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Relationship between Serum Vitamin D Deficiency and Hormonal Imbalance in Obese Female Patients with Polycystic Ovarian Syndrome

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Abstract

Background: Polycystic Ovarian Syndrome (PCOS) is a common endocrine condition. It is characterized by hyperandrogenism and irregular ovulation. Obesity is often linked to PCOS. This study aimed to compare serum 25-hydroxyvitamin D (25OHD) levels between Saudi women with and without PCOS, considering factors such as BMI, Vitamin D binding protein (DBP) level, lipid profile, and hormones levels. Additionally, we explored the potential relationship between vitamin D deficiency and these parameters.

Methods: This study involved 120 female Saudi participants (aged 18-45 years) divided into two groups: control and obese patients with PCOS. Serum concentrations of both 25OHD and DBP were determined by the sandwich ELISA method. Serum lipid profiles and hormones were measured, BMI was estimated, and insulin resistance was evaluated by measuring serum insulin concentrations alongside the Homeostasis Model Assessment.

Results: In PCOS obese patients, there were significant increases " p<0.001" in BMI, TC, TG, LDL-C, testosterone, prolactin, and Dehydroepiandrosterone sulfate (DHEA-S) levels, and significant decreases " p<0.001" in 25OHD, DBP, HDL-C, and Sex hormone-binding globulin (SHBG) in comparison to controls. Significant positive associations were found between vitamin D and DBP, HDL-C, and SHBG, and negative correlations with BMI, TC, TG, LDL-C, testosterone, prolactin, and DHEA-S in all patients group. No significant correlations between vitamin D and each of Follicle-stimulating hormone (FSH), Luteinizing hormone (LH), Estradiol (E2), progesterone.

Conclusions: Our study shows a significant correlation between vitamin D, DBP, and hormonal dysfunction in PCOS. Fluctuations in hormone levels are linked to reduced vitamin D levels in obese PCOS patients.

Introduction

Polycystic ovary syndrome (PCOS) is an endocrinal illness impacting reproductive- age women, marked by multiple ovarian cysts, abnormal ovarian function and hyperandrogenism associated with irregular menstrual cycles [1]. Recent evolutions have made significant progress in understanding the intricate mechanisms underlying PCOS. This complex condition involves an association of congenital, hormonal, metabolic, and ecological factors, which together contribute to its development and manifestation [2].

PCOS is one of the causes of hormonal disturbance within the body. This disturbance primarily affects androgens and insulin levels, which cause insulin resistance. High insulin levels in the bloodstream stimulating the ovaries to produce excessive androgens resulting in disruption of the hormonal balance [3]. Impaired follicle growth is a key feature of PCOS. In a normal menstrual cycle, ovarian follicles undergo growth and rupture of graafian follicle to release an ovum. While, in individuals with PCOS, there is follicular abnormalities in the development and maturation processes within the ovary, which causes formation of multiple small cysts on the ovaries. This is one of the defining features of the syndrome. It is worth mentioning that PCOS can be deceiving because it is a complicated issue with multifactor other than occurrence of cysts [4].

Gonadotropins are hormones responsible for regulating the menstrual cycle and induce ovulation, they are released from the pituitary gland. PCOS is associated with imbalance in gonadotropins secretion as there is irregularity in the secretion of these hormones, elevation in luteinizing hormone (LH) levels compared to follicle-stimulating hormone (FSH) levels. This imbalance can inhibit ovulation process contributing to the PCOS manifestation. It is important to note that these hormonal imbalances are just one aspect of PCOS [5].

Earlier studies have shown that there is a family history in some cases of PCOS which indicates that there is likely a genetic component to cause this syndrome [5]

Vitamin D deficiency can play a role in insulin resistance associated with PCOS [2, 6]. As vitaminD receptor (VDR) is the gate through which vitamin D influences various organs [7].

