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Relation of Vitamin D Deficiency in Women with Polycystic Ovarian Syndrome in Kirkuk

Sundus Abdul kareem Mardan, Jacklen Zaea Khoshaba, Salwa Saadoon
Department of Obstetrics and Gynecology, Kirkuk General Hospital, Kirkuk, Iraq
sunduskareem@yahoo.com, jaklen_khoshaba@yahoo.com, salwa_sadoon484@yahoo.com

ABSTRACT

Polycystic ovary syndrome is one of the most chronic diseases affecting women. Some studies indicate that the level of vitamin D is related to the development of polycystic ovary syndrome. This vitamin-like hormone has a certain effect on insulin sensitivity and restoring reproductive capacity in women with polycystic ovary syndrome. Therefore, it was planned to study the relationship between vitamin D deficiency and PCOS. This study planned to show the relationship between vitamin D deficiency, total cholesterol level, and the appearance of polycystic ovary syndrome in patients attending Kirkuk General Hospital.

Keywords: Vitamin D, Polycystic ovary, cholesterol

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علاقة نقص فيتامين (د) لدى النساء المصابات بمتلازمة تكيس المبايض في محافظة كركوك

سندس عبدالكريم مردان, جاكلين زيا خوشابا, سلوى سعدون مصطفى

قسم النساء و الولادة, مستشفى كركوك العام, كركوك, العراق

sunduskaream@yahoo.com, jaklen_khoshaba@yahoo.com , salwa_sadoon484@yahoo.com

الخلاصة

يعدُ مرض متلازمة تكيس المبايض المتعدد من اكثر الامراض المزمنة التي تصيب النساء. بعض الدراسات تشير الى ان مستوى فيتامين (د) له علاقة بتطور متلازمة المبيض المتعدد الاكياس. حيث أن هذا الفيتامين مثل الهرمون له تأثيرات معينة على حساسية الأنسولين واستعادة القدرة على الإنجاب لدى النساء المصابات بمتلازمة المبيض المتعدد الاكياس. لذلك، تم التخطيط لدراسة العلاقة بين نقص فيتامين (د) و متلازمة المبايض متعدد الاكياس. الهدف من الدراسة: هذه الدراسة خططت لإقامة علاقة بين نقص فيتامين (د)، ومستوى الكولسترول الكلي، وظهورمتلازمة المبيض المتعدد الاكياس في المرضى اللاتي يُرَاجِعنَ مستشفى كركوك العام.

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1. Introduction

The term “polycystic” refers to a condition when many cysts developed in the ovaries of a woman. These cysts or follicles (fluid-filled sacs) contain eggs. The ovaries in the women with PCOS, do not produce enough hormones for the maturation of the eggs. When these eggs fail to escape, the follicles or cysts remain and build up in the ovaries, preventing ovulation. In addition, the ovaries tend to produce excess levels of androgens (male hormones) in women with PCOS, which can also negatively impact ovulation and fertility [1]. Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder in females affecting approximately 5% -10% of women of reproductive age. According to a cohort study conducted based on the criteria of the National Institutes of Health, the prevalence rate is 8.7% while in accordance with the criteria of Rotterdam, the prevalence is 11.2% and this number seems to decrease as the person gets older, especially from the age of 35 onwards. Definition and diagnosis of PCOS are based on criteria including clinical or paraclinical evidence of hyperandrogenism, ovarian dysfunction such as oligo-ovulation and the exclusion of other causes of hyperandrogenism such as adrenal hyperplasia, hyperprolactinemia, and thyroid disorders [2]. Polycystic ovarian syndrome (PCOS) is known to be one of the most prevalent endocrine disorders affecting 15–20% of reproductive-age women and is a primary cause of infertility. The clinical features of PCOS include menstrual irregularity, chronic anovulation, infertility, and hyperandrogenism. Hormonal imbalance in PCOS manifests as hyperandrogenism and hyperinsulinemia, with reciprocal negative effects and this corresponds with the severity of PCOS. Hyperinsulinemia could increase androgen and free androgen production by reducing the binding of androgen with sex-hormone-binding globulin (SHBG) [3]. The prevalence of PCOS can be as high as 30% in women with secondary amenorrhea, 40% in women with infertility, 75% in women with oligomenorrhea and 90% in women with hirsutism [4]. PCOS was believed to be a mere ovarian disorder. Nevertheless, increasing basic and clinical research imply that disruption in the neuroendocrine homeostasis of the hypothalamus-pituitary-gonadal axis drives and contributes to PCOS [5, 6]. Thereby in PCOS, there is an increased gonadotropin-releasing hormone (GnRH) pulsatile secretion from the GnRH neuron network. This, in turn, causes significant disturbances in luteinizing hormone (LH), follicle-stimulating hormone (FSH) and progesterone levels. Moreover, it decreases hypothalamus sensitivity to progesterone negative

