Al-Rafidain J Med Sci. 2022;2:1-7.

DOI: https://doi.org/10.54133/ajms.v2i.53

AJMS

Online ISSN (2789-3219)

Review Article

Impact of Vitamin D Deficiency on the Pathogenesis of Polycystic Ovary Syndrome

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Received: 7 Dec 2021; Revised: 29 Dec 2021; Accepted: 6 Jan 2022

Abstract

There are many metabolic and hormonal factors related with polycystic ovary syndrome (PCOS) that can be affected by vitamin D3 supplementation. To find clinical trials, *in vivo* studies, and *in vitro* studies that met the review's inclusion and exclusion criteria, we searched many databases. PCOS women's ovulation and metabolic parameters were examined in relation to the effects of vitamin D3 treatment on PCOS risk variables such as seasonal changes in body mass index, and obesity. The current review included twenty-five articles. Vitamin D3(25-hydroxy vitamin D) levels were significantly lower in the PCOS group than in the control group, and lipid profile and androgen hormone levels were significantly higher in the PCOS group, resulting in increased cardiovascular events and exaggerated hirsutism. According to the majority of research, vitamin D3 plays a beneficial role in decreasing the pathophysiology of PCOS, notably in restoring ovulation, which ultimately improves fertility. Although other studies found no effect on lipid profile, there was a minor effect on reducing cardiovascular risks. The response of patients to vitamin D3 was influenced by the dose administered and the study's methodology. In conclusion, vitamin D3 had a good effect on the pathophysiology of PCOS in the majority of investigations.

Keywords: polycystic ovary syndrome, vitamin D3, VEGF, anti-Mullerian hormone, Hyperandrogenism, insulin resistance.

تأثير نقص فيتامين (د) على الفسلجة المرضية لمتلازمة تكيس المبايض

الخلاصة

هناك العديد من العوامل الأيضية والهرمونية المرتبطة بمتلازمة تكيس المبايض التي يمكن أن تتأثر بمستوى فيتامين (D3) في الجسم. تم البحث في التجارب السريرية، والدراسات المختبرية التي تلبي معايير إدراج المراجعة والاستبعاد من خلال العديد من قواعد البيانات. تم فحص الإباضة النسائية بمتلازمة تكيس المبايض والمعلمات الأيضية فيما يتعلق بتأثير علاج فيتامين D3 على متغيرات خطر متلازمة تكيس المبايض، مثل التغيرات الموسمية في مؤشر كتلة الجسم والسمنة. وشمل الاستعراض الحالي خمسة وعشرين دراسة. وكانت مستويات فيتامين D3 (25-hydroxy vitamin D) أقل بكثير في مجموعة متلازمة تكيس المبايض منها في مجموعة التحكم، وكانت مستويات الدهون وهرمونات الاندروجين أعلى بكثير في مجموعة متلازمة تكيس المبايض، مما أدى إلى زيادة مبالغ فيها لأمراض القلب والأوعية الدموية و فرط نمو الشعر. وفقا لغالبية البحوث، فيتامين D3 يلعب دورا مفيدا في خفض مخاطر هذه المتلازمة المرضية، لا سيما في استعادة الإباضة، مما يحسن الخصوبة في نهاية المطاف. على الرغم من أن دراسات أخرى لم تجد أي تأثير على ملف الدهون، كان هناك تأثير طفيف على الحد من مخاطر اعتلال القلب والأوعية الدموية. تأثرت استجابة المرضى لفيتامين D3 بمقدار الجرعة المستخدمة ومنهجية الدراسة. في الختام، كان لفيتامين D3 تأثير واضح في الفيزيولوجيا المرضية ل PCOS في معظم الدراسات.