Binding of circulating active vitamin D to the VDR triggers the onset of its effects [8]. Vitamin D and its metabolites' transportation to target tissues is primarily facilitated through the vitamin D-binding protein (DBP) [9]. DBP is a fifty-eight kDa glycosylated alpha-globulin synthesized inside the hepatocytes, adipose tissue, kidneys, and gonads. The primary role of DBP involves binding, solubilizing, and transferring vitamin D and its metabolites [10]. DBP binds to all forms of vitamin D metabolites through a single binding site and exhibits strong attraction for 25OHD and 1,25(OH)2D. This capability facilitates the formation of a substantial circulating pool of 25OHD, preventing fast decreasing in vitamin D level when there is limited supply of new vitamin D. Additionally, DBP is crucial for the transport and overall availability of the metabolites of vitamin D in tissues and cells [11]. Regarding androgen levels, a study illustrated a positive association between vitamin D levels and total testosterone as well as the free androgen index. Hence, this discovery leads us to speculate that vitamin D might enhance female fertility by influencing androgenic activity. This is unsurprising, given that Vitamin D is found to impact the expression and functions of enzymes involved in sex hormone production [12]. Aromatase is the first enzyme that plays a role in transforming androgens such as testosterone into estrogens, including estradiol [13]. Vitamin D impacts another enzyme, 17β-Hydroxysteroid dehydrogenase (17β- HSD), crucial for inter-conversion of androgens and estrogens. Furthermore, vitamin D plays a key role in regulating the expression and function of specific Cytochrome P450 (CYP) enzymes engaged in the metabolism and synthesis of sex hormones [13].

Our study seeks to provide further insights into the connections between vitamin D, DBP, and hormonal irregularities in PCOS, with a particular emphasis on obesity and the Saudi population. By exploring this association, the study hopes to reveal significant insights that will help with PCOS diagnosis and treatment.

Methods

From December 2023 to June 2024, a case-control study has been performed in female section, of Clinical Laboratory Sciences Department at College of Applied Medical Sciences, Taif University, and King Faisal Complex. The research involved 120 Saudi women separated into two categories: Group A comprised 60 obese participants with PCOS receiving care at King Faisal Complex. Group B constituted 60 healthy females of similar age to those in Group A serving as the control group. PCOS diagnosis usually includes diversity of diagnostic procedures: assessing menstrual patterns by reviewing the medical history, clinical manifestations such as irregular menstrual periods, increased hair growth, acne vulgaris and disruption of body weight. Physical investigation, comprising a pelvic examination to recognize noticeable marks such as ovarian enlargement or extra hair growing. Hormonal concentrations and lipid profile are assessed by blood tests, because PCOS and abnormal lipid metabolism are related. Ultrasound of the pelvis is usually achieved to observe the ovaries. This imaging method aids in determining the presence of several tiny cysts (follicles), as well as their size and appearance. However, it is crucial to highlight that the existence of cysts does not imply a PCOS diagnosis.

Inclusion Criteria

Women need to have an established PCOS diagnosis based on the Rotterdam criteria described by Teede et al.[14]. PCOS diagnostic criteria of Rotterdam involve the existence of two or more of the following three characteristics: irregular or nonexistent ovulation, as well as laboratory or clinical indications of elevated androgen concentrations, or ovarian volume greater than 10 cm^3 or the presence of 12 or more follicles in a single ovary [15]. All individuals must agree to provide their informed consent to take part in our research.

Exclusion Criteria

Exclusion criteria are women complain of Cushing's syndrome, hyperthyroidism, or hypothyroidism, as they affect hormonal levels. Women suffer from adrenal or pituitary disorders are also excluded. Women with prior ovarian or uterine malignancies are not eligible. Also women used medications or supplements that can affect hormonal levels (e.g., hormonal contraceptives, corticosteroids) in the past three months are excluded.

Blood Sampling

Samples of five millilitres of fasting blood were collected from all participating patients and controls in sterile tubes. After that, samples of serum were separated and kept at -20°C till being examined. Two machines were used at the King Faisal Medical Complex's biochemistry lab to measure different parameters. Serum lipid profiles, which comprise Total Cholesterol (TC), Triglycerides (TG), HDL-Cholesterol (HDL-C), and LDL-Cholesterol (LDL-C) were measured by the first machine, called the photometric technology Cobas 6000 (c501). Hormonal concentrations include serum testosterone, SHBG, DHEA-S, prolactin, LH, FSH, E2, and progesterone were measured by the second device, the Cobas e 601. The Sandwich ELISA technique was used in the Applied Medical Sciences College biochemistry lab to measure the quantities of 25(OH)D and vitamin D binding protein. By applying a capture antibody to the plate wells, this method produces a "sandwich" shape in which the antigens are trapped between two antibody layers. The MyBioSource ELISA Kit, catalogue number MBS268910, was utilized to quantify the levels of 25(OH)D. Similarly, the Quantikine ELISA kit (catalogue number DVDBP0B) was used to assess the levels of vitamin D binding protein. The BMI [kg/m^2] was calculated using the equation = Weight (kg) / Height ($m^{2)}$. For the estimation of serum insulin levels and homeostasis assessment, fasting serum insulin levels were evaluated using a human ELISA kit for insulin from Bio-source Europe S.A., Nivelles, Belgium. The Homeostasis Model Assessment (HOMA-IR) was used to quantify insulin resistance.