feedback regulation. Such disruptions lead to increased androgen synthesis in the theca cells, causing anovulation, ovarian cysts, hirsutism and acne that are prevalent in PCOS [7]. Since obesity and insulin resistance are associated with PCOS in majority of patients, the molecules and hormones secreted by adipose tissue have been assumed to play a role in the pathogenesis of PCOS and therefore, were frequently investigated. It has been shown that adipose tissue plays an important role in the regulation of many physiological processes such as reproduction, immune response, and glucose and lipid metabolism through secretion of a variety of bioactive cytokines such as adipokine [8]. The pathogenesis of PCOS is not fully understood. One of the proposed mechanisms for hyperandrogenism is follicle maturation abnormalities, in which the growing follicle does not progress to a dominant follicle. Follicle maturation depends on the levels of follicle-stimulating hormone (FSH), which are reportedly suppressed to a level below the threshold for aromatase enzyme activation in patients with PCOS, resulting in high androgen levels. Another proposed pathology related to follicle maturation abnormality is reduced follicle sensitivity to FSH stimulation by Anti- Müllerian hormone (AMH) [9]. Moreover, testosterone, low serum 25(OH) vitamin D are also characteristic features in PCOS. It is well documented that 25(OH) vitamin D is a crucial player in follicular development, sensitivity to FSH and Anti-Müllerian hormone (AMH) signalling [7]. Dyslipidemia is also common in PCOS and includes high levels of total cholesterol and LDL, triglycerides and low HDL. Lipid disorders are seen in about 65–81% of these women [10]. Metabolic syndrome, which involves abnormalities in the metabolism of sugar, fat, protein, and maintenance of blood pressure, is an important complication of PCOS [2]. Insulin resistance and the resulting hyperinsulinemia are proposed to be the underlying deleterious causes for the relationship of metabolic disturbances and reproductive dysfunction in PCOS. The metabolic phenotype of PCOS is exacerbated by increased adiposity, and the prevalence of PCOS is greater with overweight and obesity [11]. Adipose tissue dysfunction has been implicated as a contributor to insulin resistance in women with PCOS figure (1.1). However, a substantial number of lean women affected by PCOS have insulin resistance as well, independent of obesity. Vitamin D deficiency has been proposed as the possible missing link between insulin resistance and PCOS [12].

