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# The Role of Vitamin D in Treatment of Polycystic Ovary Syndrome Depending on Phenotype

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## Abstract

The goal of the study is to explore the changes of vitamin D, hormonal indices, fat, and carbohydrate metabolism in the blood of women with polycystic ovary syndrome (PCOS), as well as to define the appropriateness of prescribing cholecalciferol in the complex treatment of this pathology. To achieve this goal, we have examined 80 women, aged 1835 years, with PCOS and underlying overweight and obesity, who were divided into four phenotype groups, according to the consensus of the PCOS Workshop Group in Amsterdam (2011). All women underwent a general medical examination, having measured their anthropometric parameters, body mass index (BMI) and clinical manifestations of hyperandrogenemia. Their serum was checked for the content of 25-hydroxyvitamin D (25(OH)D) , LH, FSH, progesterone, estradiol, androstenedione, dehydroepiandrosterone sulfate, 17-hydroxyprogesterone, anti-Müllerian hormone, insulin, and leptin. The study results found a decrease in vitamin D in the blood of women with PCOS in all clinical phenotypes, which lowered with the progression of obesity. Cholecalciferol deficiency was associated with insulin resistance, hyperinsulinemia and hyperleptinemia. The correlation between the vitamin D content and hormonal indices in women with PCOS showed an inverse correlation between 25(OH)D and AMH levels, positive between insulin and 25(OH)D, and negative between vitamin D level and hirsutism score. Prescription of vitamin D in the complex treatment of women with PCOS leads to stabilization of hormones, decrease of HA signs, normalization of the menstrual cycle and restored ovulation.

**Keywords:** Hyperandrogenism, Insulin resistance, Obesity,Polycystic ovarian syndrome, Vitamin D deficiency.

## Background and Aims

For many years polycystic ovary syndrome (PCOS) has been one of the most important medical and social issues since it is a significant component in the structure of diseases that cause female infertility. PCOS causes more than half of all cases of endocrine infertility (5075%) and approximately 2022% of cases of infertility in general [1]. However, the impact of PCOS is not limited to infertility only. Today, the syndrome catches the attention not only as causing the pathology of the reproductive system but also by impairing the functioning of almost all organs and systems of the body. The metabolic components of the syndrome increase the risk of diabetes mellitus type 2 (DMTII) ten times, cardiovascular pathology, as well as cancer, seven times, which, of course, affects not only the quality but also the life expectancy of a woman [2, 3]. Thus, in the final report of the US National Institutes of Health on PCOS, this pathology was identified as one of the priorities in maintaining the health and quality of life of women, requiring interdisciplinary research to study the mechanisms of ovarian, hypothalamic-pituitary-adrenal, and metabolic dysfunction, defining the prevalence of PCOS phenotypes and their contribution to the risk of cardiovascular pathology, DMTII,and cancer [4, 5, 6].

PCOS is diagnosed in 36% of women of fertile age [7, 8]. The frequency of PCOS diagnostics is quite variable due to its heterogeneous, clinical, and endocrinological

manifestations. The incidence of PCOS is much higher among women with overweight and obesity [9].

The main clinical manifestations of PCOS are: menstrual dysfunction with chronic anovulation and androgen-dependent dermatopathies that have been experienced since adolescence; 50% of women suffer from obesity [10, 11].

For a more detailed understanding of the pathogenesis of the disease, clinical picture and prognosis for reproductive and somatic health, the phenotypes of PCOS were identified at the third consensus of the American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE)] in Amsterdam in 2011. .

