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Effects of Vitamin D Deficiency in Polycystic Ovarian Syndrome

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Abstract

Polycystic ovary syndrome is a very common cause of female infertility. This study aims to assess the prevalence of vitamin D deficiency and its association with clinical and anthropometric characteristics of Iraqi women with and without polycystic ovary syndrome. Fifty eightwomen with the disease and their matched control group were included. Their blood pressure was measured. Serum level of 25 hydroxy vitamin D of <20 ng/mL was graded as vitamin D deficiency. The polycystic ovary syndrome group had significantly lower levels of 25 hydroxy vitamin D, higher body mass index, and higher waist to hip ratio in contrast to the control group. The difference in body mass index was more significant in the obese category. Within subjects with the waist to hip ratio of ≥0.85, who were all vitamin D deficient, vitamin D was significantly lower and waist to hip ratio was significantly higher in patients than in controls. Vitamin D levels were significantly lower in patients than in controls in the non-hypertensive category. Further studies are needed to investigate the role of vitamin D in the pathogenesis of polycystic ovary syndrome.

Keywords: PolycysticOvary Syndrome, Vitamin D, Body Mass Index, Waist-to-Hip-Ratio, Blood pressure.

تأثير حالة النقص في فيتامين د على متلازمة تكيس المبايض

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الخلاصة

تعد متلازمة تكيس المبايض من الاسباب الشائعة جدا لعقم النساء. تهدف الدراسة الى تقييم مدى انتشار نقص فيتامين (د)وارتباطه بالخصائص السريرية والتمثيل الغذائي للمرأة العراقية المصابة بمتلازمة تكيس المبايض وغير المصابة به. اشتركت 58 امرأة مصابة بمتلازمة تكيس المبايض ومجموعة مماثلة من غير المصابات في هذه الدراسة. و قد تم قياس ضغط الدم لديهم. صُنف مستوى المصل من 25 هيدروكسي فيتامين (د) (أقل من 20 نانوغرام / مل) على أنه نقص فيتامين (د). أظهرت النتائج ان لدى مجموعة مرضى متلازمة

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تكيس المبايض مستويات أقل بكثير من 25 هيدروكسي فيتامين (د) ، ومؤشر كتلة جسم أعلى ، ونسبة أعلى من الخصر إلى الورك من المجموعة المماثلة.كان الفرق في مؤشر كتلة الجسم أكثر وضوحا في فئة السمنة. ضمن فئة (نسبة الخصر إلى الورك البالغة 0.85) حيث ان جميع هذه الفئة كانت لديها نقص فيتامين (د) ، كان فيتامين (د) أقل بشكل ملحوظ ونسبة الخصر إلى الورك أعلى بكثير في المرضى مقارنة بالمجموعة التي لا تعاني من المرض. كانت مستويات فيتامين (د) أقل بشكل ملحوظ في المرضى عنها في المجموعة المماثلة في الفئة التي لا تعاني من ارتفاع ضغط الدم.هناك حاجة لدراسات إضافية تستقصي دور فيتامين (د) في التسبب في متلازمة تكيس المبايض.

1. Introduction

Polycystic ovary syndrome (PCOS)is one of the commonest causesof female infertility.Clinical features caused by high levels of androgens, oligomenorrhea, and polycystic ovarian morphology are necessary for diagnosis[1]. There is a dynamic relationship between activities of hypothalamic-pituitary-(adrenal/ and or ovarian axis) and metabolic diseases such as obesity, with involvement of compensatory hyperinsulinemiaand insulin resistance [2, 3]. PCOS raises the risks ofdyslipidemia,hypertension, andhyperglycemia [4], thus raising the risk of developing cardiovascular diseases [5].

Vitamin Ddeficiency is noticed innumerous countries[6]. In vitamin D deficiency, the emergence of many diseases can be caused by defect in the metabolism of calcium and the building up of pro-inflammatory cytokines. It has been reported to lead to the development of cancer, diabetes, atherosclerosis and hypertension [7, 8]. Despite this, there is no agreement on the differences in serum vitamin D levels among women having and not having PCOS. Many studies reported that vitamin D of patients with PCOS wasinversely correlated with metabolic disturbances [9-22]. Increased risk of PCOS or its associated endocrine/metabolic disturbances were linked with polymorphism of vitamin D receptor gene, which presents the effect of vitaminD in PCOS pathogenesis [12, 13, 16].