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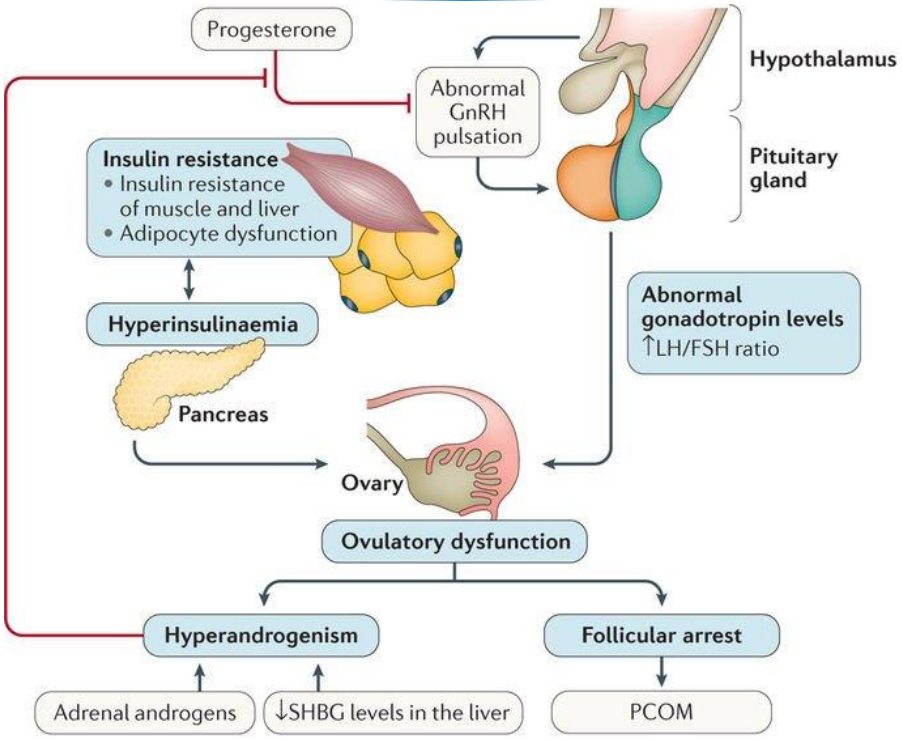

Fig. 1 Pathophysiology of PCOS [13]

2. PCOs and Vitamin D disturbance

Some studies have suggested that there is a relationship between serum levels of vitamin D and obesity and also other metabolic parameters in women with PCOS, including fasting glucose levels, fasting insulin resistance, high blood pressure, lipid disorders, fertility and other clinical and laboratory-related parameters associated with PCOS [14]. Some studies reported that obesity is a well-recognized risk factor in vitamin D deficiency. It was demonstrated an inverse correlation between body mass index and serum 25(OH)D concentrations in PCOS women [15]. Vitamin D receptor (VDR) is distributed across various tissues representing an active role of vitamin D in those tissues. The vitamin D receptor and vitamin D metabolizing enzymes are found in reproductive tissues of women and men. A study reported that vitamin D is involved in female reproduction including polycystic ovary syndrome (PCOS). In PCOS women, low 25-hydroxyvitamin D (25(OH)D) levels are associated with obesity, metabolic, and endocrine disturbances and vitamin D supplementation might improve menstrual frequency and metabolic disturbances in those women. Moreover, vitamin D might influence

steroidogenesis of sex hormones (estradiol and progesterone) in healthy women and high 25(OH)D levels might be associated with endometriosis [16]. Vitamin D is a steroid hormone. Vitamin D precursor 7-dehydrocholesterol is a normal intermediary in the cholesterol pathway and is present in the skin. Ultraviolet radiation induces the conversion of 7-dehydrocholesterol to provitamin D_3, which spontaneously isomerizes to cholecalciferol (vitamin D_3). A small amount of the body's total vitamin D is also derived from diet and/or supplements. This may derive from plants or fungi containing ergocalciferol (vitamin D_2) or fatty fish or cod-liver oil containing vitamin D_3. Vitamin D from the skin and diet is metabolized in the liver by the enzyme 25-hydroxylase (encoded by *CYP2R1*) to 25(OH)D, which is used to determine a patient's vitamin D status into vitamin D sufficient (25(OH)D ≥30 ng/ml; multiply by 2.496 to convert nanograms per milliliter to nanomoles per liter), vitamin D insufficient (25(OH)D 20–29 ng/ml), and vitamin D deficient (25(OH)D <20 ng/ml) [16]. Vitamin D3, a fat-soluble vitamin, can be produced in two ways: by intestinal absorption and endogenous synthesis from a precursor of 17-hydroxyl cholesterol on the skin with sufficient exposure to ultraviolet sunlight [17]. Serum 25(OH)D is the major circulating form of vitamin D and is used as the main indicator of vitamin D status. Its half-life is 2–3 weeks compared to only 4–6 hours for 1, 25(OH)2D [18]. Moreover, this assumption is supported by the finding that the active vitamin D-vitamin D receptor complex regulates over 300 genes, including genes that are important for glucose and lipid metabolism as well gonadal function [19]. Besides its role in calcium and bone metabolism, its deficiency causes a wide range of skeletal and extra-skeletal effects, with impact on glucose homeostasis, cardiovascular disease, cancer, autoimmune diseases and psychological disorders [20].

