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The Role of Vitamin D Deficiency in Pathogenesis of PCOS: A Case-Control Study Among Females in Mosul City

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Abstract

Background Polycystic ovary syndrome (PCOS) is a common endocrine condition primarily affecting women of reproductive age. The prevalence of PCOS is 3 to 10%. According to the pathogenesis of PCOS; obesity, hyperandrogenemia, insulin resistance (IR), hormonal imbalances and metabolic dysregulation are patterns of PCOS. Vitamin D deficiency may be associated with PCOS and it has been shown that low vitamin D levels may worsen PCOS symptoms.

Objective To prove the role of vitamin D deficiency in pathogenesis of PCOS.

Methods A case control study with a sample size of (80) women. The females included in this study were single or married but not pregnant. They were divided in to 2 groups: 40 females having PCOS and 40 females without PCOS. Parameters measured were total serum testosterone, serum prolactin level and vitamin D level by i-chroma, also body mass index (BMI) (kg/m^2) and waist-hip ratio (WHR).

Results In PCOS group, (97.5%) of patients had low vitamin D levels, which is significantly higher than those of the control group who only (65%) of them had low vitamin D level. Also, PCOS group had significantly higher serum prolactin and serum testosterone than control group. The percentage of PCOS patients with irregular menstrual cycle was 80%, and with hirsutism was 57%, while with acanthosis was 42%.

Conclusion There is a relationship between vitamin D status and a variety of PCOS symptoms, emphasizing the possible contribution of vitamin D deficiency to symptom severity.

Keywords Polycystic ovary syndrome, vitamin D, serum prolactin, serum total testosterone.

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List of abbreviations: AN = Acanthosis Nigricans, BMI = Body mass index, CVD = Cardiovascular disease, GnRH = Gonadotropin releasing hormone, HDL-C = High-density lipoprotein cholesterol, HOMA-IR = Homeostasis model assessment of insulin resistance, IR = Insulin resistance, LDL-C = Low-density lipoprotein cholesterol, LH = Luteinizing hormone, PCOS = Polycystic ovary syndrome, TGs = Triglycerides, WHR = Waist to hip ratio

Introduction

In women of reproductive age, polycystic ovary syndrome (PCOS), an endocrine condition, may affect a significant percentage of them [(1)]. PCOS prevalence ranges from 3 to 10%, the prevalence is thought to be unknown for specific population and varied according to geographical location. The diagnostic criteria used and the populations investigated in various geographic areas can affect the prevalence [(2,3)]. Obesity, insulin resistance (IR) and hyperandrogenemia, are all patterns of PCOS, according to the etiology of the condition, along with hormonal

abnormalities and metabolic dysregulation [4]. Compared to healthy women, PCOS women were more likely to have dyslipidemia, which is characterized by higher levels of triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), and lower levels of high-density lipoprotein cholesterol (HDL-C) [5].

Other factors, such as endothelial connectivity, systemic inflammation, and IR, add to this constellation of signs and symptoms and increase patients' risk of cardiovascular disease compared to those without PCOS [5,6]. Reduced insulin sensitivity may inevitably result in compensatory hyperinsulinemia, which may stimulate ovarian theca cells chronically, resulting in the development of hyperandrogenism [6,7].

Several studies linked the association between deficiency of vitamin D and the presence of PCOS [8]. Vitamin D is a steroid hormone that is produced in the body when skin is exposed to ultraviolet rays from the sun as shown in figure (1).