Results

The study recruited a total of 120 participants, comprising 60 Saudi obese female patients with PCOS and 60 healthy females who served as the control group. The patients had a mean age of 29.08 ± 7.3, and the control group was matched with them in terms of age.

Variable	Number (No)	Percent (%)
18- 25	20	33.3%
26- 35	25	41.7%
36- 45	15	25%
Married	40	66.7%
Non married	20	33.3%
Fertile	13	32.5%
Infertile	27	67.5%
Amenorrhea	28	46.7%
Oligo-menorrhea	32	53.3%
Hirsutism present	35	58.3%
Hirsutism absent	25	41.7%
Acne present	15	25%
Acne absent	45	75%
Overweight	10	16.7%
Obese	50	83.3%
Normal blood pressure	27	45%
Hypertensive	33	55%
Nondiabetic	7	11.7%
Prediabetic	19	31.7%
Diabetic	34	56.6%

Table 1: Frequency and percentage distribution of demographic and clinical characteristics of studied PCOS patients

Parameters	Patients	Controls	P value
BMI (kg/m^2)	37.03±4.08	21.53±2.30	"p<0.001"
Total Cholesterol (mg/dL)	237.9 ± 18.43	162.5 ± 19.88	"p<0.001"
Triglycerides (mg/dL)	187.2 ± 18.76	136.1 ± 13.02	"p<0.001"
LDL-C (mg/dL)	133.7 ± 13.18	98.88 ± 7.526	"p<0.001"
HDL-C (mg/dL)	34.38 ± 8.636	77.75 ± 10.75	"p<0.001"
25Hydroxy vitamin D (nmol/L)	25.21 ± 6.45	49.65 ± 7.57	"p<0.001"
Vitamin D Binding Protein (ng/mL)	32.22 ± 7.42	44.02 ± 5.96	"p<0.001"
Total testosterone (ng/mL)	1.194 ± 0.29	0.5047 ± 0.16	"p<0.001"
Total SHBG (mg/L)	2.616 ± 0.97	6.464 ± 1.4	"p<0.001"
DHEA-S (µg /dL)	355.5 ± 81.41	126.1 ± 18.05	"p<0.001"
Prolactin (µg /mL)	522.5 ± 136.5	208.1 ± 47.28	"p<0.001"
LH (mIU/mL)	5.14 ± 1.23	4.86 ± 1.17	"p>0.05"
FSH (mIU/mL)	5.51 ± 0.97	5.34 ± 1.1	"p>0.05"
Estradiol (pg/mL)	148.6 ± 12.33	143.0 ± 14.01	"p>0.05"
Progesterone (ng/mL)	5.61 ± 1.1	5.48 ± 1.13	"p>0.05"
TSH (µg /mL)	2.99 ± 0.48	2.92 ± 0.51	"p>0.05"
Free T3 (pmol/L)	4.77 ± 0.70	4.58 ± 0.81	"p>0.05"
Free T4 (pmol/L)	16.47 ± 1.52	16.25 ± 1.53	"p>0.05"

Table 2: Comparison of anthropometric and biochemical parameters of patient and control group