3. Objective

To establish the relationship between vitamin D deficiency, total cholesterol level, and the appearance of polycystic ovary syndrome in patients attending Kirkuk General Hospital.

4. Material and method

A cross-sectional study was made on 100 women aged 18-45 years old (60 women with polycystic ovary syndrome and 40 women with non-polycystic ovary syndrome as a control

group) selected from women attending Kirkuk General Hospital (Obstetrics and Gynecology Department), during the period from December 2018 to February 2019. Pregnant females, females taking multivitamins or smokers were excluded. A pre-tests questionnaire was used to obtain information from the participants about age, past medical history. A blood sample was obtained by using 5cc syringe, to examine 25-hydroxy vitamin D and total cholesterol levels. Patient with PCOS, females with PCO (ultra-sonographic detection of PCOs (> 12 follicles measuring 2-9mm) along with LH/ FSH ration >1 IU/L with oligomenorrhea (cycles > 35 days) or amenorrhea (fewer than 3 cycles in the past 6 months). In control group, females without PCO (normal female) were included. Controls selected as age-matched females who come as attendants with the patients. A blood sample was taken after at least 10 hours of fasting, for serum cholesterol investigation, serum concentration of 25(OH) D was measured by ELISA technique (LDN immunoassay and services, Germany). Statistical analyses characteristics are presented as mean & SD for continuous variables. T-Test probability interpreted as follows:

P value <0.01: Highly Significant.

$0.1 \leq (P\ value) \leq 0.5$: Significant.

P value > 0.05 : Non- Significant (NS).

5. Results

5.1. Relation of vitamin D with PCOS

Our study shows that serum vitamin D concentrations were highly variable in both PCOS patients and controls, also, there was a significant difference between PCOS patients and the control group concerning vitamin D level. The lowest mean of vitamin D was recorded among PCOS women (13.04±5.4 vs. 20.89±9.39), as shown in table (1.1) and figure (1.2). Normal level of Vitamin D: Deficient: less than 20 ng/ml, Insufficient: 20-29 ng/ml, Sufficient: 30 – 100 ng/ml.

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Table 1 Relation of vitamin D and PCOS

Parameters		PCOS (n:60)	Control (n:40)	T. Test	*P. value*
Serum Vitamin D	Mean	13.04	20.89	3.07	<0.05
	SD	5.4	9.39		

