with Polycystic Ovary Syndrome

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Abstract:

Background: Polycystic ovary syndrome (PCOS) is a common endocrinopathy in women of reproductive age with primary features of infertility, menstrual irregularity, and clinical or biochemical evidence of hyperandrogenism (hirsutism, acne and high androgen level). Vitamin D has a role in the development of metabolic and endocrine abnormalities in PCOS mediated by insulin resistance.

Objective: Measure serum 25-hydroxy vitamin D levels in women with polycystic ovary syndrome and compare their levels with age and body mass index matched healthy controls. Also, assess the correlation between insulin resistance and 25-hydroxy vitamin D among women with PCOS.

Subjects and Methods: Eighty eight women were involved in this study with age range (18-34 years). Subjects were divided into two groups: Group 1- forty five women with PCOS and Group 2- forty three women without PCOS (as controls).

Serum 25-hydroxy vitamin D, insulin, free testosterone, Luteinizing hormone (LH), Follicle stimulating hormone (FSH) were measured by enzyme linked immunosorbent assay (ELISA), while serum calcium and fasting serum glucose were measured by spectrophotometer.

Results: Significant increase in mean value of fasting serum glucose, insulin, homeostatic model assessment of insulin resistance (HOMA-IR), LH, LH/FSH ratio, and free testosterone with significant decrease in mean value of serum FSH, 25-hydroxy vitamin D, and calcium for patients with PCOS comparing to age and body mass index match controls. Additionally, significant negative correlations were found between serum 25-hydroxy vitamin D levels with fasting serum glucose (r= -0.484, p=0.01), fasting serum insulin (r= -0.422, p=0.04), and HOMA-IR (r= -0.542, p=0.0001) in women with PCOS.

Conclusion: Vitamin D has a role in metabolic and hormonal disturbance seen in PCOS through impact of vitamin D on insulin releasing and function.

Keywords: Polycystic ovary syndrome, vitamin D, insulin resistance.

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Introduction:

Polycystic ovary syndrome (PCOS) is a common endocrinopathy in women of reproductive age with primary features of infertility, menstrual irregularity, and clinical or biochemical evidence of hyperandrogenism (hirsutism, acne and high androgen level) (1). Insulin resistance (IR) is predominant in women with this disorder independent of obesity and is contributed to reproductive and metabolic defect seen in this syndrome (2). There is some evidence that vitamin D has role in reproduction through binding to nuclear receptors which has been distributed in the uterus, oviduct, ovary, placenta, and fetal membranes (3). Binding of vitamin D to its receptor in ovarian cell, leading to production of progesterone by 13%, estradiol by 9%, and estrone by 21% (4). Various mechanisms may demonstrate role of vitamin D in reproduction. First, a probable mechanism could be achieved by active vitamin D that stimulate expression of aromatase gene in reproductive tissues (5).

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Second, active vitamin D upregulate HOXA10 expression in human endometrial-stroma cells meaning that modified vitamin D signaling may influence HOXA10 expression and fertility (3). However, HOXA10 expression is necessary for uterus development and has influential role for development of endometrium, permitting uterine receptivity to implantation (6).

Subjects and Method:

Eighty eight women were involved in this study with age range (18-34 years). Women were attended to Infertility Center in Baghdad Teaching Hospital and Gynecology Private Clinic during the period from March 2017 to June 2017. Subjects were divided into two groups: Group 1- forty five women with PCOS and Group 2- forty three women without PCOS (as controls). Polycystic ovary syndrome were diagnosed according to Rotterdam criteria (7) when two out of three following criteria are found, these include oligoovulation and/or anovulation, clinical and/or biochemical hyperandrogenism and polycystic ovaries as defined by ultrasonography. Controls defined as healthy female in reproductive age with regular menstrual periods and no other signs and symptoms of PCOS, they came to clinic for checkup.Women with Cushing's syndrome,

hyperprolactinemia, congenital adrenal hyperplasia, androgen secreting tumors, and impaired thyroid, renal or hepatic function were excluded from this study. In addition, serum 25-hydroxy vitamin D, insulin, free testosterone, luteinizing hormone (LH), Follicle stimulating hormone (FSH) were measured by enzyme linked immunosorbent assay (ELISA), while serum calcium and fasting serum glucose were measured by spectrophotometer.