The aim of this study is to assess the prevalence of vitamin D deficiency and its association with clinical and anthropometric characteristics of Iraqi women with and without polycystic ovary syndrome.

2. Materials and Methods

Across-sectionalcomparative analytical study designwas applied on two unpaired groups. This studywas conducted in the Central public health laboratory/Ministry of Health, Baghdad, Iraq,fromJuly 2017to October 2017. PCOS was diagnosed by using the 2003 Rotterdam criteria. According to these criteria, diagnosis requires the presence of at least two of the following three findings: hyperandrogenism, ovulatory dysfunction, and polycystic ovaries [23].Fifty-eight female patientsaged 18-45 years, single and marriedwere included in this study. They had been diagnosed with PCOS atAl-ElwieyaEducational Hospital and Kamal Al-Samarrai Hospital for fertility and infertility. They have never been diagnosed with any endocrine disorder (diabetes mellitus, hyperprolactinemia, Cushing syndrome), virilizing tumors, renal, or liver diseases, and never taken calcium or vitamin D supplements,.Fifty-eight adultfemales without PCOS were enrolled as controls,matched with the patients based on age and BMI with the matching ratio between the two groupshaving the value ofone.An oral consent has been taken from all participants.

Standard conditions were used for blood pressure measurement.

It was found that the best method for evaluating vitamin D status is by measuring 25-hydroxy vitamin D level [24]. Serum concentration of 25-hydroxy vitamin D [25-(OH) D]was measured using mini VIDAS immunoassay analyzerby the Enzyme-Linked Fluorescent technique (ELFA) usingVIDAS25 OH VITAMIN D TOTAL (VITD) kit(BIOMERIEUX,France).Vitamin Dlevels were considered sufficient when 25-(OH)D concentrationwas≥30 ng/mL,insufficient when the concentration was20-29 ng/mL, and deficientwhen the concentrationwas <20 ng/mL [26, 27].

3. Results and Discussion

Table 1 illustrates that vitamin Ddeficiency was spotted in 93.1% of patients and 75.86% of controls, while 6.9% of patients and 24.14% of controlshadinsufficient vitamin D. No one of the subjects in both patients and controls had a sufficient level ofvitamin D (≥30 ng/mL).

Table 1-Generalcharacteristics ofPCOS patients and controls

Characteristics	Group			
	PCOS		Control	
	N	%	N	%
Age				
≤ 20	10	17.4%	2	3.4%
21-30	14	24.1%	18	31%
31-40	24	41.3%	20	34.6%
≥ 41	10	17.2%	18	31%
Marital status				
Married	38	65.5%	40	68.9%
Unmarried	20	34.5%	18	31.1%
BMI				
Under weight	0	0	2	3.4%
Normal weight	10	17.2%	20	34.5%
Over weight	14	24.2%	16	27.6%
Obese	34	58.6%	20	34.5%
WHR				
< 0.85	16	27.5%	26	44.8%
≥ 0.85	42	72.5%	32	55.2%
Vitamin D levels				
Deficiency	54	93.1%	44	75.86%
Insufficiency	4	6.9%	14	24.14%
Sufficiency	0	0%	0	0%
Blood pressure status				
Hypertension	4	6.89%	6	10.34%
Normal	54	93.10%	52	89.66%

This study focused on vitamin D status in terms of the estimation of its deficiency in the two groupsand its correlation with BMI, WHR, and HTN. We found a highly significant difference invitamin D levels between PCOS women and controls(Tables 2 and3). The same highly significant correlation between PCOS patients and controls was also found in BMI and

WHR.PCOS patients and controls did notshow a significant differencein blood pressure (Table 2).

Table 2-Physical and biochemical parameters of PCOS patients and controls

Parameters	Group		P-Value
	PCOS (N= 58) Mean ± SD	Control (N=58) Mean ± SD	
BMI	31.5 ± 6.8	27.4 ± 5.7	< 0.001**
WHR	0.87 ± 0.06	0.84 ± 0.05	< 0.001**
Vitamin D levels (ng/mL)	10.2 ± 4.01	13.3 ± 6.3	< 0.001**
Systolic blood pressure (mmHg)	117.6 ± 12.3	116.5 ± 13.8	> 0.05*
Diastolic blood pressure (mmHg)	76.5 ± 10.01	75.8 ± 11.4	> 0.05*
*=N.S. - **=H.S.			

