Article Review

Effectiveness of Vitamin D Therapy on the Lipid Profile of Patients with Polycystic Ovary Syndrome

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Abstract
Polycystic ovary syndrome (PCOS) is characterized by chronic hyperandrogenism and anovulation that is also associated with various clinical and biochemical features. Vitamin D deficiency is a common problem that affects up to half of the adult population worldwide, including patients with PCOS. Based on these considerations, we are interested in further exploring the effectiveness of vitamin D in improving lipid profiles in PCOS.

Key words: PCOS, Lipids, Vitamin D

Efektivitas Terapi Vitamin D pada Profil Lipid Penderita Sindrom Ovarium Polikistik

Abstrak
Sindrom Ovarium Polikistik (PCOS) ditandai dengan hiperandrogenisme kronis dan anovulasi yang juga berhubungan dengan berbagai gambaran klinis dan biokimia. Kekurangan vitamin D adalah masalah umum yang mempengaruhi setengah populasi orang dewasa di seluruh dunia, termasuk pasien PCOS. Tinjauan literatur ini dilakukan untuk mencari artikel asli dan review mengenai pertanyaan spesifik mengenai efektivitas terapi vitamin D terhadap profil lipid pasien PCOS.

Kata kunci: PCOS, Lipid, Vitamin D
Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder found in 5-10% of women of reproductive age. This syndrome is characterized by chronic hyperandrogenism and anovulation that is also associated with a variety of clinical and biochemical features, including hirsutism, acne, menstrual irregularities, obesity, infertility, hyperinsulinemia, glucose intolerance, and dyslipidemia.1-3

Dyslipidemia is probably the most common metabolic disorder in PCOS. According to the National Cholesterol Education Program (NCEP) guidelines, as many as 70% of women with PCOS have abnormal serum lipid concentrations.4-6

Vitamin D deficiency is a common problem affecting up to half of the adult population worldwide, including patients with PCOS.4-6

Until now, the management of dyslipidemia in general still uses statins and fibrates, but their efficacy is still limited and has hepatotoxic and myopathic effects. Based on these considerations, the authors are interested in further exploring the effectiveness of vitamin D in improving lipid profiles in patients with PCOS, such as complementary therapy along with low doses of statins, fibrates, diet, and physical activity, as well as using vitamin D as monotherapy.

Method

This literature review was conducted to search original and review articles regarding specific questions on the effectiveness of vitamin D therapy on the lipid profile of patients with PCOS. We used several search engines, including in the Google Scholar, Science Direct, Elsevier, and Pubmed, and obtained literature published in 2013–2023 that was available in full-text PDF format. The type of article references might be in the form of original articles, meta-analyses, systematic reviews, and literature reviews, with keywords and topics that fit the theme and the title of the literature review. The journal articles that fit the predetermined criteria were then included in this review.

Definition

PCOS was defined by the presence of at least two of the three diagnostic criteria (Table 1).1-3

Table 1. Definition PCOS 2

<table>
<thead>
<tr>
<th>Comparison Criteria of Diagnostic Criteria for PCOS</th>
</tr>
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<tbody>
<tr>
<td>National Institutes of Health (NIH) 1990</td>
</tr>
<tr>
<td>patient who have second characteristics following:</td>
</tr>
<tr>
<td>1. Sign hyperandrogenism in a manner that and/or</td>
</tr>
<tr>
<td>biochemistry</td>
</tr>
<tr>
<td>2. Oligo- or chronic anovulation</td>
</tr>
<tr>
<td>Etiology other than excess androgens and infertility anovulation excluded</td>
</tr>
<tr>
<td>ESHRE/ASRM or Rotterdam year 2003</td>
</tr>
<tr>
<td>Patient Who own 2 from 3 criteria following:</td>
</tr>
<tr>
<td>1. Oligo- or chronic anovulation</td>
</tr>
<tr>
<td>2. Sign hyperandrogenism in a manner that is</td>
</tr>
<tr>
<td>clinical and/or biochemical</td>
</tr>
<tr>
<td>3. Morphology for ovary polycystic</td>
</tr>
<tr>
<td>Etiology other than excess androgens and infertility anovulation excluded</td>
</tr>
<tr>
<td>Androgens Excess and PCOS Society (AE-PCOS) 2006</td>
</tr>
<tr>
<td>patient who have second characteristics following:</td>
</tr>
<tr>
<td>1. Histism and/or hyperandrogenism</td>
</tr>
<tr>
<td>2. Oligoanovulation and/or ovary polycystic</td>
</tr>
<tr>
<td>Etiology other than excess androgens and infertility anovulation excluded</td>
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</tbody>
</table>