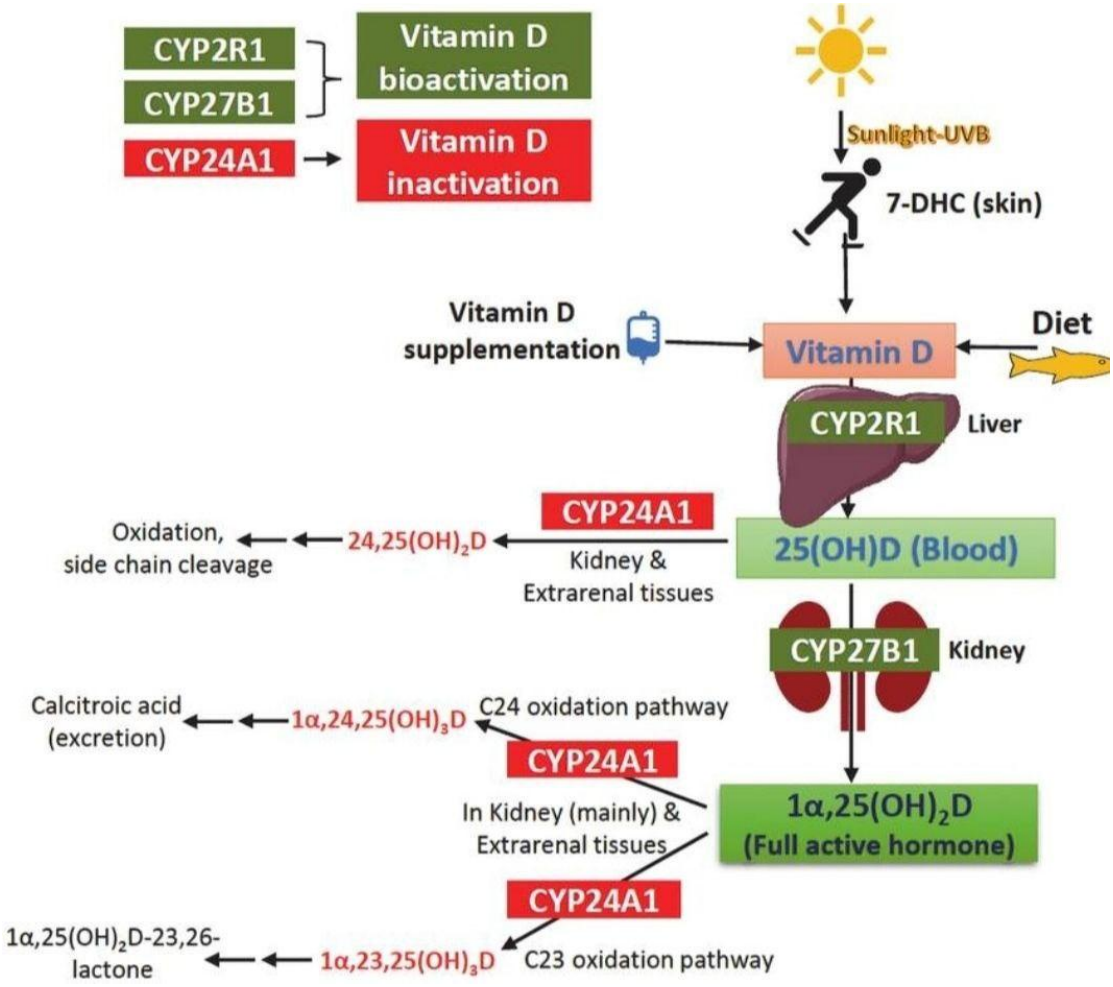

Figure 1. Vitamin D synthesis [9]

The body's various vitamin D receptors, which are found in the intestine, breast, bones, pancreas, kidney, immune cells, ovary, and uterus, allow the active form of vitamin D, 1,25-dihydroxyvitamin D, to influence organ metabolism and function. Additionally, vitamin D stimulates pancreatic cells to produce and secrete more insulin [9]. Although it has been

established that PCOS women have lower vitamin D levels than healthy women, the connection between vitamin D and metabolic variables in PCOS women is still up for debate. According to several research, women with PCOS exhibited lower levels of vitamin D than healthy women, and vitamin D insufficiency was linked to homeostasis model assessment of insulin resistance (HOMA-IR) [8,10]. Low vitamin D levels have been demonstrated to exacerbate PCOS symptoms; hence, there is an inverse relationship between serum vitamin D levels and the metabolic, hormonal symptoms of PCOS [11,12].

Because of the steroidogenic hyperactivity that results from the disruption in ovarian hyperandrogenism, the ovary produces both androgens and estrogens. Hyperandrogenism typically manifests as hirsutism and acne [13]. The increased secretion by the hypothalamus of gonadotropin releasing hormone (GnRH) and subsequent release of luteinizing hormone (LH) by the pituitary gland, consider the primary cause of hyperandrogenism [14,15].

Insulin, which acts directly through the insulin receptor or indirectly through the growth factor 1 receptor, exacerbates the hyperstimulation of theca cells by LH [16]. Lipocytes, the liver, and skeletal muscle all exhibit IR, whereas steroidogenic tissues exhibit insulin sensitivity [17].