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Article citation: Raheem NM, Marouf BH. Impact of vitamin D deficiency on the pathogenesis of polycystic ovary syndrome. *Al-Rafidain J Med Sci*. 2022;2:1-7. doi: 10.54133/ajms.v2i.53.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex, heterogeneous endocrine disorder, that affects female health at reproductive age, in which it is responsible for secondary infertility in women. The syndrome is associated with endocrine, reproductive, and metabolic dysfunction. The prevalence of PCOS in women is about 5–10% [1]. Women with PCOS suffer from metabolic dysfunctions such as hypertension, cardiovascular diseases, dyslipidemia, obesity, anxiety, and depression. In addition, women with PCOS have gonadotropic imbalances such as elevated levels of luteinizing hormone (LH), a high LH/FSH ratio, and a high testosterone level [2,3]. The Rotterdam criteria are used for diagnosing women with PCOS. Usually two criteria must be present to confirm PCOS, like hyperandrogenism, menstrual irregularities, and > 12 antral follicles in one or both ovaries and/or ovarian volume > 10 cm^3 [4]. Insulin resistance is a major metabolic disorder, predominantly found in women with PCOS, and plays a central part in the pathogenesis of PCOS and consequently leads to type 2 diabetes mellitus (Figure 1).

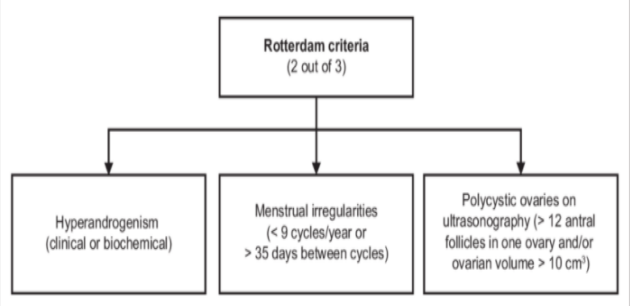

Figure 1: The Rotterdam criteria for diagnosis of PCOS.

The high insulin level is responsible for the formation of non-alcoholic fatty liver disease (NAFLD) in women with PCOS because it causes a reduction in sex hormone-binding globulin, which elevates the serum level of free testosterone in the blood [5] as shown in Figure 2.

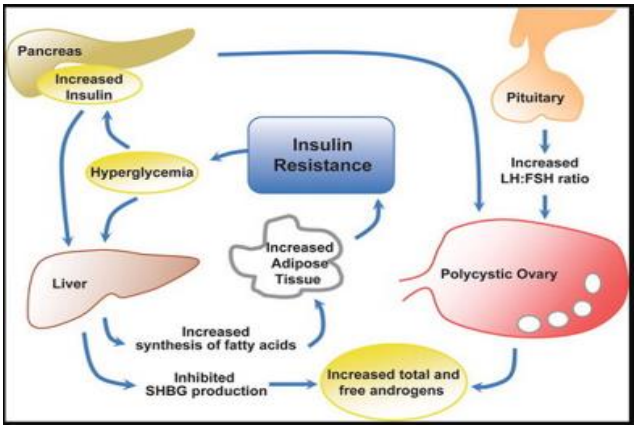

Figure 2: The metabolic disorders that linked to PCOS [6]

Anti-Mullerian hormone (AMH) is a glycoprotein synthesized by the granulosa cells in the ovary. In PCOS, the AMH level increases dramatically, 2-3 fold more than the normal level in healthy women. It increases the intrafollicular level, which causes abnormal folliculogenesis and prevents the formation and growth of the dominant follicle in the ovary, which causes anovulation and hyperandrogenism [7]. An increase in the vascularity of the ovary is linked to the angiogenesis effect of vascular endothelial growth factor (VEGF), in which its level is dysregulated in the ovary of PCOS women. VEGF plays an important role in PCOS pathogenesis. It has been shown that women with PCOS display elevated VEGF levels in serum and/or follicular fluid. Therefore, the upregulated VEGF level has been correlated with an augmented risk of ovarian hyperstimulation syndrome (OHSS) following follicular stimulation [8,9]. The vitamin D3-deficiency is approximately 67-85% prevalent in PCOS women [10]. Studies have demonstrated that, women with PCOS have low serum level of 25-hydroxyl vitamin D3 less than 20 ng/ml, and increase vitamin D3 intake might alleviate the symptoms of PCOS. Vitamin D3 alleviates the symptoms that associated with the pathophysiology of the disorder (Figure 3).