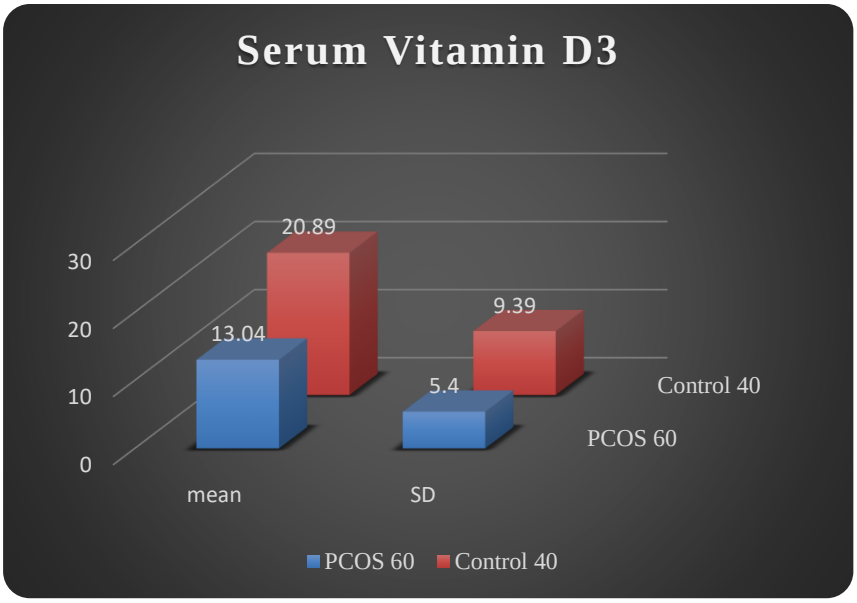

Fig. 2 Relation of vitamin D and PCOS

5.2. The relation between total cholesterol and PCOS

This study showes that the mean of total cholesterol in the PCOS women is higher than the mean in the control group (205.8±14.5 *vs.* 168.1±20.8 mg/dl), as seen in the table (1.2) and figure (1.3).

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Table 2 Relation between total cholesterol and PCOS

Parameter		PCOS Group	Control Group
		60	40
Total Cholesterol (mg/dl)	Mean	205.8	168.1
	SD	14.5	20.8
P- Value		0.01	

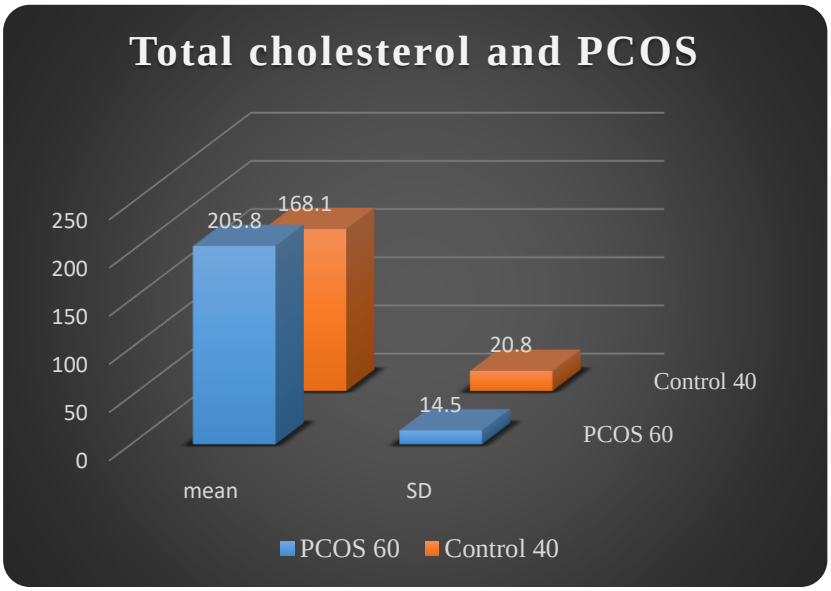

Fig. 3 The relation between total cholesterol and PCOS

5.3. Correlation of vitamin D with cholesterol

Our study shows that there is a highly significant correlation (*p*-value is .000053) between vitamin D and cholesterol in PCOS women and control group as seen in figure (1.4).