We found a significant correlation in the BMI value between PCOS patients and controls ofthe normal weight group. The correlation becomes highly significant in the obese category, which indicates the potential relationship between obesity and PCOS (Table 3). The same highly significant correlation was noticed in WHR between PCOS patients and controls inthe ≥0.85 category (Table 3).

Table 3-Distribution of vitamin D levels, BMI, and WHR in PCOS patients and controls.

Characteristics	Group				P.Value
	PCOS		Control		
	N	M ± SD	N	M ± SD	
Vit. D levels (ng/mL)					
Deficiency	54	10.6 ± 3.9	44	13.1 ± 6.3	< 0.001***
Insufficiency	4	22.1 ± 1.5	14	22.8 ± 1.1	> 0.05*
Sufficiency	0	0	0	0	0
BMI					
Under weight	0	0	2	27.13 ± 5.9	0
Normal weight	10	21.1 ± 1.3	20	22.2 ± 1.5	= 0.05**
Over weight	14	27.6 ± 1.9	16	26.8 ± 1.5	> 0.05*
Obese	34	36.1 ± 3.9	20	34 ± 2.9	< 0.001**
WHR					
< 0.85	16	0.79 ± 0.04	26	0.79 ± 0.02	> 0.05*
≥ 0.85	42	0.91 ± 0.04	32	0.88 ± 0.02	< 0.001***
*=N.S. -**=S. - ***=H.S.					

Previous researches reported that vitamin D in PCOS patients had a mean value of<20 ng/mL [26-27, 35]. In this study, vitamin D in PCOS group had a mean of lowerthan 20 ng/mL (10.2±4.4 ng/mL) (Table 2) and the deficiency state(<20 ng/mL) was observed in 93.1% of patients (Table 1). Previous studies recorded a prevalence of vitamin Ddeficiencyin the general populations of 10% to 60% of adults [28, 29]. As illustrated in Table 1, the control group in our study also had a vitamin D deficiency of 75.86%, with a mean level of 13.3±6.3 ng/ mL (Table 2). Wehr *et al*. reported that vitamin Dlevel was lowerin comparisonwith controlsin a study of 545 women with PCOS [13].

Another study reported that PCOS women have significantly higher vitamin D concentrations in contrast to controls with similar BMI and age [10]. Thus,we can assume that vitamin D deficiency ispredominant in both groups, regardless of the inconsistency in literatures concerning the fact that vitamin D levels were different between women with PCOS and control subjects.

The high prevalence of vitamin D in the current study can be caused by more than one factor. Vitamin D synthesis in the skin is one of the main sources of the vitamin. Women staying most of the day at indoor places, those putting sun-screen lotion on their skin to prevent the harmful effect of sunrays, especially during summer season, and those with certain wearing styles are susceptible to vitamin D deficiency [30- 37]. Moreover, dietary habits of Iraqi people who consume poor vitamin D-containing food must be kept in mind as a further cause [36].

Actually, we observed the insufficiency in vitamin D in 6.89% of patients and 24.13% of controls (Table 1). These findings strengthen the above possibility of the presence of many factors other than PCOS that may play important roles in affecting vitamin D status in our studied group.

Several researches reported inverse correlations between many obesity measures (e.g. body fat, BMI, and waist circumference) and vitamin D levels in PCOS women and matched controls [11, 15, 21].Li *et al*.showed an inverse correlation between BMI and the 25(OH)D levels, in which72%of PCOS subjects had vitamin D deficiency and 44% had severe deficiency (<25 ng/mL) [18]. Wehr *et al*. observed the same association in a sample of 206 PCOS patients, among which 72% had vitamin D deficiency. An inverse relationship between 25(OH) D levels and BMI was also recorded in another study [19]. Sidabutar *et al*.recorded an inverse associationof 25(OH) D with both BMI and WHR. In PCOS women group, they found that not all incidents of the deficiency of vitamin Dareassociated with PCOS because its levels were still normal in nine patients, but five patients had insufficiency and nine had deficiency [20].