The diagnosis of PCOS in women should be confirmed at least with two of the three criteria: chronic anovulation, hyperandrogenemia (HA), the polycystic structure of ovary (20 or more follicles with at least one ovary volume over 10 $cm^3$ in the absence of a dominant follicle and yellow body cyst). According to these features, there are four phenotypes of PCOS:

I incomplete classic phenotype: HA (clinical and biochemical) and chronic anovulation (H-CA);

II ovulatory form: HA and polycystic ovaries defined by ultrasound scanning (PCOm), but with ovulatory cycles (H-PCOm);

III normoandrogenic form: chronic anovulation and non-HA polycystic ovaries (CA-PCOm);

IV complete or classic phenotype: HA, chronic anovulation and polycystic ovaries (H-CA-PCOm) [12–15].

For a long time, medical care for PCOS patients aimed at restoring women's menstrual and fertile function. The purpose of the treatment was to restore the ovulatory menstrual cycle and fertility, eliminate the manifestations of androgen-dependent dermopathy, and normalize body weight [16, 17]. However, according to some authors, the treatment approach for such women should be determined by the mechanisms of disease development. Today, priority is given to the complex treatment of women with PCOS, taking into account their age, hormonal state, fertility, and there is a focus on the diagnostics and correction of metabolic disorders that impair the quality and life expectancy of patients [18–20].

In the last decade, modern science has been enriched by new data regarding the biological role of vitamin D, which suggested reviewing the importance of this vitamin in the body. There is increasing information on the role of vitamin D in the pathogenesis of not only the pathology of the bone system, but also obesity, DMTII, dyslipidemia, and disorders of the reproductive system [21]. Currently, there is evidence that low levels of vitamin D are associated with obesity and, conversely, deficiency of this nutrient may predict the excessive adipose tissue. Some examinations have found an inverse correlation between 25(OH) D content and IR in women with PCOS. There is an opinion that high levels of this vitamin are associated with a high ovarian reserve, and hypovitaminosis D may be one of the factors that lead to premature ovarian depletion [22–26].

Vitamin D, which enters the body with food and is also produced by insolation, is biologically inert. In order to activate it, it is necessary to undergo two stages of hydroxylation. In the liver, it is converted to 25(OH) D, cholecalciferol, - its most common form. Level 25(OH) D indicates the content of this nutrient in the blood. Under the action of the enzyme 1-α-hydroxylase in the kidneys 25(OH) D produces its active metabolite (1,25 (OH) 2D3, calcitriol,) through which the vitamin makes its clinical effect on the body. Thus, vitamin D can act both directly - through specific VDR receptors, and indirectly - stimulating the synthesis of steroid hormones (estrogen, progesterone, testosterone). These receptors are present in women's ovaries, endometrium, fallopian tubes, as well as in the decidual membrane [27, 28].

Nowadays there are strong proofs showing the role of vitamin D in the pathogenesis of PCOS. Some researchers have diagnosed the inverse correlation between anti-Mullerian hormone (AMH) levels in the blood and vitamin D in women with PCOS. Other scientists have proved that vitamin D deficiency causes a decrease in the content of sex-binding globulin (SHBG), which in


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its turn leads to the development of HA, as well as to the increased synthesis of insulin and, as a result, hyperinsulinemia and insulin resistance (IR). A number of publications have demonstrated a correlation between vitamin D hypovitaminosis and testosterone and dehydroepiandrosterone sulfate (DHEA-S) levels. In vitro studies have shown that insufficiency of vitamin D in the body is accompanied by impaired follicle maturation, cyst formation, absence of yellow bodies, and stromal sclerosis [28, 30]. However, there is not enough data to fully understand the mechanisms through which vitamin D influences PCOS and how appropriate it is to use this nutrient in complex therapy of PCOS.

## The Goal of the Study

To explore the role of vitamin D for effective treatment of women with PCOS depending on the phenotype.

## Materials and Methods

To achieve this goal, we examined 80 women, aged 1835 years, with PCOS and underlying overweight and obesity (experimental group) and 20 women of same age in good physical and gynaecological health (control group). The studies were performed at the Department of Endocrinology, LNMU by Danylo Halytskyi and Intersono Clinic in Lviv (Ukraine). Diagnostics of PCOS was performed according to Rotterdam requirements. Exceptional cases were women with severe endocrine and somatic pathology and conditions that were contraindications to COCs.