Epidemiology

In the general population, the reported
prevalence of PCOS has an incidence rate of approximately 3%–10% in women of the reproductive age. The prevalence of PCOS worldwide ranges from 5% to 25%, depending on the diagnostic criteria used.\textsuperscript{3,7}

**Etiology and Risk Factors**

High ratios of luteinizing hormone (LH) to follicle-stimulating hormone (FSH) and increased gonadotropin-releasing hormone (GnRH) are known to be the underlying causes of PCOS.\textsuperscript{7,8}

External factors of PCOS include genetics and the environment. Exposure to environmental toxins, such as endocrine-disrupting chemicals that mimic endogenous hormones and advanced glycation end products (AGEs), can program reproductive and metabolic functions leading to PCOS.\textsuperscript{2,8}

Stress also triggers the hypothalamus–pituitary–adrenal axis to release cortisol. Cortisol causes IR by stimulating visceral fat accumulation, gluconeogenesis, and lipolysis. Stress is also involved in increasing insulin levels.\textsuperscript{8}

Saturated fatty acid intake plays a role in PCOS by causing inflammation and reducing insulin sensitivity. Dietary fats and proteins can form AGEs in the bloodstream.\textsuperscript{2,8}

Therefore, one of the management strategies for PCOS is to limit exposure to AGEs. Foods of animal origin that are high in fat and protein are generally rich in AGEs and are more prone to AGE formation during cooking.\textsuperscript{2,8}

Internal factors include insulin resistance (IR), which causes compensatory hyperinsulinemia, which encourages the emergence of the phenotypic characteristics of PCOS. Insulin resistance and compensatory hyperinsulinism contribute to androgen excess.\textsuperscript{2,8,9}

Hyperinsulinemia contributes to androgen excess in several ways, including increased LH-stimulated androgen synthesis by ovarian theca cells, potentiated adrenal androgen synthesis mediated by corticotropin, and inhibited hepatic synthesis of sex hormone-binding globulin. The combination of hyperandrogenism and hyperinsulinemia inhibits the growth of ovarian follicles. This cessation is associated with menstrual irregularities, anovulatory subfertility, and the deposition of immature follicles.\textsuperscript{2,8,9}

Studies have shown that women with PCOS have higher plasma concentrations of testosterone, which can then be converted to estrone in adipose tissue. This increase in the change of estrone to estradiol affects follicular growth and increases the ratio of LH to FSH, which causes ovulation dysfunction. Hyperandrogenism, whether clinical or biochemical, is required in the diagnosis of PCOS.\textsuperscript{2,8,9}

Obesity also plays a role in hyperinsulinemia, IR, and HA. The presence of obesity worsens insulin resistance, degree of hyperinsulinemia, severity of ovulatory and menstrual dysfunction, and pregnancy outcome in women with PCOS.\textsuperscript{2,8}

**Classification**

PCOS can be classified into types A, B, C, and D. Classic PCOS (Phenotypes A and B), PCOS phenotype A is often referred to as the “complete” PCOS phenotype, and phenotypes A and B are often referred to as “classic” PCOS. “Classic” PCOS (phenotypes A and B) is often associated with more irregular menstrual patterns and a greater likelihood of insulin resistance and dyslipidemia compared with ovulatory or nonhyperandrogenic phenotypes (phenotypes C and D). Ovulatory PCOS (Phenotype C) referred to as “ovulatory” PCOS. The hirsutism scores, androgen and lipid levels, and the risk of metabolic syndrome in women with phenotype C are between classic PCOS and phenotype D.\textsuperscript{2,3,10} Nonhyperandrogenic PCOS (Phenotype D) patients have normal...
androgen levels, and in most studies, patients with nonhyperandrogenic PCOS have the mildest degree of endocrine and metabolic dysfunction and the lowest prevalence of metabolic syndrome.\textsuperscript{3,10}