In addition, homeostasis model assessment of insulin resistance (HOMA-IR) calculates IR by dividing the product of fasting plasma glucose (mg/dl) × fasting plasma insulin (μU/ml) by a constant, 405 (8).

Statistical Analysis:

Analysis of data was carried out using the available statistical package of SPSS-24 (Statistical Packages for Social Sciences- version 24). Data were presented in simple measures of mean, standard deviation, and range (minimum-maximum values). The significance of difference of different means (quantitative data) were tested using Students t-test for difference between two independent means or ANOVA test for difference among more than two independent means. Pearson correlation was calculated for the correlation between two quantitative variables with its t-test for testing the significance of correlation. Statistical significance was considered whenever the P value was equal or less than 0.05.

Results:

Patients and controls were matching in age, body mass index (BMI), and waist circumference (W.C.). In addition, significant increase in mean value of fasting serum glucose, insulin, HOMA-IR, LH, LH/FSH ratio, and free testosterone with significant decrease in mean value of serum FSH, 25-hydroxy vitamin D, and calcium for patients comparing to controls as shown in Table (1). Moreover, mean value of serum 25-hydroxy vitamin D levels was calculated according to body mass index (normal weight, overweight, and obese). The results found no significant difference in mean value of 25-hydroxy vitamin D levels between normal weight group, overweight group, and obese group for patients as well as for controls as demonstrated in Table (2). Besides, mean value of serum 25-hydroxy vitamin D levels was calculated according to LH/FSH ratio (2:1; 1:1) for patients group which found significant decrease in mean value of serum 25-hydroxy vitamin D levels for patients group with LH/FSH ratio (2:1) than group with LH/FSH ratio (1:1) as elucidated in Table (3). Significant negative correlations were found between serum 25-hydroxy vitamin D levels with fasting serum glucose (r= -0.484, p=0.01), fasting serum insulin (r= -0.422, p=0.04), and HOMA-IR (r= -0.542, p=0.0001) in women with PCOS as shown in Figure (1), (2), and (3) respectively.

Table (1): Mean value of age, BMI, waist circumference, fasting serum glucose, insulin, HOMA-IR, LH, FSH, LH/FSH ratio, free testosterone, 25-hydroxy vitamin D and calcium for patients and controls.

	Mean±SD	Mean±SD	
Age (yr)	25.40±4.60	26.12±4.71	0.472
BMI(Kg/m^2)	27.32±3.59	26.47±3.59	0.275
W.C (cm)	85.91±7.95	84.93±7.89	0.609
Fasting serum glucose(mg/dl)	93.71±3.58	87.34±4.07	0.0001*
Fasting serum insulin (μU/ml)	14.01±1.29	6.23±1.11	0.0001*
HOMA-IR	3.243±0.33	1.349±0.283	0.0001*
serum LH (IU/l)	8.92±2.62	5.68±0.46	0.0001*
serum FSH (IU/l)	5.10±0.52	5.75±0.43	0.0001*
serum LH/FSH	1.752±0.50	0.995±0.129	0.0001*
serum free T (pg/ml)	5.31±0.47	1.38±0.52	0.0001*
serum 25OH vitamin D(ng/ml)	7.305±2.458	18.443±6.314	0.0001*
serum calcium (mg/dl)	8.21±0.09	9.06±0.26	0.0001*

Table (2): Mean value of serum 25-hydoxy vitamin D levels according to body mass index for patients and control.

	25-OH Vitamin D (ng/ml)			
	PCOS		Controls	
BMI (kg/m^2)	No	Mean±SD	No	Mean±SD
Normal weight (18.5-24.9)	15	7.25±2.30	19	19.90±5.57
Overweight (25-29.9)	18	7.46±2.86	16	18.73±7.54
Obese (=>30)	12	7.13±2.18	8	14.40±3.58
P value	0.936		0.114	

Table (3): Mean value of serum 25-hydroxy vitamin D levels according to LH/FSH ratio for patients group.