All women underwent a general medical examination, having measured their anthropometric parameters, body mass index (BMI) and clinical manifestations of HA (hirsutism score (HS) by Ferriman-Gallwey scale). Pelvic ultrasound was performed by Siemens ultrasound machine (Germany) and laboratory tests were taken at the Intersono Medical Center. The levels of LH, FSH, progesterone (Ps), estradiol (Es), androstenedione (A), dehydroepiandrosterone sulfate (DHEA-s), 17-hydroxyprogesterone (17-OHP), anti-Mullerian hormone (AMH), insulin, leptin were measured with ECLIA method - electrochemiluminescent immunoassay (using automatic analyzers and reagents of Roche Diagnostics (Germany)) and enzyme-immunoassay (using standard kits of Immunotech (Czech Republic)) on 3rd5th days of the menstrual cycle. The index of free testosterone (FAI) was calculated by the formula: FAI = TT/SHBG x 100. The content of 25(OH)D in serum was measured by chemiluminescent immunoassay using LIAISON analyzer and LIAISON 25OH TOTAL kits (DiaSorin Inc., USA). Vitamin D deficiency was diagnosed at the level of 25(OH) D at <20 ng/mL, deficiency at concentration of 25(OH) D at 2030 ng/mL, adequate levels -> 30 ng/mL. The insulin resistance index (IR) was calculated by the NOMA-IR formula: fasting glucose (mmol/L) x fasting insulin (mcU/mL)/22.5.

All women were divided into four phenotype groups, according to the consensus of the PCOS Workshop Group in Amsterdam (2011). Group 1 included 20 women with HA and polycystic ovaries (ovulating); Group 2: 19 women with HA and chronic anovulation (no multifollicular ovaries); Group 3: 23 women with polycystic ovaries and anovulation (no signs of HA); Group 4: 18 women with HA, chronic anovulation and polycystic ovaries (complete syndrome). In addition, all patients in each group were further divided into two subgroups, depending on the BMI. The 1st subgroup included overweight women (BMI of 2529.9 kg/m$^2$), and the 2nd group consisted of obese patients (BMI>30 kg/m$^2$). We have been thoroughly studying the medical history of patients and their lifestyles, evaluating objective data and complaints. The treatment approach was chosen according to the identified PCOS phenotype and metabolic disorders. Half of the patients of each phenotype group, at their request, were additionally prescribed a vitamin D dose of 20004000 IU (depending on the background level of the nutrient). The effectiveness of the therapy was evaluated after six months of treatment.

Statistical processing of the obtained data was performed using standard methods of descriptive and categorical statistics and the Statistica 8.0 Certified Software Package (Statsoft

Inc., USA). Quantitative indices were presented as mean ± standard deviation. Quantitative indices in groups were compared using the Mann-Whitney U-test. The correlation between quantitative indicators was studied by Spearman's rank correlation method. The difference was considered significant in the case of $P<0.05$. Examination of patients was carried out in accordance with the requirements of the Declaration of Helsinki (2004).

## Results of the Study and Discussion

Having analyzed the hormonal state in women with PCOS in different phenotypic groups, we found in their blood a significant increase in the LH levels, a decrease in the concentration of FSH and insufficient content of Es and Ps, especially in patients with chronic anovulation ($P<0.01$); a tendency for an increase in FAI and androgens, especially in phenotypic groups with present HA; an increase in the AMH level, in particular in women with PCOS (Table 1).

Analysis of leptin content in women with PCOS defined the presence of hyperleptinemia in all examined patients. The concentration of leptin in their blood increased proportionally to the increase in BMI.

The dynamics of leptin concentration was accompanied by similar changes in insulin content and NOMA-IR scores, in particular, higher insulinemia and NOMA-IR were diagnosed in the PCOS group of women with verified obesity, which increased with the degree of obesity; this allows to consider the excess body mass as an adverse factor provoking the development of hyperinsulinemia and progression of IR in this nosology (Table 2).