**Clinical Features and Physical Examination**

Starting with a through history, including a detailed family history and a complete physical examination, the overall prevalence of the main clinical features of PCOS is 15% (12-18%) for ovulatory dysfunction; 13% (8-20%) for hirsutism; 11% (8-15%) for biochemical hyperandrogenism; and 28% (22-35%) for PCOM.\textsuperscript{1,10,11} The most reliable clinical marker of androgen excess is hirsutism, whereas acne and alopecia are additional clinical signs of hyperandrogenism, but independently neither acne nor alopecia in women are specific for hyperandrogenism, especially in the absence of hirsutism.\textsuperscript{1,10,11}

Biochemical assessment of HA in clinical practice by measuring quantitative free testosterone.\textsuperscript{2,11} Menstrual dysfunction in women with PCOS can range from amenorrhea to oligomenorrhea to episodic menometrorrhagia with anemia. In many women with PCOS, amenorrhea and oligomenorrhea occur due to anovulation.\textsuperscript{1}

PCOM on ultrasound is the most common feature of PCOS and is found in one-third of women. The most recent International PCOS Guidelines for the diagnosis of PCOS, in 2018, revised the criteria for defining PCOM (PCO morphology) by recommending ≥20 antral follicles (2–9 mm in diameter) per ovary and/or ovarian volume ≥10 mL as the diagnostic threshold using a transducer frequency ≥8 MHz. For older ultrasound equipment (<5 MHz), the criterion is ovarian volume ≥10 mL.\textsuperscript{2,10,11}

**Additional Examination**

Investigations include laboratory investigations that usually include prolactin levels, thyroid function, dehydroepiandrosterone-sulfate, lipid profile, total testosterone, androstenedione, SHBG, DHEAS, glucose tolerance test, and if clinically indicated, 24-h urine cortisol-free screening for Cushing’s disease and 17-hydroxyprogesterone for congenital hyperplasia. Endometrial biopsy, oligo-amenorrhea or prolonged amenorrhea, and the presence of hyperinsulinemia increase the risk of endometrial hyperplasia and carcinoma in patients with PCOS, particularly if obesity is present. Endometrial biopsy is also recommended in women of age with abnormal bleeding and in younger women with anovulatory bleeding that is refractory to hormonal treatment.\textsuperscript{1,11}

Ultrasonographically, the sonographic criteria for polycystic ovaries include ≥20 small cysts (2 to 9 mm in diameter) or increased ovarian volume (>10 mL) or both.\textsuperscript{1,3,10}

![Figure 1 Ovaries with Polycystic Morphology, Multiple Ovarian Follicles with Peripheral Arrangement](Quoted from: Bakir MB, et al, 2021)
Treatment

The choice of therapy for each symptom of PCOS depends on the patient’s goals and the severity of the endocrine dysfunction. 13 Conservative treatment in obese women with PCOS is important for lifestyle changes that focus on diet and exercise. First-line therapy for menstrual irregularities is the combined oral contraceptive (COC) pill, which can induce menstrual cycles, lower androgen levels, and thin the endometrium. In particular, COC suppresses the release of gonadotropins, which decreases ovarian androgen production.1,13

Insulin-sensitizing agents such as metformin are most frequently prescribed, particularly in women with impaired glucose tolerance and insulin resistance. Metformin can lower levels of androgens in women with PCOS which are thin or obese, leading to an increased rate of spontaneous ovulation.1,13

Although ovarian wedge resection is now very rare, laparoscopic ovarian drilling can restore ovulation in many clomiphene citrate-resistant PCOS women.