This study presented a highly significant variation in serum vitamin D level within the WHR≥0.85 category between PCOS and matched controls (Table 4).Nonetheless,no significant correlation was found betweennormal, overweight, and obese groups with serum vitamin D level in patients and matched controls (Table 4).

The correlation between serum 25-OH vitamin D levels and the percent of body fat is strongerwhen compared to its correlation with body weight or BMI. Athletes and well-trained people may still have relatively high BMI and may be considered overweight or even obese despite the quite low total fat mass. This indicates that it is adiposity, not simply body mass that influences the serum level of 25-OH vitamin D [31]. These causes could contribute to the finding of our study. In addition to that, scientists found that, independent of BMI, women with PCOS have a higher prevalence of upper-body obesity, as demonstrated by increased waist circumference and waist-hip ratio, as compared to BMI-matched control women; a finding that strengthen the role of adiposity measured by WHR in PCOS [32].

Table 4-Distribution of the vitamin D levels in PCOS patients and controls based on BMI and WHR

Characteristics	Vit. D levels (ng/mL)				Value
	PCOS		Control		
	N	Mean ± SD	N	Mean ±SD	
WHR					
< 0.85	16	11.6 ±6.3	26	16 ± 6.8	<0.05 **
≥ 0.85	42	9.7 ± 2.5	32	11.2 ± 5.0	< 0.001 ***
BMI					
Under weight	0	0	2	21.2 ± 0.1	-
Normal weight	10	10.6 ± 5.3	20	15.4 ± 7.6	> 0.05*
Over weight	14	10.6 ± 5.5	16	12.4 ± 5.9	> 0.05*
Obese	34	10.06 ± 2.70	20	11.23 ± 4.24	> 0.05*
Blood pressure status					
Hypertension(mmHg)	4	11.1± 3.1	6	9.1± 1.4	> 0.05*
Normal(mmHg)	54	10.16 ± 4.1	52	13.8 ± 6.5	< 0.001 ***
***=N.S. -**=S. - ***=H.S.**					

At the time that PCOS patients within the WHR≥ 0.85 category were found only in vitamin D deficient category, PCOS patients within the WHR< 0.85 category, along withcontrols in both WHR categories, were found in both insufficient and deficient vitamin D categories(Table 5). Similarly, the obese group in BMI classification lied also in the vitamin D deficient category only, unlike the other BMI categories (Table 5)

Higher WHR and BMI are associated with obesity. The above findings could be explained by the fact that obesity is associated with high prevalence of vitamin D deficiency. Causes may be attributed to volumetric dilution into the greater volumes of fat, serum, liver, and muscle, despitethat the complete exclusion of other mechanisms is not possible, as they may contribute concurrently. On the other hand, low vitamin D could not yet be excluded as a cause of obesity [33].

Our results point out the role of vitamin D in the pathogenesis of PCOS.Vitamin D by itself can be a cause of PCOS. Evidences verify that vitamin D plays an essential role in reproductive activities and that the reproductive system, including ovaries, the endometrium, and the placenta, has receptors forvitamin D. Also, it has been found that calcium dysregulation, a condition related to vitamin D deficiency, is responsible for the increase in the follicular arrest and results in menstrual and fertility disorders in women with PCOS [22].ThePCOS group in our study had a significantly lower vitamin D concentration than the control group.

Only 6.89% of PCOS patients and 10.34% of controls in our study had HTN (Table 1) and they lied in the vitamin D deficient category only (Table 5).

Zhang and his colleagues suggested that the risk of hypertension increased substantially below 75 nmol/L as 25(OH) D decreased [34]. Kota *et al*. found that inadequacy of vitamin D causes an increase in systolic and diastolic blood pressure, proposing that vitamin D

deficiency is associated with renin-angiotensin-aldosterone system regulation [35]. This could explain why only the vitamin D deficient category has hypertension.

Vitamin D concentrations were significantly lower in PCOS patients than in controls in the non-hypertensive blood pressure category, while this significant correlation was not present in the hypertensive category (Table 4).

The numbers of PCOS patients and controls in the non-hypertensive category (54 and52, respectively) were remarkably higher thanthose numbers in the hypertensive category (4 and6, respectively).Thisconfersmore statistical power in detecting significant differences and could explain the above finding.

