



The Role of Diet and Microbiome in the Treatment of PCOS

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Abstract

Polycystic ovary syndrome (PCOS) is one of the most prevalent metabolic and endocrine disorders of pre-menopausal women. It occurs both in the organisms of girls who are entering puberty as well as in women past the age of 40. Different authors assume that PCOS affects from 4 to 12% of women and it is diagnosed in 3 to 6% of teenage girls. Etiology of this disease is heterogenic and not fully understood. It includes epigenetic, genetic and environmental factors, with the emphasis on lifestyle and diet. The diagnosis of PCOS is based on a combination of symptoms such as the excess of androgens, which manifests itself in hirsutism, male pattern baldness, acne, and ovary dysfunction which causes ovulation disorders and even infertility. Components of metabolic syndrome – insulin resistance, obesity, cardiovascular diseases, are often associated with this condition. It is not clear whether they should be considered as causes or consequences. Treatment of polycystic ovary syndrome is individual, long term and focused on mitigating symptoms of hyperandrogenism, abnormalities caused by ovary dysfunction as well as linked metabolic disorders. The aim of this article is to review current knowledge about the etiology, pathophysiology and treatment of PCOS, with a special focus on dietary aspect.

Key words: polycystic ovary syndrome, diet, microbiome.

Definition

Polycystic ovary syndrome was described for the first time by Stein and Levental in the 1930s. This endocrine-metabolic condition presents many difficulties in diagnosis, despite having many symptoms. PCOS manifests itself in hormonal disbalance, mainly in the abundant production of androgens by ovarian theca cells. Rising level of androgens stimulates excessive production of luteinizing hormone (LH), whereas it also lowers the level of follicle-stimulating hormone (FSH). This directly affects the development and maturation of ovarian follicles [1].

There are three main definitions of PCOS of which the primary one uses the Rotterdams Criteria, which were established in 2003 by the European Society of Human Reproduction and Embryology and the American Society of Reproductive Medicine. These criteria suggest that the main indicators of PCOS are:

1. clinical/biochemical hyperandrogenisation
2. ovulation disregulation
3. occurrence of cysts in the morphology of an ovary

It is assumed that the existence of at least two of the above conditions allows the diagnosis of polycystic ovary syndrome. In addition to the abovementioned characteristic determinants, specific disorders that give similar symptoms to PCOS should also be excluded. These include congenital adrenal hyperplasia, hyperprolactinemia, thyroid dysfunction, Cushing's syndrome, and the presence of androgen-secreting tumors [2].

PCOS is characterized not only by unclear pathophysiology, but also by the various severity of the progression. By definition, not all patients exhibit the same PCOS symptoms associated with heterogeneous background and individual exposure to risk factors. Each criterion also has different health consequences. Excess of androgens causes skin lesions such as hirsutism, acne and androgenetic alopecia. Anovulation and menstrual disorders (oligomenorrhoea) result in difficulties in getting pregnant and maintaining it. In addition, research indicates that hormonal imbalance and ovarian dysfunction can cause endometrial hyperplasia

or malignant neoplasms originating from the epithelial layer of the skin. Ovarian cysts correlate with the risk of ovarian hyperstimulation syndrome during induction of ovulation. Each case of PCOS is evaluated individually, there is also a simple dependence – the more criteria met, the more severe the course of the disease is [3].

Etiology and pathogenesis

The genesis of PCOS, despite numerous studies, is still not completely understood. It is suggested that the greatest role in the etiology of this disease is played by imbalance in the production of LH and FSH, aberrations of the androgen pool, as well as insulin resistance and obesity related to it [3].

Polycystic ovary syndrome is caused both by environmental factors, like broadly understood unhealthy lifestyle, which comprises of a diet rich in monosaccharides and highly saturated fats, sedentary lifestyle, infectious mediators, and hereditary genetic predisposition. These factors increase the risk of polycystic ovary syndrome. A number of cascade reactions are associated with this disease. Insulin is described as ovarian gonadotropin. Insulin resistance, and its increased concentration, interferes with the ovaries, which, in response, raise androgen level, leading to menstrual disorders – oligo- and anovulation. Another factors that cause PCOS are the aberrations in the amount of gonadotropins such as follicle stimulating hormone (FSH), luteinizing hormone (LH) and prolactin (PRL) [4].

In addition to the environmental components, a single gene polymorphism (SNP) is suspected to play a significant role in the etiopathology of PCOS. A change in a single nucleotide in the DNA sequence leads to defects in the transcriptional activity of the gene which leads to the production of a non-functional protein, which in turn leads to the development of PCOS. Recent research has proved existence of 241 variants of genes involved in the development of PCOS. These genes mainly encode receptors of androgens (StAR), luteinizing hormone (FTO), follicle stimulating

hormone (FSHR), leptin, insulin (IR/IRS) and vitamin D (VDR). Defects in the expression of genetic information of these genes disrupts biochemical pathways, which leads to abnormal ovarian function [5].