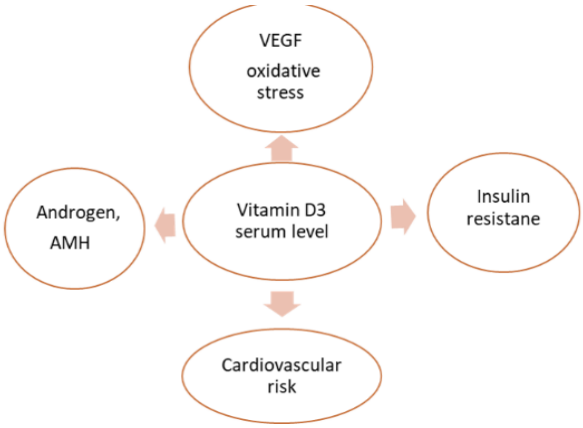

Figure 3: Schematic diagram elaborating correlation between vitamin D3 and metabolic disorder parameters adopted from [13,3], AMH; Anti-Mullerian hormone, VEGF; Vascular endothelial growth factor.

There are studies suggesting that consuming vitamin D3 by PCOS women, improve clinical and laboratory parameters, and attenuate the long-term complication that associated with PCOS. Some finding supports the positive effect of vitamin D3 on decreasing the cardiovascular events, insulin resistance, minimizing androgen level, normalizing AMH level, reducing oxidative stress, and increase fertility. Also it has the capacity in reducing inflammation and oxidative stress through its effect on inhibiting damaged DNA proliferation in cellular level [11]. Vitamin D3 co-supplementation with other nutrients have synergistic effects in minimizing the PCOS manifestation [12]. On the other hand, many studies found no change in metabolic parameters after vitamin D3 administration. The aim of this

review was to gather up-to-date clinical, *in vitro*, and *in vivo* studies, and combine the data of different aspects that related to vitamin D3 possible influence upon PCOS parameters with no bias.

METHODS

The writing of the current review article has been carried out by searching google scholar, ResearchGate, PubMed, and PubMed Central (PMC) database to obtain open access articles from 2010-2020. The key words that have been used were "vitamin D3", "PCOS", "metabolic disturbance", "hormonal disturbance", "insulin resistance", "hyperandrogenism", "ovulation dysfunction". Summary of the search strategy and information of the included articles are illustrated in Figure 4.

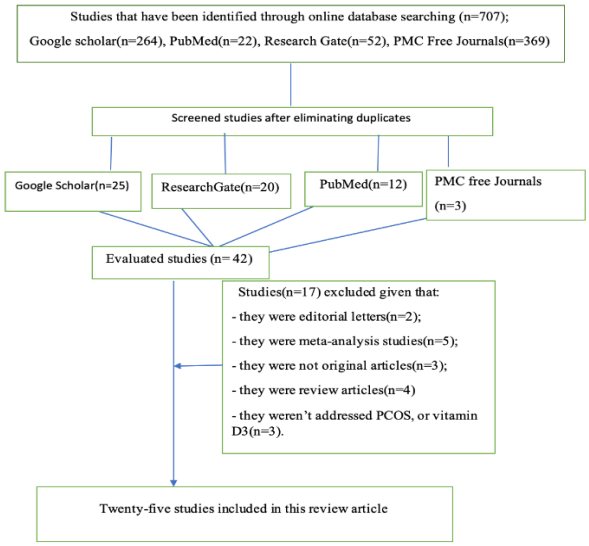

Figure 4: Flow chart of the review including eligibility of the articles and searching strategy of the literature review.

Inclusion criteria

Inclusion criteria include published articles in peer reviewed journal relevant to PCOS studies such as clinical trials, *in vivo* and *in vitro* studies.

Exclusion criteria

We excluded systematic review articles, meta-analysis, conference comments, commentaries, case report, editorial letters, overviews, viewpoints, journal pre-proof and studies carried out before 2010.