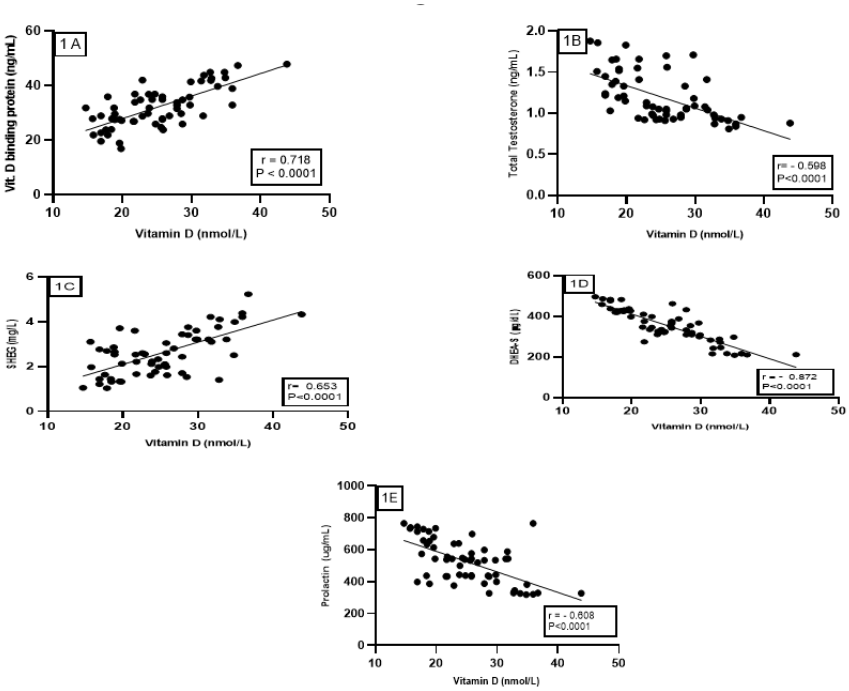

Figure 1 (1A-1E): Correlation coefficient analysis for assessing the association between serum amounts of vitamin D and each of vitamin D binding protein (1A), total testosterone (1B), SHBG (1C), DHEA-S (1D) and prolactin hormone (1E) in PCOS patients, showed significant correlations between vitamin D and all parameters.

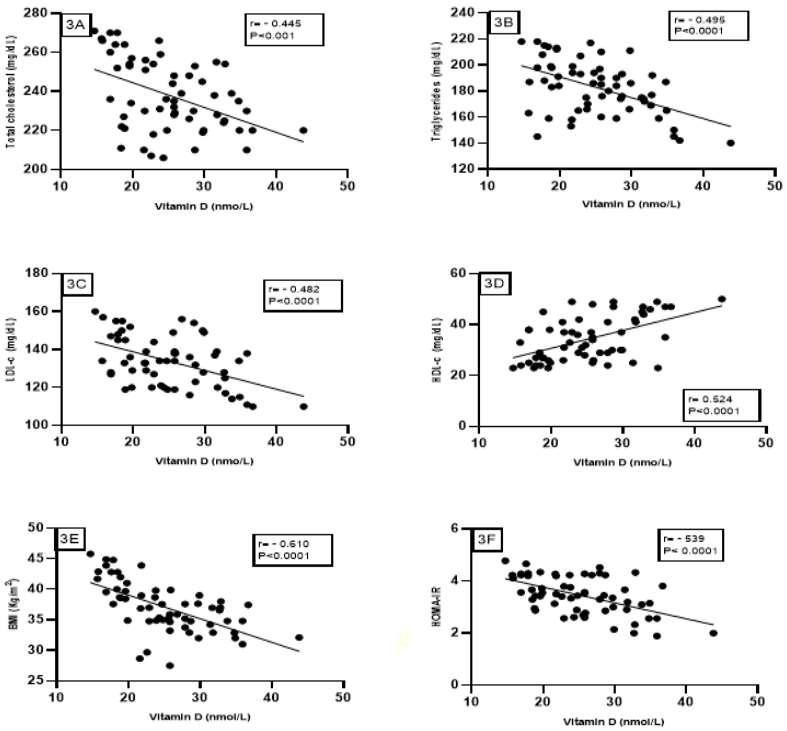

Figure 2 (2A-2D): Correlation coefficient for assessing the association between serum levels of vitamin D and each of LH (2A), FSH (2B), estradiol (2C) and progesterone (2D) hormones in PCOS patients.