Progression and severity of PCOS increases with the level of insulin and androgens. Hyperinsulinemia affects theca cells of the follicle – one of their functions is androgens production. Thus, excess of insulin via positive feedback loop leads to an increase in androgens level. Higher than normal androgens concentration inhibits the pathways of hepatic biosynthesis of SHBG – sex hormone binding glycoprotein and IGFBP-1 – insulin-like growth factor binding protein. As a consequence, more free androgens and insulin are found in the circulation, which induce a number of subsequent reactions [6].

It has been observed that abundance of androgens stimulates visceral adipose tissue cells, which in response activate the process of lipolysis, generate free fatty acids, which contribute to insulin resistance. Free fatty acids, after reaching the liver, induce inflammation of the parenchyma, reduction of androgen clearance and inhibition of SHBG synthesis. The most important effect is the inhibition of insulin uptake, which, while remaining in the circulation, causes hyperinsulinemia. Free fatty acids also compete with glucose as energy substrates used by skeletal muscles. All these factors contribute to type 2 diabetes [7].

Hyperandrogenism is another characteristic of PCOS. One of its causes is the inhibition of transformation of steroid precursors into estrogens. This happens because of malfunctioning aromatase, an enzyme that converts these compounds. It occurs in the cell forming the granular layer of ovarian follicles. This enzyme is found to be often inactive in patients with PCOS, as a result of mutations at the nucleotide level or it is inhibited by high amounts of an enzyme involved in steroidogenesis – 5 α -reductase. This reductase produces 5 α -dihydrotestosterone, whose abnormal concentration inhibits aromatase activity, diminishing estrogen pool. This phenotypically manifests as excessive hair growth, male pattern baldness or acne [8].

Clinical picture

The symptoms associated with PCOS are often non-specific. The most common ones are:

1. Irregular and rare menstruation (less than 9 menstrual cycles per year, cycles lasting on average 36–40 days), including anovulation, which is a consequence of oligomenorrhea. Anovulation occurs in about 30% of cases [11]. Frequent diagnosis is made in the absence of menstruation during 3 months preceding the test [10].
2. Infertility in result of irregular menstruation and restricted ovulation. It is also noted that women with PCOS have problems with carrying the pregnancy to term [9].
3. Hyperandrogenism – the most characteristic symptom. This condition includes hirsutism, masculinization, androgenetic alopecia, and seborrheic acne. Analyzes of patients have shown in 60–80% cases ovarian as well as adrenal-based hyperandrogenism [4].
4. Numerous cysts that according to Rotterdam criteria are found in one or both ovaries. There should be at least 12 cysts, 2-mm in diameter. Transvaginal tests should be conducted for correct diagnosis. Peripheral distribution of follicles and hypertrophy of ovarian matrix may also be present, although it is not critical for diagnosis [12].
5. Excessive weight, which results in an increase in the number of PCOS symptoms due to the release of large amounts of free fatty acids and LDL fraction of cholesterol. These factors contribute to insulin resistance and enhance effects of androgens and also allows the creation of secondary metabolic processes [13].
6. Cardiovascular diseases – patients with PCOS have significantly higher levels of biomarkers that are used to assess cardiovascular diseases, including C-reactive protein [14] and lipoprotein A [15]. They also manifest features characteristic for atherosclerosis such as endothelial dysfunction or coronary artery calcification [14].

Women affected by PCOS often show symptoms of anxiety disorders and depression, and they can suffer from insomnia [16].

In order to identify the nature of the illness, secondary origins of the symptoms that are characteristic not only of PCOS should be excluded. It is crucial to reject other diseases that manifest similar symptoms. These include rare, but life-threatening, brain tumors, pituitary glands, as well as adrenal and ovarian tumors, Cushing's disease and congenital adrenal hyperplasia. The diagnosis of PCOS can be established when the symptoms of androgen excess begin to appear in any other period preceding or following puberty. Rapid virilization/defeminization is also one of the determinants [17].

Microbiome

Recent studies have also shown that the composition of the microbiota in patients with PCOS is changed in comparison to healthy women. It indicates that certain gut bacteria may serve as pathogens and trigger PCOS. The composition and diversity of the intestinal flora has been proven to be affected by diet, insulin resistance, imbalance of sex hormones and obesity [18].

One of the most beneficial symbionts of our digestive system are found in the genus *Bifidobacterium* and *Faecalibacterium prausnitzii*. They play an important role in protecting the organism against pathogens, stimulating immune responses and producing Short Chain Fatty Acids (SCFA), which also have pre-inflammatory properties. Decreasing number of these advantageous bacteria in patients suffering from PCOS results in lower level of SCFAs, which affects the host's metabolism, intestinal barrier integrity and immunity [19].