		PCOS	
		No	Mean±SD
LH/FSH	Ratio (1:1)	24	8.05±2.06
	Ratio (2:1)	21	6.45±2.64
	P value	0.028*	

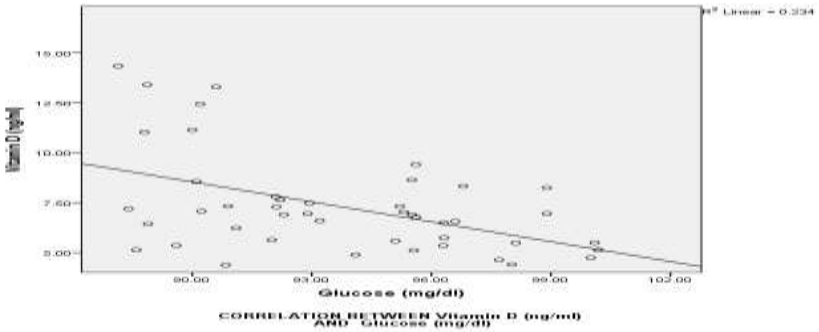

Figure (1): Significant negative correlation between serum 25-hydroxy vitamin D levels and fasting serum glucose for patients (r= -0.484, p=0.01).

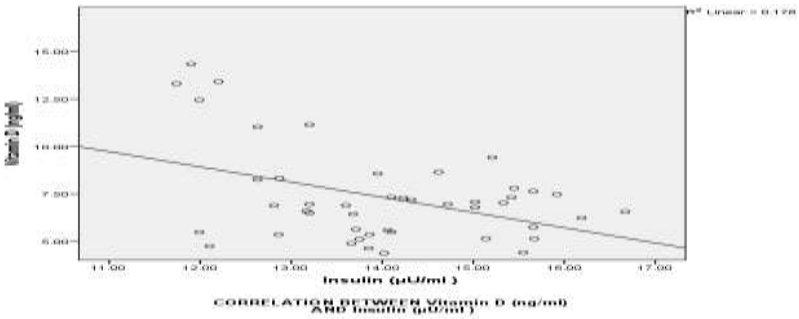

Figure (2): Significant negative correlation between serum 25-hydroxy vitamin D levels and fasting serum insulin for patients (r= -0.422, p=0.04).

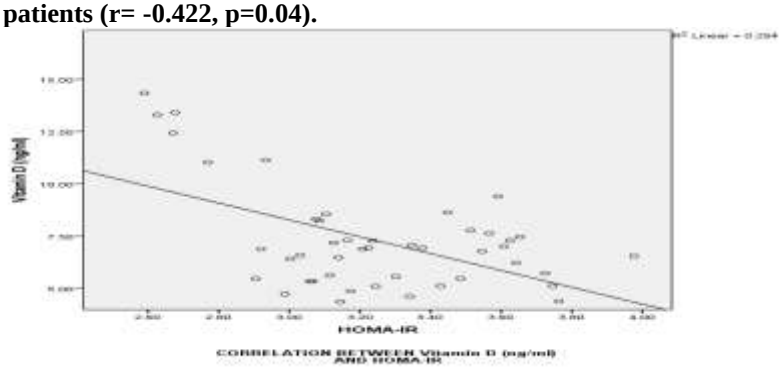

Figure (3): Significant negative correlation between serum 25-hydroxy vitamin D levels and HOMA-IR for patients (r= -0.542, p=0.0001).