Table 5-Vitamin D status in PCOS patients and controls ased on BMI, WHR and bloodpressure

Characteristics	Vit. D levels (ng/mL)							
	PCOS				Control			
	Insufficiency		Deficiency		Insufficiency		Deficiency	
	N	M±SD	N	M±SD	N	M±SD	N	M±SD
BMI								
Under weight	0	0	0	0	2	21.2± 0.1	0	0
Normal weight	2	20.8± 0.1	8	8.1± 0.1	10	22.8± 0.8	10	8 ± 0.2
Overweight	2	23.4± 0.1	12	8.5± 1.2	2	24.4± 0.1	14	10.7±3.9
Obese	0	0	34	9.9± 2.7	0	0	20	11.2 ± 4.2
WHR								
< 0.85	4	22.10 ± 1.50	12	8.25± 0.2	12	22.58±1.00	14	10.4 ± 4.05
≥ 0.85	0	0	42	9.70 ±2.5	2	24.42±0.02	30	10.29±3.70
Blood Pressure (mmHg)								
Hypertensive	0	0	4	11.1± 3.1	0	0	6	9.1 ± 1.4
Normal	4	22.1 ± 1.5	50	9.2±2.3	14	22.8 ± 1.1	38	10.5±3.9

This study records no significant difference in blood pressure between PCOS and control groups in all BMI, WHR, vitamin D, and blood pressure categories (Table 6).

As we noticed earlier, our study showed variable findings in the studied groups regarding blood pressure status (Table 1). In addition, both systolic and diastolic blood pressure values did not differ significantly between PCOS and controls (Table 2). These findings make it unlikely to find significant differences in blood pressure between the two groups when studied based on other different parameters. Furthermore although we adjusted for BMI and WHR when we compared the blood pressure between the two groups (Table 6), scientists reportedthat even in the studies which did adjust the analyses for BMI, either statistically or by study design involving matching control women by BMI, the association between hypertension and PCOS was not always clear [30].This could explain the variable findings regarding blood pressure in our study.

Table 6-Association ofsystolic and diastolicblood pressure in patients and control groupbased on different parameters

Characteristics	Blood pressure (mmHg)									
	Systolic BP				P.value	Diastolic BP				P.value
	Patients		Control			Patients		Control		
	N	M ±SD	N	M±SD		N	M±SD	N	M±SD	
BMI										
Under weight	0	-	2	116.3±13.8	-	0	-	0	-	-
Normal weight	12	117.9 ±12.4	20	116.4± 14.2	> 0.05*	10	67.3± 22.6	20	66.3± 21.3	> 0.05*
Over weight	16	118.5± 12.7	16	118.3± 12.3	> 0.05*	12	66.3± 23.8	18	67.5± 20.5	> 0.05*
Obese	30	117.7± 12.4	20	116.6± 13.9	> 0.05*	36	67.5± 22.5	20	66.5± 21.5	> 0.05*
WHR										
< 0.85	16	118.5± 12.5	22	116.5± 12.9	> 0.05*	16	66.2 ± 22.3	28	71.5 ± 6.6	> 0.05*
≥ 0.85	42	117.7± 12.4	36	116.7± 13.8	> 0.05*	42	68.1 ± 0.06	30	62.5 ± 26.6	> 0.05*
Vit. D levels (ng/mL)										
Deficiency	54	117.8±12.7	44	120.0±12.94	> 0.05*	54	67.7 ±10.3	44	78.2±11.7	> 0.05*
Insufficiency	4	115.00±5.8	14	105.71 ±10.9	> 0.05*	4	75.00±5.8	14	68.6±6.6	> 0.05*
Sufficiency	0	0	0	0	-	0	0	0	0	-
Blood Pressure (mmHg)										
Hypertensive	4	150.0 ± 11.5	6	140.0±0.0	> 0.05*	4	100.0 ± 8.2	6	100.0 ± 6.3	> 0.05*
Normal	54	115.2 ± 8.4	52	113.8±11.9	> 0.05*	54	74.8 ± 7.9	52	73.1 ± 8.3	> 0.05*
*=N.S.										

4. Conclusions

Vitamin D concentration was significantly lower in the PCOS group than in the control group. Further research is needed for studying the role of vitamin D in the pathogenesis of this disease.

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