Insenser hypothesized that the microbiota also plays a role in the level of sex hormones and on the contrary – sex hormones can modify the gut flora. His research has shown evidence that patients with hyperandrogenization have higher amounts of *Catenibacterium* and *Kandleria* in comparison to healthy women. His previous experiments demonstrated

that increased quantity of *Catenibacterium* is one of the markers of autoimmune diseases and infections [20]. In addition, the number of bacteria from this genus rises with higher consumption of 'Western diet', which is rich in simple carbohydrates [18].

Treatment

Polycystic ovary syndrome does not have a singular cause, and for this reason there is no universal method of treatment. Both symptoms, severity and progression of the disease can be reduced to some extent, but are not fully curable and can be treated temporarily by mitigating the symptoms [9].

The most important factor in the treatment of PCOS is a healthy lifestyle, which includes a balanced, low-fat and low-sugar diet that is also high in fiber, with a combination of moderate physical activity. Studies have shown that the vast majority of patients suffering from PCOS is also obese/overweight and reducing weight by 5–10% allows better management of symptoms associated with this disease [21].

Oral Contraceptive Pills (OCP) are used to regulate the menstrual cycle and hyperandrogenism in combination with meds such as metformin, which increases tissue sensitivity to insulin. OCP inhibit the hypothalamus-pituitary-ovaries axis, leading to a decrease in LH secretion and an increase in the secretion of sex hormone binding globulins, which translates into a decrease in free testosterone [22]. Metformin, on the other hand, reduces hepatic gluconeogenesis, increases the usage of glucose as energy source in muscles, and on top of this reduces the concentration of free fatty acids (FFA), C-reactive protein and fasting insulin concentration, while lowering blood pressure and thereby improving vascular blood flow [23].

The procedure of *in vitro* fertilization (IVF) is being broadly used to treat infertility. It is often accompanied by the intake of gonadotropins [9].

The effects of hyperandrogenism – acne and hirsutism are treated with cosmetic procedures, especially lasers (3).

Diet, probiotics and prebiotics

The basic advice in order to alleviate the symptoms or prevent from polycystic ovary syndrome is a change in lifestyle. Patients suffering from obesity are suggested to reduce their weight by changing their eating habits in combination with a physical activity. The beneficial effect of reduction of visceral fat is especially pointed out. Recommended weekly amount of physical activity is estimated around 3 hours of exercise or 20–25 minutes of moderate exercise per day [24].

Current dietary recommendations emphasize the significant, positive role of mono unsaturated fats (MUFA). It is also recommended to switch to low-carbohydrate meals. The harmful effects of a carbohydrate-rich diet has been also noticed. Products with a high glycemic index cause a rapid increase of sugar in the blood stream and associated it with rapid increase of insulin, which contributes to type 2 insulin resistance. Studies carried out by Douglas showed improved results of patients with polycystic ovary disease after just two weeks of following a diet rich in protein and with a restriction of monosaccharides. The research has shown a decrease in the level of insulin, high-saturated cholesterol lipoprotein fractions and plasma glucose. The eucaloric diet used in the study consisted of 43% carbohydrates, 45% fats, of which less than 8% were the detrimental saturated fatty acids, while protein accounted for 12% of daily consumption. In addition, abundance of fiber, whole grains, fruits and vegetables has been proven to be beneficial [25].

Very recent randomized, double-blind, placebo-controlled studies indicate that supplementation with probiotics (*Lactobacillus (L) acidophilus*, *L casei* and *Bifidobacterium bifidum*) has a positive effect on the metabolic profile of women with PCOS by reducing fasting plasma glucose and serum insulin. Furthermore, it leads to a decrease in the level of triglycerides and VLDL cholesterol fraction. It has been suggested that the consumption of *Bifidobacterium lactis* promotes the production of SCFAs which are made by microorganisms, i.e. *Akkermansia*, *Butyricimonas* and *Faecalibacterium prausnitzii*. These fatty acids affect the secretion

of mediators of gut-brain axis, i.e. ghrelin and YY peptide (PYY). Fluctuations in their level affect the hypothalamus and pituitary gland, which, in turn, secrete amounts of sex hormones adequate to the signal [26].

Prebiotics, which can be found in products such as leeks, asparagus, garlic, onions, bananas and oats, also have been proven to have a positive effect on the level of metabolic markers that are associated with promoting development of the 'good' gut flora. The use of prebiotics supports growth of bacteria such as *Bifidobacterium* and *Lactobacillus*, which in the reaction of fermentation, convert substrates (probiotics) to SCFAs, such as acetates, propionates and butyrates. The positive effect of prebiotics has been confirmed to be linked with managing healthy lipid profile and blood glucose [27,18].

Summary

Polycystic ovary syndrome, despite the fact of being known for centuries, is not fully understood yet and requires further research, both in the fields of etiology and treatment. Holistic way of looking into this disease is very crucial. Noticing the dietary aspect associated with a proper diet, in particular with the limitation of simple sugars and saturated fats. New solutions such as probiotic and prebiotic supplements are also being used in the therapy.

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