RESULTS AND DISCUSSION

The *in vitro*, experimental and clinical studies related to the subject of this review articles are listed in Table 1. Vitamin D3 has been proven in animal experiments to be useful in restoring or reducing the metabolic disturbances associated with PCOS in experimental animals [33]. In vitamin D3-treated rats, the damage caused by dihydrotestosterone (DHT) was completely reversed, but there was no significant effect on cardiovascular events. Furthermore, Safaei *et al*. found that vitamin D3 increased ovulation by decreasing follicles atresia and minimizing the growth of immature follicles. This was accomplished by boosting mitochondrial biogenesis and improving mitochondrial membrane integrity in PCOS mice granulosa cells [14]. Grzesiak *et al*. recently published a study on letrozole-treated rats that revealed crucial PCOS characteristics. The findings show that vitamin D3 metabolism is disturbed in the ovary and peri-ovarian adipose tissue of rats with induced PCOS. When compared to healthy tissues, those tissues had a low concentration of 1,25(OH)2D3, implying that PCOS leads to vitamin D3 insufficiency and that this could be a factor in treating this etiology [16]. In another *in vitro* investigation, Sara *et al*. found that vitamin D3 dramatically reduced systemic vascular insulin resistance in the gracilis arterioles of a DHT-treated mouse model, as well as restored systemic insulin responsiveness in these cells [35]. Bakhshalizadeh *et al*. found that vitamin D3 lowered the mRNA and protein expression levels of steroidogenic enzymes in PCOS mice's cultured granulosa cells. Vitamin D3 also inhibited the aromatase enzyme, resulting in lower levels of 17-estradiol and progesterone, which increased follicular development and maturation, as well as fertility [31]. Furthermore, according to Subashree *et al*. (2017), women with PCOS have high insulin resistance and low vitamin D3 levels, which predispose them to endocrine problems including hypothyroidism [27]. In comparison to healthy normal women, Khan *et al*. found a relationship between vitamin D3 insufficiency and decreased metabolic parameters in PCOS women. When there is obesity, metabolic abnormalities become considerable, according to the study [18]. Similarly, in other studies, females with low serum 25(OH) levels have higher metabolic disturbance, higher insulin resistance, a worse lipid profile, and anovulation compared to fertile women, supporting the Endocrine Society's recommendation to increase serum vitamin D3 concentration to above 75 nmol/L [25,38]. Normalization of vitamin D3 levels positively affects ovulation, mainly due to the availability of vitamin D receptors within the female reproductive system. Treatment with a dose of vitamin D3, threefold the daily allowance, produced a significant decrease in insulin resistance and anti-Mullerian hormone, eventually increasing fertility. Furthermore, infertile women with PCOS who took a high dose of vitamin D3 saw an increase in insulin sensitivity as well as a drop in total cholesterol and LDL levels. Other lipid measurements, however, did not show any change [24]. Rashad *et al*. found that the clinical manifestations, metabolic indices, and androgenic aspects of PCOS have improved. Body composition measures, BMI, and waist-hip ratio all decreased significantly in the intervention group [17]. Furthermore, after getting vitamin D3 medication, cardio-metabolic risks were reduced, and a novel finding in this clinical trial was a reduction in pro-inflammatory biomarkers. In addition, after receiving four-fold the recommended daily amount of vitamin D3 for a lengthy period of time, very low-density lipoprotein (VLDL), cholesterol, and triglyceride serum were considerably reduced in women with PCOS [26].

Table 1: summary of the characteristics and data of the included studies.