Prognosis

PCOS has significant reproductive implications for women and their long-term future health, including an increased risk of anovulatory infertility, miscarriage, and pregnancy-related complications. In addition, patients also have an increased risk of developing type II diabetes mellitus and cardiovascular disease later in life.1–3

Lipid Profile in PCOS Patients

Lipids or fats are non-heterogeneous compounds that are insoluble in water, including fatty acids and their derivatives, namely triglycerides, phospholipids, and sterols14

The digestion and absorption of fat can be divided into luminal and mucosal phases.14 Metabolic disorders in patients with PCOS are associated with obesity, insulin resistance, hyperinsulinemia, dyslipidemia, oxidative stress, and chronic inflammation. 4 In women with the androgenic phenotype PCOS (A, B, and C), there are changes in carbohydrate metabolism characterized by impaired glucose tolerance or insulin resistance, as well as lipid disturbances associated with the development of the metabolic syndrome, compared with the nonandrogenic anovulatory phenotype D.

The Role of Vitamin D in PCOS Patients

Vitamin D plays an important role in the female reproductive system. During pregnancy, vitamin D deficiency increases the risk of gestational diabetes, recurrent abortion, preeclampsia, and premature birth. Studies on the relationship between vitamin D and the female reproductive system have shown that vitamin D can be used as a treatment for ovulation dysfunction, such as polycystic ovary syndrome and infertility in women of reproductive age. In the immune system, active and native vitamin D, calcitriol, and cholecalciferol induce tolerogenic properties in dendritic cells (dendritic cells, DCs) because these cells also express the CYP27B1 enzyme.15

Vitamin D regulates calcium metabolism and increases the intestinal absorption of calcium, thereby reducing the intestinal absorption of fatty acids. However, a study conducted by Dastorani et al. (2018) found that supplementing vitamin D 50,000 IU every week for 8 weeks reduced total cholesterol and LDL in infertile women due to PCOS.15

Another study in 2019 showed that vitamin D supplementation at a dose of 4000 IU/day for 12 weeks lowered total cholesterol. A meta-analysis study by Luo et al. (2021) found that from 7 to 10 RCTs, there
was a decrease in LDL levels, VLDL levels, triglycerides, and total cholesterol, and there was no increase in HDL levels in PCOS patients, given doses of vitamin D ≤5000 IU/day and a duration of 12 weeks either given vitamin D supplementation alone or as additional supplementation therapy. Vitamin D deficiency (serum 25(OH)D value <30 ng/mL) has been associated with a reduced chance of live birth in the population undergoing various infertility therapies. Several observational studies have shown that low vitamin D concentrations are associated with increased BMI, IR, testosterone, and DHEAS values in women with PCOS. Supplementing vitamin D 50,000 IU every week for 8 weeks reduced total cholesterol and LDL in infertile women.

Conclusions

Metabolic disorders in patients with PCOS are associated with obesity, insulin resistance, hyperinsulinemia, dyslipidemia, oxidative stress, and chronic inflammation. In women with the androgenic phenotype PCOS (A, B, and C), there are changes in carbohydrate metabolism characterized by impaired glucose tolerance or insulin resistance, as well as lipid disorders associated with the development of the metabolic syndrome, namely increased triglycerides, LDL, free testosterone, DHEAS, androstenedione, and SHBG in the blood, as well as a significant decrease in HDL compared with the nonandrogenic anovulatory phenotype D.

Table 2 summarizes the findings from the study reporting the effectiveness of vitamin D therapy on the lipid profile of patients with PCOS.

