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Role of vitamin D in polycystic ovary syndrome

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SUMMARY

Polycystic ovary syndrome (PCOS) is a disease with clinical manifestation of endocrine and metabolic disorders. In recent years, the interest in vitamin D has increased greatly, which is associated with its deficiency in many populations of the world, regardless of age. In addition, the coexistence of 25(OH)D_3 deficiency and many chronic diseases, including PCOS, has been noted. Based on many observations, vitamin D supplementation seems reasonable. The exact mechanism of action of this vitamin in PCOS has not been explained. The need of further research and observations is incontestable.

Key words: polycystic ovary syndrome; vitamin D; calcitriol; puberty

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder that affects 4–11% of women of child-bearing age, which makes it the most common cause of female infertility [1]. It is estimated that 16% of girls reporting to a gynecological clinic with menstruation disorders are ultimately diagnosed with PCOS [2]. The etiology of this syndrome is still unclear. It is known, however, that the genetic predisposition may have a particular influence on its development.

Vitamin D is a fat-soluble compound of a steroid structure. The biological activity of cholecalciferol and ergocalciferol is strictly associated with phosphate and calcium metabolism, which translates to their pleiotropic action and impact on the function of the body systems, such as: nervous and muscular, endocrine, reproductive and immune. Population-based studies have shown considerable vitamin D deficiency in the population. This problem concerns even 20–45% of adults [3–5]. A vitamin D level below the cut-off point believed to be the lower limit of normal is detected in 67–85% of women with PCOS [6]. This is undoubtedly associated with hormonal dysregulation and metabolic disorders [7].

Although the impact of vitamin D levels on hormonal and metabolic abnormalities in PCOS remains unclear, there are reports that interpret vitamin D deficiency as the missing link joining PCOS with insulin resistance, impaired glucose tolerance and type 2 diabetes mellitus, which coexist with this syndrome.

POLYCYSTIC OVARY SYNDROME

In order to diagnose PCOS in adults, the Rotterdam, AES (*Androgen Excess Society*) and NIH (*National Institutes*) criteria are applied. However, uniform criteria for PCOS diagnosis in adolescent girls have not been established. Adopting the criteria used in adults may cause

PCOS overdiagnosis [8]. Menstrual disorders can be considered as a criterion of PCOS only 2 years after the first menstruation because they may persist for some time after menarche and are not a sign of a disease. Currently, the Rotterdam criteria are used for establishing the diagnosis in girls with a reservation that all three of three criteria must be met, i.e.: menstrual disorders with disorders of ovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries on a US image [9].

Concomitant prediabetes (impaired fasting glycemia and impaired glucose tolerance), type 2 diabetes, hyperinsulinemia, insulin resistance and obesity are typical of PCOS. Observations have shown that vitamin D deficiency and secondary hyperparathyroidism are seen significantly more frequently in PCOS patients [10].

The therapeutic management in polycystic ovary syndrome in girls during puberty mainly targets anovulation, hyperandrogenism and insulin resistance. Maintaining proper body weight or its loss in cases of obesity are therapeutic priorities. Research shows that a loss of 10% of initial body weight contributes to a return of regular cycles, improvement in fertility and metabolic parameters as well as an increase in insulin sensitivity of tissues [11]. Early therapeutic intervention in high-risk adolescent girls with precocious puberty is significant. This can prevent metabolic and clinical consequences of PCOS [12].

Medical therapy of PCOS involves the usage of metformin, a biguanide derivative, which is an oral hypoglycemic agent. Its positive effects are associated with its action on hormonal and metabolic parameters as well as cardiovascular protection. The main aim of metformin usage in girls is to increase tissue response to insulin by lowering androgen concentration and improving cycle regularity [11]. The usage of anti-androgenic agents and oral contraceptive pills is popular management in PCOS. Anti-androgenic agents may positively affect ovulation and metabolism, particularly in girls with hirsutism, acne and positive history of precocious puberty [11]. A study of Chung et al., conducted in a group of 76 girls during puberty, demonstrates a marked positive influence of a combined anti-androgenic product (cyproterone and ethinylestradiol) on reducing acne, LH/FSH ratio and testosterone level compared with medroxyprogesterone acetate [13]. The only gestagen recommended in PCOS for cycle regulation is dydrogesterone. It promotes only the progesterone receptor and does not exacerbate metabolic disturbances, such as hyperinsulinemia, atherogenic lipid profile or increased levels of adipokines and proinflammatory factors.

VITAMIN D_3

Active vitamin D metabolite precursors can be found in both vegetable products (ergocalciferol – vitamin D_2) and animal products (cholecalciferol – vitamin D_3). Sun rays play a significant role in vitamin D synthesis, particularly those from the UV-B range. Photons cause 7-dehydrocholesterol isomerization in keratinocytes. This step is particularly important and is affected by the duration of sun exposure and latitude.

Other biochemical modifications are hydroxylations. The first binding of a hydroxyl group takes place in hepatocytes where 25(OH)D is formed in the presence of liver enzymes. Subsequently, it is metabolized to $1,25(OH)_2D$, mainly in the kidneys. Dihydrocalciferol, being a lipophilic substance, is capable of crossing cell membranes. Its activity is regulated by the nuclear receptor (VDR) which is responsible for expression of approximately 3% of the human genetic material. Vitamin D deficiency causes metabolic disturbances by influencing calcium metabolism, consequently affecting production and secretion of proinflammatory cytokines participating in the pathomechanism of various diseases, such as diabetes mellitus, hypertension or atherosclerosis [14–16]. Effects of vitamin D on certain organs are presented in Table 1.