Publication	Study Design	Participants and Treatment intervention	Results
Safaei *et al*., 2020 [14]	*In vitro* study; granulosa cells of PCOS mouse model	granulosa cells divided into three groups; granulosa cells with vitamin D3(100 nM) for 24 hours; granulosa cells nil treatment; granulosa cells of normal mouse as control.	Vit. D3-treated granulosa cells showed a significant increase in mitochondria's DNA compared to untreated group; increased mitochondrial biogenesis.
Mesinovic *et al*., 2020 [15]	Cross-sectional study	46 blood samples from premenstrual women with PCOS to compare vitamin d3 level, SHBG, and total testosterone levels.	Vit. D3 metabolites are not correlated with total testosterone, and SHBG
Grzesiak *et al*., 2020 [16]	Animal study	Female rats allocated into the control (n=32) and letrozole-treated (n =16) groups.	Letrozole-treated rats showed a decreased level of vitamin D3 compared with controls
Rashad *et al*., 2019 [17]	Randomized, placebo-controlled clinical trial	95 patients with PCOS; 55 received 42000 IU vit. D3/week, plus 500mg calcium carbonate/day for 12 weeks; 40 received only calcium carbonate for 12 weeks.	In vit. D3 group, elevated serum 25(OH)D, decreased androgenic profile, inflammatory biomarkers, BMI and WHR, improved and hirsutism score.
Khan *et al*., 2019 [18]	Cross-sectional study	comparison of vit. D3 levels between 169 women with PCOS and 164 without PCOS.	In PCOS patients, lower vit. D3 level with hyper androgenism and insulin resistance compared to healthy controls.
Kadoura *et al*., 2019 [19]	Randomized placebo-controlled clinical trial	40 women with PCOS divided to 2 groups; 20 received metformin 1500 mg/day plus placebo, 20 received metformin 1500 mg/day plus calcium 1000 mg and vit. D3 6000 IU daily for 8 weeks.	Vit. D3 and calcium levels increased with enhancing menstrual irregularity compared to metformin only. Gonadotropins and IGF-1 levels are not affected.
Lumme *et al*., 2019 [20]	Population-based study	Serum 25(OH)vit. D were estimated in women with self-reported PCOS (n=280) vs. controls (n=1573) at age of 31 years.	Women with PCOS presented showed high BMI, insulin resistance, low-grade inflammation, and testosterone levels compared to controls.
Sukul *et al*.,2019 [21]	Randomized controlled trial	50 PCOS women *vs*. 50 age-matched normal women.	Negative correlation of serum Vit. D with FBS, serum insulin, IR, and serum testosterone.
Javed *et al*.,2019 [22]	Randomized, double-blind, placebo-controlled study.	20 PCOS women received 3200 IU vitamin D3/day for 3 months *vs*. 20 received placebo for 3 months.	In intervention group, vit. D3 was elevated with modest decrease in HOMA-IR and ALT levels.
Trummer *et al*., 2019 [23]	Randomized, double-blind, placebo-controlled study.	108 women with PCOS and 25-(OH) vit. D3 <75 nmol/L divided randomly to either receiving 20000 IU vit. D3/week for 24 weeks, or placebo.	Vit. D3 level was increased with no effect on endocrine and metabolic parameters.
Dastorani *et al*., 2018 [24]	Randomized, double-blinded, placebo-controlled study.	40 infertile PCOS women, 20 received 50000 IU vit. D3/every other week for 8 weeks vs. 20 received placebo.	Vit. D intake decreases serum AMH, insulin levels, HOMA IR, and LDL-c, and elevates quantitative insulin sensitivity check index.
Krul-Poel *et al*., 2018 [25]	Cross-sectional study	639 women with PCOS and 449 fertile women; serum 25(OH)D stratified into severe (<25 nmol/l), moderate(25-50 nmol/l), and adequate (>75 nmol) groups.	In PCOS women, serum 25(OH)D was lower than in ferti le controls; the group with lowest serum 25(OH) had higher HOMA-IR, lipid profile among the PCOS groups independent of BMI, season, and ethnicity.
Foroozanfa *et al*., 2017 [26]	Randomized clinical trial	90 women with PCOS, 30 received vit. D3 4000 IU/day, 30 received 1000 IU/day, and 30 received placebo for 12 weeks.	In the 4000 IU vit. D3/day group, vit. D3 was elevated with decreased FPS, serum insulin, HOMA-IR and TGs. No significant effect on QUICKI and serum HDL-c was reported.
Sabashere *et al*., 2017 [27]	Clinical trial	45 PCOS women (19-34 years) vs. 45 healthy women as control.	In PCOS group, serum vit. D3 and Ca^{+2} levels were decreased with insulin compared to controls.
Irani *et al*., 2017 [28]	Randomized placebo-controlled trial	68 women with PCOS, allocated into vit. D3 and placebo groups. Vit. D3 group received 50000 IU/week.	Serum 25(OH)D level was increased with decreased serum VEGF, intermenstrual intervals, Ferryman-Gallwey hirsutism score, and TG compared with placebo group.
Karamali *et al*., 2017 [29]	Randomized double-blind, placebo-controlled trial	55 women with PCOS assigned into 2 groups; 28 received 200 IU vit. D, 500 mg calcium and 90 µg vit. K twice daily for 8 weeks, and 27 received placebo twice daily for 8 weeks.	In intervention group, serum insulin, HOMA-IR, TG, and VLDL-c were decreased with significant increase in quantitative insulin sensitivity check index compared with placebo group.