Pubescent girls and adult women with polycystic ovaries are more likely to be obese. Obesity aggravates IR [18]. Free fatty acids, triglycerides, and lipogenesis were all elevated as a result of IR reduced lipolysis inhibition [19]. Any excess fat is stored in the muscle, liver, and pancreas due to the rise of lipids in the fatty tissue [20]. Abdominal fat accumulation is thought to increase the risk of cardiovascular disease [21].

Clinical manifestations of PCOS

1. Infertility

The pathogenesis of infertility is linked to LH oversecretion; also, the ratio of LH/FSH is increased resulting in an ovarian hyperandrogenism [22].

2. Hirsutism

The enzyme 5 α-reductase in hair follicles is enhanced by hyperandrogenemia and insulin [23], this enzyme inside the hair follicle converts testosterone to dihydrotestosterone and subsequently binds to the receptors, androgen transforms the vellus hair into terminal hair.

3. Alopecia (Androgenetic)

Characterized by frontal baldness. This may be caused by high levels of androgen receptors and the enzyme 5 α -reductase [24].

4. Acne.

In comparison to the normal population, it is proposed that patients had higher androgens receptor sensitivity [25], although there are many factors combine to cause acne, among these factors is androgenic hormones especially DHT that stimulates sebaceous glands activity and increases sebum production.

5. Acanthosis Nigricans (AN)

The upper layers of the skin thicken and darken in AN; histologically characterized by hyperkeratosis and papillomatosis changes of the skin [26]. The posterior neck and the axilla are the usual sites of involvement. The prevalence of AN in India population varies from 7% to 30-40% [26]. AN often correlates to IR or obesity in obese populations, AN is most commonly associated with the disorders which are associated with IR, which include obesity, type 2 diabetes, and PCOS [2].

The aim of the study was to prove the role of vitamin D deficiency in pathogenesis of PCOS, understand the complexities of PCOS and underscore the importance of addressing vitamin D deficiency in its management and compare these with control.

Methods

This study was a case-control study conducted during the time period from March 2023 to March 2024.The sample size was (80) women. The females included in this study were single or married but not pregnant. Consent was taken in a consent form from the participants in the study. The research was agreed in College of Pharmacy, Ninevah University and approved by Ethical Committee of the College of Pharmacy at Ninevah University (Approval Letter no. 1 on 18.01.2024). After informed the females and taking their agreement for inclusion in the study, they were divided in to 2 groups: the first group patients: forty females having PCOS according to the criteria mentioned previously, 39 of them had abnormal level of vitamin D, either deficiency when serum D level less than 20 ng/ml or insufficient when a serum level of 20-30 ng/ml [27].

These patients attending private clinic for dermatological and venereal disease in Mosul city. The age of these females is within the reproductive age ranging from 14-45 years, these patients either complaining from one or more symptoms of PCOS like hirsutism according to ferrymen–galley scoring system of hirsutism, acne, androgenic alopecia, AN, and menstrual irregularity.