Discussion:

Polycystic ovary syndrome is a heterogeneous androgen excess disorder with various degrees of gonadotropic and metabolic disturbance (9). The result of this study revealed that significant increase in mean value of serum free testosterone levels in women with PCOS comparing to controls, similar to other studies done by Wehr and coworkers (10) and El-Shal and followers (11). Moreover, Huang *et al.*, found that 75% of patients with PCOS have hyperandrogenism, and more than 80% of the patients present with elevated free testosterone levels (12). The results of this study also showed significant increase in mean value of serum LH, and LH/FSH ratio with significant decrease in mean value of serum FSH in women with PCOS as compared with controls, these findings consist with previous study which showed higher levels of LH and lower levels of FSH in PCOS group comparing to controls group (13). Alterations in gonadotropin releasing and insensitivity of ovaries to hypothalamic secretion of gonadotropin releasing hormone (GnRH) causing increased LH pulse amplitude and frequency. Also, impairment in FSH secretion lead to an elevation in LH/FSH ratio in PCOS patients (14). In addition, the data of this study demonstrated that higher levels of fasting serum glucose, insulin, and HOMA-IR in PCOS group when compared with controls group which agree with previous studies (15, 16, 17, 18). Hyperinsulinemia, peripheral insulin resistance, and impaired glucose tolerance are principle metabolic abnormalities seen in PCOS (19). Hyperinsulinemia found in PCOS, may due to functional problems of the insulin. Insulin receptors have been found in ovaries (20). Thus, insulin has ability for enhancing steroidogenesis and ovarian growth, result in increased intra ovarian androgens synthesis as well as disrupts normal folliculogenesis, this leading to the development of numerous ovarian cysts and enlarged ovary (15). This study revealed that significantly lower levels and higher percentage of vitamin D deficiency in women with PCOS

comparing to age and BMI matched controls, this finding in agreement with prior researches (11, 15), which suggested that high prevalence of IR and low vitamin D levels which in turn could responsible for the metabolic and endocrine abnormalities in PCOS (15). In this issue, Hahn *et al.* proposed that low vitamin D levels might be a primeval factor in the initiation and progression of PCOS, and that dietary abundance of vitamin D could help to restore normal menses in female with this syndrome (21). Several studies also assumed that vitamin D deficiency might be a causal factor in the pathogenesis of IR and the metabolic disturbance found in PCOS (22, 23). In addition, recent studies which concluded that low vitamin D levels may aggravate the symptoms of PCOS, including IR, ovulatory dysfunction, irregular menses, impaired fertility, and hydperandrogenism (24, 25). The result of this study also found negative correlation between 25-hydroxy vitamin D levels with fasting serum glucose, insulin and HOMA-IR in patients group similar to other studies (11, 15, 26, 27, 28). Certain evidence regarding the role of vitamin D in the development of metabolic and endocrine abnormalities in PCOS mediated by IR (29). Vitamin D may have useful impact on insulin action via enhancing the expression of insulin receptors and thus stimulating insulin action for glucose metabolism (30). It was suggested that vitamin D response element found in the promoter region of the human insulin gene (31) and transcription of insulin gene stimulated by active vitamin D (32). Also, vitamin D has an impact on the immune system (33). Low vitamin D levels could enhance a higher inflammatory response that correlated with IR (34). The data of this study showed significantly lower serum calcium levels in patients comparing to controls, this result similar to (16, 35). Possible explanation that decreasing calcium absorption when the serum 25-hydroxyvitamin D levels ≤ 20nmol/l (36). Vitamin D has important role in regulation of calcium concentration and flux through the β-cells of pancreas (37). Thereby, calcium enhances insulin secretion from pancreas (38). Thus, any modification in calcium flux could have an adverse effect on insulin secretion (39). Recent concept suggested that impact of vitamin D on reproduction may be not direct, but secondary to the accompanying low calcium or estrogen dysregulation (40).

Conclusion:

Vitamin D has a role in metabolic and hormonal disturbance seen in PCOS through impact of vitamin D on insulin releasing and function.

Authors' Contributions:

Study conception, Study design and Critical revision: Rana Ali Hamdi, dr.Zina Hassan Abdul-Qahar and dr.Ekhlas Jabbar Kadhum.

Acquisition of data analysis, Drafting of manuscript and Interpretation of data: Rana Ali Hamdi and dr.Zina Hassan Abdul-Qahar, and dr.Fatin Abdul - Aziz Alsaeed

Samples were provided by: dr.Ekhlas Jabbar Kadhum, and dr.Fatin Abdul-Aziz Alsaeed

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