Gupta *et al*., 2017 [30]	Randomized, placebo-controlled, double-blind study.	50 women with PCOS allocated into 2 groups; 25 received 60000 IU vit. D3/wk for 12 weeks, 25 received placebo for same period.	In vit. D3 group, significant change was seen in IR, serum fasting insulin, and increase in insulin sensitivity determined by QUICKI.
Bakhshalizadeh *et al*., 2017 [31]	Granulosa cell from a PCOS mouse model	Granulosa cells treated with vitamin D3, while other group is not treated.	Vit. D3 reduces mRNA and protein expression levels of steroidogenic enzymes in cultured granulosa cells. It reduces aromatase and 3β-HSD activity that minimizes 17β-estradiol and progesterone release.
Garg *et al*.,2015 [10]	Randomized double-blind controlled trial	36 women with PCOS;15 received 4000IU/day for 6 months, 17 received placebo. Both groups received metformin doses.	Vit. D3 do not change the parameters of HOMA-IR, and cardiovascular risk factors between two groups.
Raja-khan *et al*., 2014 [32]	Randomized, placebo-controlled trial	28 women with PCOS; 14 received 12000 IU vit. D3 /day for 12 weeks, 14 received placebo for 12 weeks.	Serum vit. D3 increases in intervention group, lowers 2-hour insulin and lower 2-hour glucose and BP.
Masszi *et al*., 2013 [33]	*In vitro* study	Leukocyte, aorta, and ovarian tissues have been immune-stained with nitrotyrosine antibodies to evaluate nitrosative stress.	Vit D3 partially restores relaxation of aorta and reverse the nitrosative effects on the ovary tissue.
Thomson *et al*., 2013 [34]	Retrospective, unplanned secondary analysis of two cohorts during different seasons.	50 overweight/obese women with PCOS, 50 healthy normal weight as a control.	The winter cohort had lower 25OH-D levels at baseline, which increased over 20 weeks, whereas the summer cohort started with higher levels which reduced. Changes in 25OH-D were inversely correlated with changes in weight and cholesterol when controlling for baseline values. The elevated 25OH-D was associated with greater reductions in WC and cholesterol.
Sara *et al*.,2012 [35]	Controlled experimental animal study.	30 female Wistar rats (21–28 weeks); 10 received vit. D3 (120 ng/100 g/week, 20 served as control.	Vit. D3 regains insulin relaxation and norepinephrine-induced contractility; it fails to alter NO-dependent relaxation.
Dehghani Firouzabadi *et al*., 2012 [36]	Case control study	100 infertile PCOS women; 50 treated with metformin 1500 mg/day, 50 treated with metformin 1500 mg/day plus Calcium 1000 mg/day and Vit. D 100000 IU/month for 6 months.	BMI significantly decreased in group II; improvement in menstrual irregularity, follicle maturation, and fertility enhanced in group II compared with group I.
Bonakdara *et al*., 2012 [37]	Randomized placebo-controlled clinical trial	51 women with PCOS; group 1: treated with 0.5μg calcitriol; group 2: 1000 mg metformin; group 3: placebo, for 3 months.	Metformin decreases weight, insulin level, and insulin resistance. Calcitriol reduces PTH level, and increases serum vit. D3. Ovulation was restored significantly in calcitriol group after 3 months compared with other groups.

SHBG (Sex Hormone Binding Protein), HOMA-IR (Homeostatic Model Assessment for Insulin Resistance), BMI (Body Mass Index), WHR (Waist/Hip Ratio), FBS (Fasting Blood Sugar), IR (Insulin Resistance), QUICKI (Quantitative Insulin-Sensitivity Check Index), 3β-HSD (3β-Hydroxysteroid Dehydrogenase), PTH (Para-Thyroid Hormone).