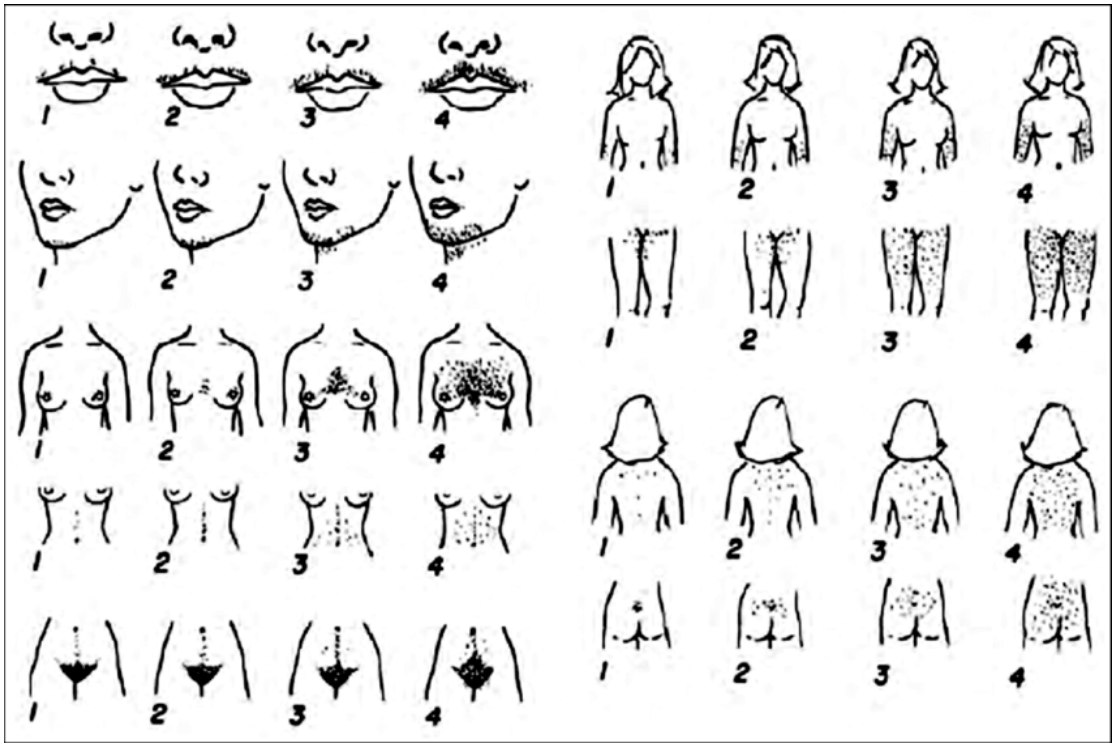

Figure 2. Diagram of ferryman–galley scoring system [28]

The second group controls: 40 females who did not have PCOS but have either normal or abnormal level of vitamin D, some of them had acne only. Their age was ranging from 14-45 years.

The parameters measured are:

- Total serum testosterone level (ng/ml)
- Serum prolactin level (ng/ml)
- Vitamin D level (ng/ml)

These three parameters measured by i-chroma-1

- BMI (kg/m^2) this as calculated by dividing weight (in kilograms) by height (in meters) squared.
- The waist-hip ratio (WHR), this is the waist circumference in centimeters divided by the hip circumference in centimeters.

Diagnosis of PCOS

1- National Institutes of Health Criteria (NIH) [29]; only two characters available:

- Oligo/amenorrhea anovulation.
- Clinical and/or biochemical hyperandrogenism.

2- Rotterdam criteria [30]

Depend upon existence of 2 or 3 of the following characters:

- Oligo ovulation.
- The hyperandrogenemia signs including: acne, alopecia, and hirsutism.
- Ultrasound examination of PCOS: At least 12 follicles or more with a diameter of 2 to 9 mm are existed in one ovary and/or an expanded ovarian size of more than 10 ml.

Statistical analysis

Microsoft Excel 2007 sheets were used to summarize the study's data collection. The statistical package for social science (SPSS) version 20 was used for the statistical analysis. The Shapiro-Wilk test was used to check whether these data were normal.

The numerical data were expressed in median, quartiles (25th and 75th), range, minimum, and maximum values while the categorical data were expressed in frequencies and percentages. Mann-Whitney U test has been used to find the association between the numerical data while Chi square test was performed for comparison between categorical variables and if any cell had an expected value below 5, the fissure exact teas has been used instead of Chi square test. Odd's ratio (OR) and 95% confidence interval (95% CI) was used as a measure of association between risk factors and development of disease. The P value ≤0.05 considered as significant.

Results

Comparison of the age and anthropometric measurements between patients and controls female without PCOS is demonstrated in table (1) and showed that the median age among the PCOS group was higher than that among controls group but not significant statistically (P = 0.595). While the medians of BMI and WHR (30.0 kg/m^2, 0.95) among the PCOS group were significantly higher than that among the controls group (26.0 kg/m^2, 0.76) at (P = 0.001, 0.000) respectively.

Table 1. Comparison of the age and anthropometric measurements between cases and controls

Age and anthropometric measurements	PCOS cases Median (IQR) (Range)	Controls group Median (IQR) (Range)	P value*
Age (year)	23.5 (17.0,30.8) (14.0-42.0)	25.5 (17.8,31.0) (14.0-44.0)	0.595
BMI (kg/m^2)	30.0 (26.0,32.4) (23.0-40.0)	26.0 (24.0,29.5) (23.0-31.0)	0.001
WHR	0.95 (0.9,1.2) (0.7-1.02)	0.76 (0.7,0.8) (0.6-1.0)	0.000

*Mann-Whitney U test has been used

Comparison of the blood tests between cases and controls is seen in table (2) and showed that the median of serum vitamin D among the PCOS group (10.6 ng/ml) was lower from that among the controls (21.0 ng/ml) (P = 0.000). While the median of serum prolactin among the PCOS (22.5 ng/ml) was significantly higher than that among the controls group (20.0 ng/ml) (P = 0.000). The medians of serum testosterone were (1.6 ng/ml) and (0.65 ng/ml) among PCOS and controls groups respectively; the difference was significant statistically (P = 0.000).