A meta-analysis has provided evidence on positive effects of vitamin D supplementation. Commercially available preparations contain

Table 1. Effects of vitamin D_3 on certain organs

Atypical effects of vitamin D	
Endometrium	**Implantation**
Pancreas	Insulin secretion Insulin resistance
Ovary	Sex hormone steroidogenesis Folliculogenesis
Testicles	Spermatogenesis Androgenesis
Intestine	Ca^{2+} absorption Phosphate absorption Vitamin D binding protein expression
Kidneys	$25(OH)D_3$ hydroxylation Ca^{2+} and phosphate resorption
Bones	Bone turnover regulation (regulation between osteogenesis and osteolysis)

ergocalciferol and cholecalciferol as well as alfacalcidol (a precursor of active vitamin D_3 metabolite). Moreover, products containing calcifediol (vitamin D_3 metabolite), which is used in deficiencies that accompany long-term glucocorticoid and antiepileptic therapies in liver diseases, are also available. The first control of serum 25(OH)D_3 level is recommended after 3 months of supplementation. Moreover, it is advised to control concentrations of alkaline phosphatase, ionized and total calcium in the serum as well as calcium level in urine [17]. Contraindications to vitamin D supplementation must be underlined. They include: hyperparathyroidism, hypercalcemia, malabsorption syndrome and renal insufficiency. Adverse effects that can occur during supplementation include: headache and dizziness, nausea, vomiting, loss of appetite and dryness in the oral cavity [18].

ROLE OF VITAMIN D IN POLYCYSTIC OVARY SYNDROME

The study conducted in 35 women diagnosed with PCOS has shown that there is a relationship between VDR gene polymorphism and the risk of PCOS [19]. Molecular tests conducted in PCOS patients have revealed the presence of Apa-I and Fok-I vitamin D receptors [20]. It seems highly likely that these variants affect expression of luteinizing hormone, testosterone and sex hormone binding globulin (SHBG), which underlies the pathogenesis of PCOS [21–22]. Research proves that vitamin D activates aromatase in ovarian granulosa cells which is responsible for testosterone–estrogen conversion [23]. This is how the androgen–estrogen balance in patients with PCOS is maintained.

The meta-analysis shows that 67–85% of PCOS patients have vitamin D_3 deficiency, which is defined as serum concentration below 25–30 ng/mL [24]. Causes of low vitamin D levels in girls with PCOS have not been established thus far. Apparently, patients with more severe hirsutism, skin lesions and obesity avoid sun exposure due to their appearance. However, the situation seems to be much more complex [25]. Latitude plays an undoubted role in low vitamin D levels. In regions with less sunlight, Poland included, the average daily ultraviolet radiation exposure is too low and too short to initiate hydroxylation in the skin. It must be remembered that along vitamins A, E and K, vitamin D belongs to fat-soluble substances. In patients with excess fat tissue, vitamin D is stored in adipocytes and the active substance concentration is reduced.

Another hypothesis on vitamin D deficiency in PCOS patients is linked with abnormal function of fibroblast growth factor 23 [26]. Numerous diseases accompanied by serum calcium and vitamin D deficiency are also characterized by increased levels of FGF23. The cause for this might be impaired degradation of this factor or its overexpression. Research has shown that an increased FGF23 level inhibits renal CYP enzymes that participate in cholecalciferol hydroxylation [27,28].

Ghadimi et al. have found that all PCOS patients had lower serum levels of vitamin D, and its average value was significantly lower than in controls [29]. It has also been observed that 25-hydroxy calcitriol deficiency in adult women with polycystic ovaries, insulin resistance and obesity coexists with hyperparathyroidism [30].

Vitamin D deficiency is frequently accompanied by increased HOMA-IR index, dyslipidemia mixed with an HDL fraction decrease and elevated C-reactive protein [7]. It has been demonstrated that 25(OH)D_3 may affect hair follicle cycling by the presence of VDR in keratinocytes of the outer root sheath. An exact mechanism and potential use of vitamin D in the treatment of hirsutism have not been established [25].

The latest research suggests that a low level of vitamin D may be one of the primary factors that trigger PCOS and promote its development. That is why managing this deficiency might restore normal menstrual cycles in patients diagnosed with PCOS [31]. Vitamin D deficiency can therefore be considered as a modifiable risk factor of cardiovascular complications and features of metabolic syndrome [32]. Vitamin D_3 supplementation in adolescent girls with PCOS is significant not only with respect to the underlying disease, but also primary rickets prophylaxis.

CONCLUSION

Polycystic ovary syndrome is a heterogeneous disease and therefore uniform treatment schemes cannot be established. Each therapy should be adjusted to individual needs. The relationship between vitamin D deficiency and polycystic ovary syndrome in adolescent girls cannot be unequivocally established based on available research. There are too few data regarding this age group in the literature. Further, more de-

tailed investigations with age group division, including girls during puberty, are needed to define the role of vitamin D in PCOS with certainty. Nevertheless, serum vitamin D deficiency, both in girls with PCOS and in healthy ones, is a common phenomenon. That is why the latest guidelines recommend vitamin D supplementation [17].

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