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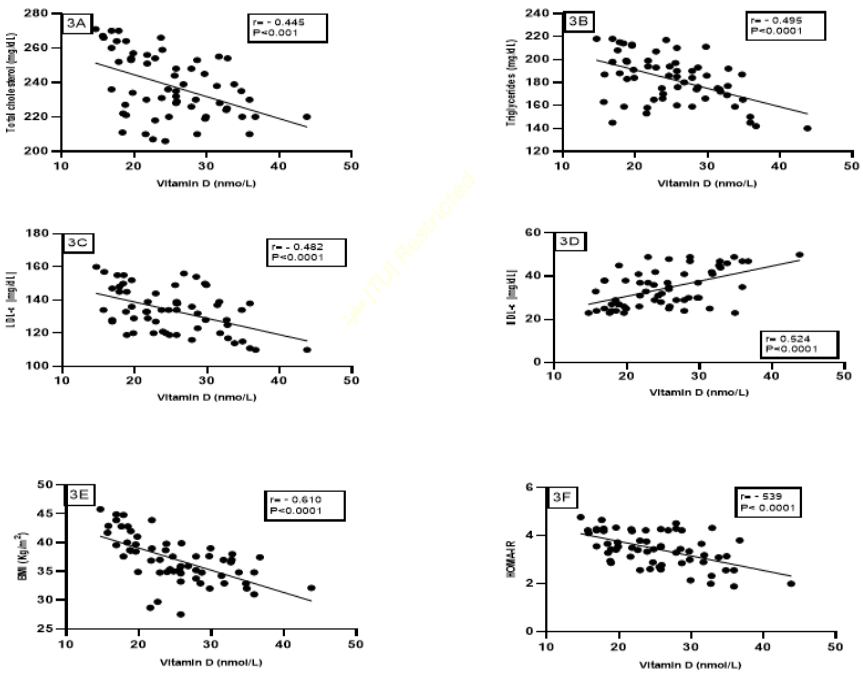

Figure 3 (3A-3F): The correlation of serum vitamin D levels and each of serum lipid profile (3A-3D), BMI (3E) and HOMA-IR (3F) in PCOS patients, presented significant correlations between vitamin D and all parameters.

Discussion

PCOS is a condition that affects the endocrine system. Common symptoms include irregular menstrual cycles, ovulatory problems, and hirsutism. PCOS is a diverse disorder that often includes metabolic syndromes such as hyperandrogenemia, dyslipidemia, and insulin resistance [16]. Based on the epidemiological data investigation, 38–88% of females having PCOS were overweight or obese [17]. A recent study confirmed the association between obesity and PCOS based on an epidemiological data [18].

In present study, our results demonstrated that the BMI in the PCOS obese patients' group 37.03 ± 4.08 were considerably higher than those in the control group 21.53 ± 2.30 " p<0.001" . In consistent with our study, The research by Song et al. indicated that [19] revealed that women with PCOS have a higher body weight compared to controls, with mean ± SD values of 24.0 ± 4.7 and 21.1 ± 2.6, respectively. Additionally, Yu and Wang [20] suggested that BMI may influence the levels of reproductive hormones in PCOS. Furthermore, the study found that the case group had a greater BMI than that of the control group, with the case group showing a BMI mean of 28.6 kg/m². Therefore, increased BMI is considered a significant exacerbating factor in several aspects of PCOS, contributing to its clinical presentation and metabolic manifestations.

LDL-C serum levels "p<0.001" with a significant decrease HDL-C serum levels "p<0.001" in comparing the PCOS group to the control individuals. In accordance with our results, Bindayel [2] observed greater triglyceride concentrations in serum of patients group than in control individuals, indicating a potential correlation between PCOS and elevated triglycerides. A research achieved by Valkenburg et al., [21] involved 557 females with PCOS and 295 controls. The study revealed that PCOS women exhibited greater concentrations of TG, and LDL-C, along with lower levels of HDL-C compared with controls all with "P values ⩽ 0.01". In the current study, we investigated the serum levels of vitamin D in patients group compared to a control group. The serum vitamin D levels in the patients' group (25.21 ± 6.45) were significantly reduced than the mean ± SD of control group 49.65 ± 7.57, indicating a potential vitamin D deficiency. Published research indicates that women with PCOS may have greater, lesser, or no noticeable difference in their serum vitamin D levels compared to healthy controls. A study conducted by Bindayl [2] supported our findings, indicating that serum vitamin D levels were markedly lower in PCOS group in comparison with the control group "p < 0.05". This consistency in results strengthens the evidence for the correlation between vitamin D deficiency and PCOS. Alternatively, another

England study done on adult females demonstrated no significant difference was found in the vitamin D level between patients with and without PCOS [22].