When analyzing the levels of 25(OH) D in the serum of the examined women, we have noted a tendency for a decrease in average vitamin D concentrations in patients of all PCOS phenotype groups compared to control groups. In most patients, vitamin D content did not correspond to its normal level (21.8% and 36.1% in groups 1 and 2, respectively). Both insufficiency and deficiency of cholecalciferol varied significantly among PCOS patients as opposed to healthy women. Their cholecalciferol deficiency increased with the development of obesity (Table 3).

Analysis of metabolic examinations has shown that IR was combined with

Table 1: Hormonal state in women with PCOS depending on phenotype.

| Index | Control group (n=20) | Experimental group (PCOS) (n=80) | | | |
|---|---|---|---|---|---|
| | | Group 1 (n=20) | Group 2 (n=19) | Group 3 (n=23) | Group 4 (n=18) |
| LH, mIU/mL | 7,3±3,5 | 13,3±3,5* | 15,6±2,7* | 16,3±2,5* | 18,3±3,2* |
| FSH, mIU/L | 5,4±2,1 | 5,1±1,1 | 4,3±0,28* | 4,2±0,32* | 3,8*±0,41* |
| Es, pmol/L | 163,0±11,8 | 157,1±11,3 | 97,1±14,2* | 78,1±8,6* | 77,4±12,3* |
| Ps, nmol/L | 1,43 ±1,22 | 1,12±0,13 | 0,58±0,14* | 0,61±0,13* | 0,62±0,13* |
| SHBG, nmol/L | 94,6±10,2 | 35,4±8,3* | 43,4±7,1* | 85,4±9,3 | 35,4±8,3* |
| fT, nmol/L | 1,6±0,1 | 4,6±0,4* | 6,6±0,2* | 1,8±0,4 | 4,6±0,4* |
| FAI, nmol/L | 60 ±20,1 | 13 ±2,1* | 12 ±0,7* | 30 ±10,1 | 10 ±1,8* |
| 17-OHP, ng/mL | 0,72±0,11 | 0,71±0,13 | 0,81±0,77 | 0,68±0,77 | 0,71±0,77 |
| A, nmol/L | 3,8±0,22 | 15,6±1,14* | 17,8±1,22* | 4,6±0,33 | 16,8±1,44* |
| DHEA, mcg/mL | 176,4±11,7 | 484,6±26,3* | 574,6±28,2* | 184,6±14,3 | 684,6±28,1* |
| AMH, ng/mL | 3,8±0,3 | 4,1±1,2 | 6,1±0,3* | 10,1±1,1* | 11,1±0,8* |
| HS (hirsutism score) | 6±1,2 | 13±0,4* | 13±1,2* | 8±0,8 | 14±1,3* |

Note. * – the significance compared to the control group, $P<0.01$.


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Table 2: Indices of leptin, insulin, and HOMA-IR in the serum of women with PCOS depending on the phenotype.

| Index | Control group (n=20) | Experimental group (PCOS) (n=80) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | I n =20 | | II n = 19 | | III n = 23 | | IV n = 18 | |
| | | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 |
| HOMA-IR | 1,77±0,11 | 2,71±0,1 | 4,32±1,1* | 2,43±1,23 | 4,43±1,23* | 2,52±2,45 | 3,52±2,45* | 3,12±3,44 | 6,12±3,44* |
| Insulin mIU/mL | 8±2,32 | 11±0,21 | 22±0,21* | 14±2,41 | 24±2,41* | 13±3,21 | 28±3,21* | 16±3,34 | 34±3,34* |
| Leptin, ng/mL | 65±11,2 | 74±6,12 | 86±6,12* | 77±5,1 | 82±9,1 | 74±6,2 | 83±10,4* | 76±7,2 | 88±13,2* |

Note. * – the significance compared to the control group, p<0,01.