Table 2: Effectiveness of Vitamin D Therapy on the Lipid Profile of Patients with PCOS

<table>
<thead>
<tr>
<th>Vitamin D deficiency (level ≤ 20 ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased cytokine production &amp; reduced pancreatic activity</td>
</tr>
<tr>
<td>Adiponectin &amp; insulin receptors decrease</td>
</tr>
<tr>
<td>Insulin Resistance</td>
</tr>
<tr>
<td>Hinder SHBG</td>
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<tr>
<td>Stimulation ovarian activity</td>
</tr>
<tr>
<td>Free androgen increased</td>
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<tr>
<td>Increased ovarian androgen synthesis</td>
</tr>
<tr>
<td>Hyperandrogenism</td>
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<tr>
<td>Enhancement activity lipase enzymes and inhibit Activation estrogen</td>
</tr>
<tr>
<td>Lower HDL, plasma levels and increase TG, LDL, VLDL</td>
</tr>
</tbody>
</table>

Figure 2: The Relationship between Vitamin D deficiency on Lipid Metabolism in PCOS Patients
Table 2 Studies Reporting the Effectiveness of Vitamin D Therapy on the Lipid Profile of Patients with Polycystic Ovary Syndrome

<table>
<thead>
<tr>
<th>First Author (Years)</th>
<th>Title</th>
<th>Type</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dastorani (2018)</td>
<td>“The Effects Of Vitamin D Supplementation on Metabolic Profiles and Gene Expression of Insulin and Lipid Metabolism in Infertile Polycystic Ovary Syndrome Candidates for In Vitro Fertilization”</td>
<td>Original Research</td>
<td>Infertile women with PCOS who were candidates for IVF received 50,000 IU of vitamin D every other week for 8 weeks and significantly reduced total and LDL cholesterol levels compared with the placebo, while other lipid profile parameters remained unchanged. The candidates also experienced a large increase in QUICKI and a significant drop in serum AMH (anti-Müllerian hormone), insulin levels, and homeostasis model of assessment-estimated insulin resistance (HOMA-IR) scores. Furthermore, vitamin D treatment markedly increased PPAR- and GLUT-1 gene expression. Vitamin D may improve insulin sensitivity and reduce PTH synthesis, thereby lowering total and LDL cholesterol.</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Research Area</td>
<td>Key Findings</td>
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<td>----------------------------------------------------------------------</td>
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</tbody>
</table>
| Luo (2021) | “Effectiveness of vitamin D supplementation on lipid profile in women with polycystic ovary syndrome: a meta-analysis of randomized controlled trials” | Original Research Article | - Vitamin D treatment for patients with PCOS led to improvements in TC, TG, LDL, and VLDL-C levels, but no change in HDL levels was observed.  
- Only at a lower dose of vitamin D (5,000 IU/day) and for a shorter period of time (12 weeks) did the amounts of TC, TG, and LDL-C statistically decrease. Higher dosages did not appear to have the same statistical effect.  
- All of the trials analyzed in this meta-analysis demonstrated that vitamin D supplementation helped PCOS women with vitamin D deficiency restore physiological serum levels of 25(OH)D, and it was also shown to have positive effects on glucose metabolism. |
| Song (2012) | “Calcium and vitamin D in obesity”                                       | Meta-Analysis | - Duration of vitamin D and calcium supplementation for less than 8 weeks significantly reduced triglycerides, total and LDL cholesterol, and increased HDL.  
- In addition to being a key factor in adipocyte apoptosis, 1,25(OH)2D3 appears to control adipocyte differentiation.  
- Vitamin D supplementation at a dose of 2000 IU for 12 weeks for improving lipid profiles in patients with metabolic syndrome resulted in no significant difference between the groups receiving vitamin D supplementation and placebo, but there was an increase in vitamin D status from the average level. |
| AlAnouti (2021) | “Effects of Vitamin D Supplementation on Lipid Profile in Adults with Metabolic Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials” | Systematic review and meta-analysis |  |
due to PCOS. Another meta-analysis in 2019 showed that vitamin D supplementation at a dose of 4000 IU/day for 12 weeks lowered total cholesterol. A meta-analysis study by Luo et al. (2021) found that from 7 to 10 RCTs, there was a reduction in LDL levels, VLDL levels, triglycerides, and total cholesterol and there was no increase in HDL levels in PCOS patients given doses of vitamin D ≤5000 IU/day and duration of 12 weeks either as vitamin D supplementation alone or as additional supplementation therapy.17,18,19

References

Fatimah Usman: The Effectiveness of Vitamin D Therapy on the Lipid Profile of Patients with Polycystic Ovary