In contrast, Kim et al., [23] found that the prevalence of vitamin D level as equally common between Korean women with PCOS and controls. Additionally, another study conducted by Daghestani, [24] reported contradictory findings to our results as it revealed that female patients with PCOS living in Makkah, Western region of Saudi Arabia, have no difference in vitamin D levels in both patients and controls. Interestingly, another study done at Al Noor Hospital in Makkah Al Mukarama showed higher vitamin D levels in PCOS females compared to controls, suggesting potential regional or environmental factors influencing vitamin D status in PCOS patients [25].

We investigated serum levels of DBP and found significant variances between control and PCOS groups, with notably lower levels in the patient's group mean ± SD: 32.22 ± 7.42 compared to controls 44.02 ± 5.96. Consistently, a study by Naderpoor et al., [26] involving 149 pre-menopausal females (90 with PCOS, 59 controls) revealed lower DBP levels in PCOS patients compared to control, suggesting DBP as a possible mechanistic marker for PCOS evolution. In contrast, study conducted by Jedrzejuk et al., [27] comprising 63 females (27 with PCOS, 36 controls), no significant correlation was detected in DBP levels between PCOS patients and controls. This suggests that DBP may not serve as a distinguishing biomarker for PCOS in this context.

urthermore, we investigated the serum total testosterone levels were considerably greater in the patients' group 1.194 ± 0.29 in comparison with controls 0.5047 ± 0.16, with a " p value <0.001". Additionally, the serum total SHBG levels exhibited a significant decrease in the patients' group 2.616 ± 0.97 in comparison with controls 6.464 ± 1.4, with a " p value <0.001". Respectively, a study conducted by Bartolone et al., [28] reported a significant increase in testosterone levels "p < 0.05" in the PCOS group compared to the control group, consistent with our findings. This emphasizes the importance of testosterone levels in diagnosing PCOS. Based on a research revealed by Song et al., [19] the concentrations of SHBG were lower in PCOS females than in the control group "P < 0.05". Lower SHBG concentrations are commonly linked to hyperandrogenic states and aspects of metabolic condition, which may help explain the lower SHBG levels observed in PCOS.

In our study, the serum levels of DHEA-S were investigated in the control and PCOS groups. The results showed that the mean ± SD of DHEA-S serum levels were considerably greater "p<0.001" in PCOS' group 355.5 ± 81.41 compared to the control group 126.1 ± 18.05. Also, we examined the serum levels of prolactin in both the control and PCOS groups. The findings revealed a significant increase "p<0.001" of serum prolactin levels in the patients' group 522.5± 136.5 compared to the control group 208.1 ± 47.28. Respectively, a study conducted Benjamin et al., [29] showed DHEA-S level was significant higher in PCOS patients when compared to healthy controls "p<0.00001". Glintborg et al., [30] revealed that prolactin concentrations raised in the study subjects in comparison to the controls. He also demonstrated that PCOS, characterized by relatively high estrogen levels and hyperandrogenemia, could stimulate prolactin secretion. Conversely, the research by Szosland et al., [31] indicated that prolactin levels in PCOS patients did not display a substantial variation " p<0.05 " in comparison to the control group. Additionally, their study proposed that hyperprolactinemia might not be more common in women with PCOS and should not be regarded as a defining characteristic of the disorder. Our current research found that there was no discernible variation in the mean ± SD of serum LH, FSH, E2, and progesterone levels between the control and PCOS groups. In contrast to our study, Oyebanji et al., [32] demonstrated a substantial raise" p<0.05 " in the concentrations of E2 and LH in PCOS subjects, along with a significant decrease " p<0.05 " in Progesterone and FSH levels in comparison with the controls.

We also explored the correlation coefficients between vitamin D and BMI, lipid profile, DBP, as well as hormone levels in the patients group. We detected "a significant negative association between vitamin D and BMI "p<0.0001, r = -0.610". This finding aligns with the results of Nowak et al., [33] who similarly demonstrated a negative association between BMI and vitamin D concentrations in PCOS patients. Furthermore, the study found an opposite association between BMI and serum 25OHD level in PCOS females [22]. A study by Ng et al., [34] indicated no statistically substantial connection between vitamin D concentrations and BMI which is inconsistent with our study. Moreover, our results demonstrated "a significant opposite association between vitamin D and HOMA-IR "p<0.0001, r = -0.539". Deficiency of Vitamin D is mainly between individuals with PCOS and can exacerbate metabolic irregularities. Obesity, a contributing factor to low vitamin D levels, is closely connected with PCOS. Obesity intensifies insulin resistance. The inherent insulin resistance characteristic of PCOS is associated with an insufficient insulin response in peripheral tissues with metabolic activity, such as skeletal muscle and adipose tissue. PCOS obese females are especially predisposed to insulin resistance, which can lead to disturbances in

metabolism of glucose and lipid. It is crucial to screen all PCOS patients for 25OHD deficiency [35, 36].