Table 3: Vitamin D level in the serum of women with PCOS.

| Group | Deficiency % | | Insufficiency % | | Optimal level % | |
|---|---|---|---|---|---|---|
| Group 1 (women with PCOS) | 36,3 | | 48,4 | | 15,3 | |
| | Subgroup 1 (BMI 2529,9) | Subgroup 2 (BMI>30) | Subgroup 1 (BMI 2529,9) | Subgroup 2 (BMI>30) | Subgroup 1 (BMI 2529,9) | Subgroup 2 (BMI>30) |
| | 11,2 | 25,1 | 14,7 | 33,7 | 9,2 | 6,1 |
| Group 2 (healthy women) | 13,5 | | 31,9 | | 54,6 | |
| | Subgroup 1 (BMI 2529,9) | Subgroup 2 (BMI>30) | Subgroup 1 (BMI 2529,9) | Subgroup 2 (BMI>30) | Subgroup 1 (BMI 2529,9) | Subgroup 2 (BMI>30) |
| | 6,2 | 7,3 | 14,3 | 17,6 | 22,5 | 32,1 |

hyperleptinemia, compensatory HI and vitamin D hypovitaminosis in women with obesity in all clinical PCOS phenotypes, which is also similar to the results of other scientists [31,32,33,34].

In the correlation analysis of vitamin D content and hormonal indices in women with PCOS, we have established an inverse correlation between levels 25(OH) D and AMH, especially in patients with polycystic ovaries; found a positive correlation between FAI and 25(OH) D levels in the blood plasma, as well as a negative correlation between vitamin D levels and hirsutism score, especially in the subgroup of patients experiencing HA, which also coincides with the results of studies of other researchers (Table 4) [35,36].

*Table 2a and Table 3a: M - mean of index in the group; δ — mean squared deviation; r (X,Y) — correlation coefficient; p — the probability of a correlation coefficient error.*

Therefore, a decrease in vitamin D is associated with an increase in BMI, an increase in free testosterone level, luteal phase defect (a decrease in progesterone), ovulatory dysfunction and IR progression. Our study confirms the role of vitamin D in the pathogenesis of PCOS, according to which hypovitaminosis D can be considered as one of the factors causing impaired reproductive function in women, which has been proven by other authors [37,38].

The subtle pathogenetic mechanisms underlying the correlation between cholecalciferol deficiency and insulin resistance and HI are still not fully understood, in particular, it is unclear whether vitamin D

Table 4: Correlation of anthropometric and hormonal indices with vitamin D content in women with PCOS.

| Index | M | Δ | r (X,Y) | p |
|---|---|---|---|---|
| ng/mL | 110,4 | 34,3 | | |
| BMI, kg/m$^2$ | 33,11 | 5,16 | 0,751 | 0,001 |
| WC (Waist circumference), cm | 107,23 | 10,60 | 0,572 | 0,001 |
| DHEA-s, ng/L | 3,27 | 1,22 | 0,241 | 0,322 |
| Insulin, mcIU/mL | 29,41 | 10,24 | 0,762 | 0,001 |
| AMH, ng/mL | 6,64 | 2,5 | 0,116 | 0,124 |
| LH, mIU/mL | 13,12 | 4,11 | 0,212 | 0,220 |
| FSH, mIU/mL | 6,87 | 3,64 | –0,171 | 0,325 |
| Testosterone, total, ng/mL | 2,72 | 0,51 | 0,221 | 0,483 |
| Estradiol, pg/mL | 0,64 | 0,24 | 0,251 | 0,532 |
| Progesterone, ng/mL | 4,73 | 1,53 | 0,117 | 0,002 |
| SHBG, pg/mL | 76,91 | 46,16 | 0,074 | 0,630 |
| Androstendione, ng/mL | 12,68 | 6,23 | 0,010 | 0,953 |
| Testosterone, free, pg/ml | 7,41 | 1,52 | 0,078 | 0,037 |
| HS (hirsutism score) | 11,24 | 2,45 | 0,582 | 0,044 |

deficiency is a result of obesity or whether obesity is a consequence of vitamin D insufficiency. On the other hand, obesity can initiate a decrease in circulating 25(OH) D levels due to the absorption of cholecalciferol by adipose tissue. A decrease in vitamin D can be considered a trigger forming hormonal imbalances in women with hyperandrogenic status.