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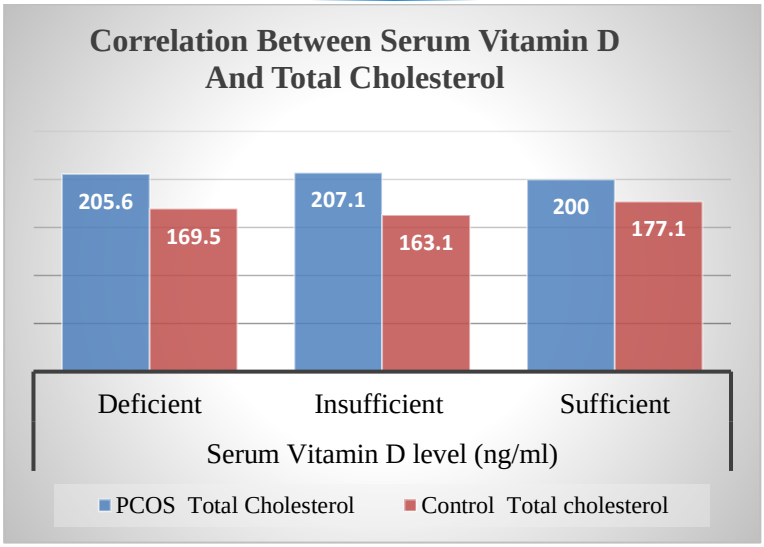

Fig. 4 Correlation of serum Vitamin D with total cholesterol in PCOS and Control group. Normal level of Vitamin D: Deficient: less than 20 ng/ml, Insufficient: 20-29 ng/ml, Sufficient: 30 – 100 ng/ml.

6. Discussion

PCOS is an endocrine disorder with multifactorial aetiology and various clinical manifestations. It's the most common cause of menstrual disorder and anovulatory infertility in women [21]. Our study showed that there was a significant difference between PCOS patients and the control group concerning vitamin D level and the lowest mean of vitamin D was recorded among PCOS women. Bashir *et al.* studies showed there was ascertained association between deficiency vitamin D and metabolic derangement seen in women with PCOs. It's fairly common for were with PCOs. That concomitant deficiency of vitamin D results in resistance to insulin, development of raised BP and biochemical derangements in Total Cholesterol, CRP, level of TG and LDL and HDL in blood [22]. Another study showed PCOs women had more predilection to cardiovascular disease than non-PCOs control (reference quote) [23]. Whereas other studies showed vitamin D higher in PCOs than in controls [24]. One meta-analysis failed to prove low levels of vitamin D in PCOs than non PCO control group [17]. A study by Mazloomi *et al* showed PCOs itself was associated with decreased vitamin D levels independent of other risk factors [15]. Thomson *et al* [26] found that vitamin D deficiency may exacerbate symptoms of PCOS, which was associated with insulin resistance, ovulatory and

menstrual irregularities, lower pregnancy success, hirsutism, hyperandrogenism, obesity and elevated cardiovascular disease risk factors and there is some, but limited, evidence for beneficial effects of vitamin D supplementation on menstrual dysfunction and insulin resistance in women with PCOS. Other study observed that most females are vitamin D deficient but no evidence is available regarding the association of POC with vitamin D deficiency. Moreover, other literature has reported controversial results [22]. Other results suggest that vitamin D treatment might improve glucose metabolism and menstrual frequency in PCOS women [27]. Our study showed that there was a highly significant relation between vitamin D and total cholesterol in PCOS patients and Control group. In a recent study, Rashidi *et al* [2] investigated the relationship between serum 25-OH-Vit D3 level and metabolic parameters in non-obese women with polycystic ovarian syndrome, they divided 88 non-obese women with polycystic ovary syndrome into two groups of normal weight and overweight (based on BMI) and evaluated serum levels of 25 (OH) D, FBS, CRP, TC, TG, LDL, HDL, INS, and IR. They observed that in 84.1% of women, there was a lack of vitamin D, but this finding did not differ significantly between the two groups. Their important finding was a significant correlation between 25 (OH) D and age and HDL serum levels. While Alexandra *et al.* reported that dyslipidemia is also common in PCOS and includes high levels of total cholesterol and LDL, triglycerides and low HDL. Lipid disorders are seen in about 65–81% of these women [10].

7. Conclusion

Our results find a considerable deficiency of vitamin D in both females that are with and without PCOs. Our results suggest that vitamin D treatment might help in treating PCOS as well.

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