Women with PCOS have oligo-menorrhea or anovulation, and after adjusting the serum vitamin D3 level, ovulation was significantly restored; these issues were linked to a number of factors [28]. VEGF, an angiogenic agent that promotes an increase in the vascularity of the ovaries in response to high insulin levels, is elevated in women with PCOS. In turn, VEGF raises AMH, a hormone that prevents ovulation [28]. Vitamin D3 also lowers VEGF, which correlates with lower triglyceride levels and, as a result, inhibits aberrant ovarian vascularization, which lowers testosterone levels and, in turn, reduces hirsutism. The usefulness of vitamin D3 in recovering ovulation was demonstrated in this study. All of the studies cited above support this conclusion. Furthermore, after administering vitamin D3, the levels of androgen and AMH in PCOS women reduced dramatically. Another study [36] found a similar result when looking at the impact of vitamin D3 in treating hyperandrogenism and fertility in PCOS women. Furthermore, Bonakdaran *et al*. found that vitamin D3 treatment dramatically lowered testosterone levels in women with PCOS. Vitamin D3's stimulating actions on the aromatase enzyme, which decreases the synthesis of dehydroepiandrosterone (an androgenic hormone), are connected to this reduction [37]. Studies conducted by Javed *et al*. and Sukul *et al*. support the beneficial effects of vitamin D3 in improving insulin resistance in obese PCOS women. Another beneficial effect of vitamin D3 is reducing hepatic inflammation and fibrosis in obese PCOS women with non-alcoholic fatty liver disease [22,21]. In contrast, the cardio-vascular risk factors and testosterone hormone levels were not changed after the intervention with vitamin D3 [21]. Furthermore, co-supplementing vitamin D3 with other micronutrients improves the metabolic disturbances and hormonal dysfunction associated with PCOS [29], though there was no effect on glucose fasting level. Similarly, Kadoura *et al*. found that combining vitamin D3 with calcium and metformin improved menstrual irregularity in PCOS women while having no significant effects on gonadotropin hormone levels, insulin resistance, or insulin sensitivity [19], which is similar to the findings of another study in which the integrated measures remained unchanged but two-hour

insulin secretion and diastolic blood pressure in PCOS women decreased. Gupta *et al*. revealed similar findings regarding vitamin D3's preventive effect in women with PCOS by lowering systolic blood pressure and improving ovulation. It also improved insulin sensitivity while lowering insulin resistance. However, there was no influence on hormonal parameters [30]. Similarly, Trummer *et al*. found comparable results with vitamin D3 since it had no substantial effect on hormonal or metabolic parameters. Furthermore, during the oral glucose tolerance test, there was a drop in plasma glucose after 1 hour [23]. In a retrospective study of obese women with PCOS conducted on a large scale to evaluate the seasonal change and lifestyle modification through elevating vitamin D3 levels, the results showed a modest increase in vitamin D3 levels and a reduction in body weight, which resulted in improved menstrual irregularity, lower cholesterol levels, and reduced cardiovascular risks, especially in the summer and autumn seasons [34]. Lumme *et al*., on the other hand, used a population-based study of women with PCOS who shared similar genetic and ethnic backgrounds. There was no link between vitamin D3 supplementation and decreased risk factors for metabolic syndrome or cardiovascular disease, despite several investigations [20]. Similarly, Garg *et al*. discovered that vitamin D3 had no positive effect on metabolic markers in women with PCOS [10]. Surprisingly, the study design can have an impact on the outcome. For example, a cross-sectional study conducted by Mesinovic *et al*. revealed no link between vitamin D3 metabolites and androgen levels in pre-menopausal women with PCOS, despite the majority of studies agreeing on the relationship between vitamin D3 and androgen levels [15].

Conclusion

The majority of women with PCOS are vitamin D3 deficient, which exacerbates metabolic and hormonal issues. A high dose of vitamin D3 may help to improve the symptoms of the syndrome, notably in the treatment of anovulation and the increase of female fertility.

Acknowledgment

The authors thank the support of the College of Pharmacy, University of Sulaimani, Kurdistan Region, Iraq.

Conflict of interests

No conflicting interests

Data sharing statement

N/A

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