Table 2. Comparison of the blood tests between PCOS cases and controls

Blood tests	PCOS cases Median (IQR) (Range)	Controls group Median (IQR) (Range)	P value*
S. Vitamin D (ng/ml)	10.6 (8.0,15.0) (6.0-33.0)	21.0 (11.3,37.5) (7.3-53.0)	0.000
S. Prolactin (ng/ml)	22.5 (15.3,31.0) (8.3-70.0)	20.0 (15.5,24.5) (12.0-80.0)	0.000
S. Testosterone (ng/ml)	1.6 (0.85,2.5) (0.7-10.0)	0.65 (0.61,0.72) (0.46-1.0)	0.000

*Mann-Whitney U test has been used

Comparison of the study parameters between cases and controls was demonstrated in table (3) and showed that irregular menstrual cycle, androgenic alopecia, hirsutism, positive ultrasound findings, acanthosis, and positive family history among PCOS group were significantly differed from these among controls group with risky associations. In contrary, marital status and Acne showed no significant differences.

Table 3. Comparison of the other parameters between cases and controls

Study parameters		PCOS cases (n=40) No. (%)	Controls group (n=40) No. (%)	OR	95% CI	P value*
Marital status	Married	22 (55.0)	26 (65.0)	0.658	0.267, 1.619	0.361
	Single	18 (45.0)	14 (35.0)			
Menstrual cycle	Irregular	32 (80.0)	10 (25.0)	12.0	4.179, 34.453	0.000
	Regular	8 (20.0)	30 (75.0)			
Acne	Positive	8 (20.0)	12 (30.0)	0.583	0.208, 1.631	0.302
	Negative	32 (80.0)	28 (70.0)			
Androgenic alopecia	Positive	10 (25.0)	1 (2.5)	13.0	1.576,107.288	0.003
	Negative	30 (75.0)	39 (97.5)			
Hirsutism	Positive	23 (57.5)	2 (5.0)	25.705	5.434,121.593	0.000
	Negative	17 (42.5)	38 (95.0)			
Ultrasound	Positive	33 (82.5)	1 (2.5)	183.85	21.50, 1572.0	0.000
	Negative	7 (17.5)	39 (97.5)			
Acanthosis	Positive	17 (42.5)	3 (7.5)	9.115	2.403,34.57	0.000
	Negative	23 (57.5)	37 (92.5)			
Family history	Positive	12 (30.0)	2 (5.0)	8.142	1.686,39.317	0.003
	Negative	28 (70.0)	38 (95.0)			

*Mann-Whitney U test has been used

Comparison of the vitamin D level between cases and controls is showed in table (4). It elicited that insufficient and deficient level of vitamin D was found among 97.5% of PCOS group and sufficient level found in only in 2.5% of this group, while among the controls group; 65.0% had insufficient and deficient level and 35.0% had sufficient level; the insufficient and deficient level of vitamin D was associated with 21 times risk for the development of PCOS and the association was statistically significant (P = 0.000).

Table 4. Comparison of the Vitamin D level between cases and controls

Vitamin D level	PCOS cases (n=40) No. (%)	Controls group (n=40) No. (%)	OR	95% CI	P value*
Insufficient and deficiency	39 (97.5)	26 (65.0)	21.0	2.601, 169.539	0.000
Sufficient	1 (2.5)	14 (35.0)			

*Chi square test has been used

Comparison of the vitamin D level regarding the study parameters between cases and controls was demonstrated that the medians levels of vitamin D among the PCOS group were significantly lower than that among the controls group regarding the married women, with irregular menstrual cycle, presence of acne, androgenic alopecia, hirsutism, positive ultrasound findings, acanthosis, and positive family history (Table 5).

Comparison of the vitamin D level regarding the study parameters among cases was demonstrated in table (6) and revealed that the vitamin D level among the married women was significantly higher than that among the single women.

Vitamin D levels among women with PCOS were significantly lower among those who had irregular menstrual cycle, those who had acne, Androgenic alopecia, Hirsutism, positive ultrasound findings, Acanthosis, and positive family history.