In the current work, we reported a negative correlation between vitamin D and TC "p<0.001, r = -0.445", TG "p<0.0001, r = -0.495", and LDL-C "p<0.0001, r = -0.482" between all patients group. Conversely, there was a significant positive correlation between serum vitamin D levels and HDL-C "p<0.0001, r = 0.524". Wang et al., [37] demonstrated similar findings, showing that in women with PCOS, serum 25OHD levels showed a significant inverse correlation with both total cholesterol and LDL-C, while exhibiting a significant positive correlation with HDL-C. Furthermore, Neelaveni et al., [38] found a significant inverse relationship between vitamin D levels and triglyceride levels. Conversely, Wang et al., [37] observed no significant statistical correlation between 25OHD concentration and serum triglyceride levels.

Moreover, we found a substantial positive correlations between vitamin D serum concentrations and DBP "p<0.0001, r = 0.718". Mesinovic et al., [39] found that total 25OHD exhibited a positive association with DBP. And a negative association between free 25OHD and DBP. However, there were no observed associations between bioavailable 25OHD and DBP. Furthermore, our study demonstrated "a significant positive correlations between serum 25OHD levels and SHBG "p<0.0001, r = 0.653". Conversely, there were inverse relationships found between serum 25OHD and testosterone "p<0.0001, r = -0.598", DHEA-S "p<0.0001, r = -0.872", and prolactin "p<0.0001", "r = -0.608". This result is reliable with the outcomes of a study by Yılmaz et al., [40] which also reported a positive correlation between vitamin D and SHBG, therefore supporting our findings. According to Kumar et al., [35] vitamin D did not show any relation with testosterone. According to Yılmaz et al., [40] vitamin D was not correlated with DHEA-S and prolactin. Regarding the serum levels of other hormones, we demonstrated that no statistical significance correlation between vitamin D and each of LH "p = 0.739, r = -0.043", FSH "p = 0.847, r = - 0.025", E2 "p = 0.833, r = 0.027", and progesterone "p = 0.083, r = -0.225" in PCOS' group. Both Yılmaz et al. [40] and Kumar et al., [35] declared that Vitamin D levels were not correlated with LH and FSH. In a study by Al-Jawadi et al., [41] a positive relationship was observed between Vitamin D and progesterone "p = 0.05, r = 0.0078". In the contrary, a significant negative correlation was detected with E2 "p = 0.05, r = 0.0391". These findings emphasize the association of PCOS with metabolic diseases such as dyslipidemia, obesity, and hyperandrogenism.

Our study demonstrates a significant statistical correlation between vitamin D, DBP, and hormonal dysfunction in PCOS. Fluctuations in hormone levels, both decreases and increases, are associated with reduced vitamin D levels in obese PCOS patients. Timely identification, effective management, and appropriate treatment are essential for reducing the risks associated with PCOS. Future research should include an obese, non-PCOS control group to better isolate metabolic changes unique to PCOS.

Author Contributions

Conceptualization: A.F.G., A.A.A.; methodology: G.E.A., H.N.A.; data collection: K.A.R, M.M.B., F.M.A.; resources: A.F.G.; performed laboratory tests: K.A.R, M.M.B., F.M.A.; writing—original draft preparation: A.F.H, A.A.A, OMO.; writing—review and editing: U.M.M.; statistical analysis: A.F.H.; supervision: A.F.G. All authors have revised the final version of the manuscript and agreed to the published version of the manuscript.

Institutional Review Board Statement

The Scientific Research Ethics Committee at King Faisal Medical Complex approved the study proposal. (Ethical Permission No. 2023-B-28). Informed written consent was obtained from all participants. The study was following the 1964 Helsinki Declaration and its later amendments.

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Informed Consent Statement:

Informed consent was obtained from subjects involved in the study.

Conflicts of Interest

The authors declare no conflict of interest.

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