Table 5 presents the changes in the hormonal state of women with PCOS after treatment with vitamin D.

Table 5: Hormonal state of women with PCOS after treatment with vitamin D.

| Index | Control group (n=20) | Experimental group (PCOS) (n=80) | | | |
|---|---|---|---|---|---|
| | | Group 1 (n=20) | Group 2 (n=19) | Group 3 (n=23) | Group 4 (n=18) |
| LH, mIU/mL | 8,1±2,5 | 9,3±3,2* | 10,6±2,5* | 8,3±2,6 | 11,3±2,2* |
| FSH, mIU/L | 5,4±2,1 | 5,3±1,1 | 6,3±0,28 | 4,9±0,32 | 4,8±0,41 |
| Es, pmol/L | 173,0±12,8 | 165,1±10,3 | 117,1±11,2* | 98,1±8,2* | 97,4±10,3* |
| Ps, nmol/L | 1,53 ±1,22 | 1,32±0,13 | 1,28±0,13* | 0,99±0,12* | 1,12±0,11* |
| SHBG, nmol/L | 94,6±10,2 | 55,4±8,3* | 53,4±7,1* | 85,4±9,3 | 55,4±8,3* |
| TT, nmol/L | 1,6±0,1 | 2,6±0,4* | 4,2±0,2* | 1,7±0,4 | 3,6±0,4* |
| FAI, nmol/L | 58 ±18,1 | 33 ±12,1* | 22 ±6,7* | 42 ±10,1 | 10 ±1,8* |
| A, nmol/L | 3,8±0,22 | 15,6±1,14* | 17,8±1,22* | 4,6±0,33 | 16,8±1,44* |
| DHEA, mcg/mL | 176,4±11,7 | 484,6±26,3* | 574,6±28,2* | 184,6±14,3 | 684,6±28,1* |
| AMH, ng/mL | 3,8±0,3 | 4,1±1,2 | 6,1±0,3* | 10,1±1,1* | 11,1±0,8* |
| HS (hirsutism score) | 6±1,2 | 13±0,4* | 13±1,2* | 8±0,8 | 14±1,3* |

Note. * – the significance compared to the control group, p<0,01.


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Results of treatment with vitamin D demonstrated a decrease in the free testosterone index, a significant decrease in hirsutism score, an increase in blood progesterone concentration (in the luteal phase), and an increase in the number of ovulations in women with PCOS.

The findings of the study indicate a deficiency of vitamin D in patients with PCOS, correspond to global science data and show the need for more research to examine the role of cholecalciferol in ovarian dysfunction. Today, there is much evidence stating that a violation of the D-vitamin content in a woman's body leads to disruption of the ovarian menstrual cycle, takes part in the development of PCOS and premature ovarian depletion. This recommends defining the level of 25(OH) D in blood plasma for the timely detection and correction of hypovitaminosis in women with the specified pathology.

## Conclusions

Women with PCOS (regardless of specific phenotype) are diagnosed with a decrease in (25 (OH) D), insufficiency of which is exacerbated as obesity progresses. The study found out the correlation between vitamin D content in the blood and the degree of obesity, HI and IR in women with PCOS. Prescription of vitamin D in the complex treatment of women with PCOS leads to normalization of hormonal state, reduction of HA signs, normalization of the menstrual cycle, and restored ovulation.

## Conflict of Interest

The authors declare no conflict of interest.

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