Table 5. Comparison of the vitamin D level regarding the study parameters between cases and controls

Vitamin D level regarding the study parameters		PCOS cases (n=40) Median (IQR) (Range)	Controls group (n=40) Median (IQR) (Range)	P value*
Marital status	Married	11.0 (8.0,15.7) (6.0-23.0)	25.0 (12.5,39.0) (8.0-53.0)	0.001
	Single	9.9 (8.0,13.5) (8.0-33.0)	13.0 (8.6,36.0) (7.3-44.0)	0.085
Menstrual cycle	Irregular	8.0 (8.0,11.0) (6.0-14.0)	15.5 (11.0,17.0) (6.0-22.0)	0.002
	Regular	17.1 (8.0,14.5) (13.6-33.0)	21.0 (11.8,36.0) (6.0-44.0)	0.332
Acne	Positive	10.0 (8.0,15.0) (8.0-33.0)	16.0 (12.3,17.0) (8.0-36.0)	0.035
	Negative	15.2 (11.5,18.0) (6.0-22.0)	21.0 (11.0,31.0) (6.6-44.0)	0.023
Androgenic alopecia	Positive	8.0 (8.0,8.3) (8.0-9.0)	12.0 (12.0,12.0) (12.0-12.0)	0.044
	Negative	23.5 (18.8,26.0) (16.0-28.0)	25.0 (18.0, 31.0) (11.0-44.0)	0.386
Hirsutism	Positive	17.0 (13.0,17.0) (9.0-27.0)	28.0 (27.0,28.0) (27.0-29.0)	0.027
	Negative	22.0 (18.0,25.0) (11.0-27.0)	24.0 (17.0,31.0) (11.0-44.0)	0.218
Ultrasound	Positive	18.0 (14.8,22.3) (9.027.0)	28.8 (28.0,28.8) (28.0,29.5)	0.018
	Negative	26.0 (25.0,27.0) (17.029.0)	26.0 (21.0,31.0) (12.0,34.0)	0.712
Acanthosis	Positive	18.0 (13.5,24.5) (9.0-27.0)	26.0 (23.0,26.0) (23.0-28.0)	0.050
	Negative	23.0 (18.0,26.0) (14.0-29.0)	27.0 (22.0,31.0) (12.0-42.0)	0.017
Family history	Positive	18.5 (12.5,19.0) (12.0-21.0)	26.5 (26.0,26.5) (26.0-27.0)	0.024
	Negative	22.0 (17.3,26.0) (13.0-27.0)	22.5 (20.8,27.0) (12.0-42.0)	0.073

*Mann-Whitney U test has been used

Table 6. Comparison of the Vitamin D level regarding the study parameters among cases

Vitamin D level regarding the study parameters among cases		PCOS cases Median (IQR) (Range)	P value*
Marital status	Married	11.0 (8.0,15.7) (6.0-23.0)	0.001
	Single	9.9 (8.0,13.5) (8.0-33.0)	
Menstrual cycle	Irregular	8.0 (8.0,11.0) (6.0-14.0)	0.000
	Regular	17.1 (8.0,14.5) (13.6-33.0)	
Acne	Positive	10.0 (8.0,15.0) (8.0-33.0)	0.037
	Negative	15.2 (11.5,18.0) (6.0-22.0)	
Androgenic alopecia	Positive	8.0 (8.0,8.3) (8.0-9.0)	0.017
	Negative	23.5 (18.8,26.0) (16.0-28.0)	
Hirsutism	Positive	17.0 (13.0,17.0) (9.0-27.0)	0.015
	Negative	22.0 (18.0,25.0) (11.0-27.0)	
Ultrasound	Positive	18.0 (14.8,22.3) (9.0-27.0)	0.006
	Negative	26.0 (25.0,27.0) (17.0-29.0)	
Acanthosis	Positive	18.0 (13.5,24.5) (9.0-27.0)	0.039
	Negative	23.0 (18.0,26.0) (14.0-29.0)	
Family history	Positive	18.5 (12.5,19.0) (12.0-21.0)	0.020
	Negative	22.0 (17.3,26.0) (13.0-27.0)	

*Mann-Whitney U test has been used

Discussion

Numerous studies suggest that a lack of vitamin D may play a role in the pathophysiology PCOS. Low vitamin D levels are associated with obesity, insulin resistance, menstrual dysfunction, hirsutism, hyperandrogenism, and increased CVD risk factors, according to numerous studies [8,10,11,31].

In the present study, we took age and anthropometric measurements (BMI, WHR) between cases and controls since these measurements had a great impact on the incidence, prevalence of PCOS. Current study

showed that the median age among the PCOS group was lower than that among control group but statistically the difference was not significant, this finding is similar to previous study which showed that there is non-significant difference in the median age between PCOS and control groups.

Many researchers have shown an inverse relation between BMI and vitamin D levels [2,3], one study reported an inverse relation between BMI and WHR with vitamin D levels [32]. In current study, the medians of BMI and WHR among the PCOS group were significantly higher than that among the controls group, the explanation for that is leptin plays a critical role in the incidence and development of obesity, and vitamin D is an important factor of generating leptin, thus vitamin D deficiency can cause obesity by triggering an increase in appetite [33].

From this study, the serum vitamin D levels were significantly lower in the PCOS group than in the control group, numerous studies have showed low levels of vitamin D in women with PCOS; through gene transcription, vitamin D is thought to affect PCOS development, and hormonal modulation affects insulin metabolism and reproductive control [34], in spite of that in current study, it is found that some of the control group also complain from vitamin D deficiency because this problem is very common in Mosul city due to poor exposure to sun light, beside this fact the diet in Mosul city is deficient to sources of vitamin D like oily fish, including mackerel, salmon and sardines. Some food is supported by vitamin D, like breakfast cereals, plant milk and fat spread, in spite of that those females did not complain from PCOS because it is a multifactorial disease and there are other risk factors for the disease as shown in this figure (3).

Figure 3. Risk factors for PCOS [35]

Serum prolactin and testosterone among the PCOS was significantly higher than that among the controls group and these results were in accordance with results of other studies showed that serum prolactin and serum testosterone among the PCOS were elevated [36]. Moreover, the median of serum prolactin among the PCOS did not match the finding of another study that reported significantly lower prolactin levels in PCOS patients compared to controls [37].

Remarkable difference for vitamin D level was observed regarding the study parameters between cases and controls, the medians levels

of vitamin D among the PCOS group were significantly lower than that among the controls group regarding the married women, with irregular menstrual cycle, androgenic alopecia, hirsutism, positive ultrasound findings, AN, and positive family history. Acne showed no significant differences in between PCOS and control group, which consistent with previous study [38], this result can be explained by the fact that acne not a result of only high testosterone level but other causes make acne is a common problem among the patient and some of the control group [39].

An agreement with our study, one study carried on 169 PCOS women and 114 controls women, it showed the difference in the level of vitamin D between PCOS and control healthy women and there is a relation between metabolic problems and vitamin D levels in women with PCOS [40].

While study carried on 45 women diagnosed with PCOS and 45 women with fertility but without PCOS, the results reported that 25(OH) vitamin D was significantly lower in PCOS group than in healthy control group. In agreement with some studies regarding BMI with vitamin D level, there were no significant association between 25(OH) vitamin D and BMI [41,42].

A study done by Hahn et al. proposed low vitamin D levels could be an important factor in the initiation and development of PCOS, and abundance of vitamin D in food might help to return normal menses in women with PCOS [43].

A woman with excess androgen may present with acne, alopecia, and hirsutism. Grading systems may quantify the severity of these signs [44].

It was shown from other study that certain androgenic and metabolic variables developing in PCOS correlate with cutaneous symptoms in PCOS [25]. The present study reported that there is appositive relationship between AN and low vitamin D level which was significantly higher in PCOS women as compared to control thus agreed with other studies that noticed a high prevalence of AN in the PCOS patients [45,46].

In conclusions, vitamin D level was lower in the PCOS group compared to the control group, supporting the notion that vitamin D deficiency is more common in PCOS women. Among PCOS patients, lower vitamin D levels were associated with hirsutism, irregular menstrual cycles, acne, androgenic alopecia, and acanthosis.

Overall, the study findings suggest that PCOS is associated with several clinical markers, including higher BMI, WHR, irregular menstrual cycles, hormonal imbalances (elevated prolactin and testosterone). It is important to consider these factors when diagnosing and managing PCOS patients, as they may contribute to the understanding and treatment of the condition.

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Author contribution

Abow: Collection of data, study design. Alsarraf: The research plan and final revision of manuscript. Dr. Ali: Statistical analysis and interpretation and writing of manuscript.

Conflict of interest

No conflict of interest.

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