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Review Article

Disorders of Glucose Homeostasis in Women with Polycystic Ovary Syndrome (PCOS)

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Abstract

Polycystic ovary syndrome (PCOS), usually arises during puberty and is marked by hyperinsulinemia and hyperandrogenism. The principle is that the diagnosis of PCOS must be based on the presence of at least two of the following three criteria: chronic anovulation, hyperandrogenism (clinical or biological), and polycystic ovaries.

A considerable role in the development of PCOS is played by genetically conditioned ovary dysfunction, resulting in the overproduction of androgens, which overlaps with the effect of environmental conditions. Insulin sensitivity disorders lead to numerous metabolic irregularities, including the development of carbohydrate metabolism disorders.

Women with PCOS are at high risk of developing type 2 diabetes and gestational diabetes mellitus. Today it is known that PCOS occurs in women with diabetes mellitus type 1.

Since glucose metabolism disorders result from insulin resistance, besides appropriately selected hormonal treatment the therapy must include medications reducing insulin resistance.

Keywords: *Hyperandrogenism; Polycystic Ovary Syndrome; Insulin Resistance; Diabetes*

Introduction

Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder in women which typically presents itself during adolescence. An important characteristic feature of PCOS is excessive secretion of ovarian androgens leading to distressing cutaneous symptoms.

PCOS is not just a disorder that affects ovarian function, it also has its consequences in the form of an increased risk of disorders of glucose metabolism and increased markers of cardiovascular morbidity [1].

Insulin resistance is one of essential factors leading to the development of polycystic ovary syndrome (PCOS).

The development of PCOS is connected with the onset of puberty as this is the period when physiological insulin resistance manifests itself. Increased insulin secretion may stimulate steroidogenesis [2-4].

A considerable role in the development of PCOS is played by the dysfunction of ovaries resulting in the overproduction of androgens, which is overlapped by the effect of environmental conditions.

Metabolic changes are connected with the increased activity of the somatotropic axis (with an increase of concentration of the growth hormone and a decrease of the glucose oxidation process at the expense of an increase of oxidation of free fatty acids.

Hyperinsulinemia also causes a reduction of the liver production of the sex hormone binding globulin (SHBG), which leads to an increase in concentration of biologically active androgen in blood serum.

Disorders in terms of sensitivity to the effect of insulin lead to numerous metabolic disorders, including the development of carbohydrate metabolism disorders. The first reports on the co-occurrence of carbohydrate metabolism disorders and hyperandrogenism date back to the beginning of the 20th century [5].

The occurrence of insulin resistance (IR) used to be associated with obesity. Today it is known that insulin resistance presents itself in lean patients, as well.

Etiopathogenesis of PCOS

Genetic and endocrine factors together with environmental influences play their role in the pathogenesis of PCOS [6]. The model of inheritance of PCOS has not been defined yet. Most authors define PCOS as a polygenic pathology. The main candidate genes are those encoding the regulation and effects of androgens. Other candidate genes are those encoding factors involved in insulin metabolism.

Research on the determination of genetic conditions of the development of PCOS is in progress [7,8].

Recently presented studies have shown that increased serum chemerin in PCOS women with or without obesity suggest that chemerin may be involved in the development of the pathogenesis of PCOS [9]. Chemerin is a newly discovered adipokine involved in inflammation, adipogenesis, angiogenesis and energy metabolism. In humans, local and circulating levels of chemerin are positively correlated with BMI and obesity-related biomarkers [28].

Abnormal glucose metabolism in PCOS

PCOS is mainly an androgen excess disorder, insulin resistance, and compensatory endogenous hyperinsulinemia. Women with PCOS are at high risk of the development of type 2 diabetes and gestational diabetes mellitus [10,11]. As follows from the observation of women with PCOS, they also develop abnormal glucose metabolism at a younger age and may demonstrate a more rapid conversion from impaired glucose tolerance (IGT) to type 2 diabetes. Studies have shown that both obese and lean women with PCOS have some degree of insulin resistance. Insulin resistance is implicated in the ovulatory dysfunction of PCOS by disrupting the hypothalamic-pituitary-ovarian axis. Given the association with insulin resistance, all women with PCOS require evaluation in terms of the risk of metabolic syndrome (MetS) and its components, including type 2 diabetes, hypertension, hyperlipidemia. It is believed that obese women with PCOS have an increased risk of MetS [12].

Insulin resistance is compensated by an increase in insulin secretion by pancreatic β cells When the response of pancreatic cells decreases, the patient develops glucose intolerance or diabetes. Some studies have suggested that PCOS *per se* increases the risk of prediabetes and type 2 diabetes independent of BMI [13]. Other authors also confirm that women with PCOS are at higher risk of impaired glucose tolerance and undiagnosed diabetes [14].

Diagnosis of glucose metabolism disorders in PCOS

Data suggest that in patients with the family history of type 2 diabetes and a higher body mass index (BMI) the need for the baseline oral glucose tolerance test (OGTT) occurs every 1 to 2 years. In women with impaired glucose tolerance (IGT) tests should be carried out yearly [15]. Recently, Korean authors have presented an increase in insulin resistance (IR) in lean women with PCOS showing normal glucose tolerance levels [16]. The authors concluded that IR should be evaluated in all women with PCOS. Other authors are of a similar opinion - they believe that IR should be assessed in all PCOS women, both lean and overweight/obese (ov-ob) subjects [17,18]. Similar observations regarding girls were presented by American authors [19]. The authors stated that despite a normal BMI, multiple aspects of metabolism appear altered in normal-weight girls with PCOS.

Currently, PCOS is known to occur also in women with diabetes mellitus type 1 [20,21].

The link between PCOS and Type 1 diabetes mellitus is believed to implicate supraphysiological concentrations of insulin within circulation. Exogenous hyperinsulinism could then contribute to the androgen excess in predisposed women. Therefore, screening tests for PCOS and for the androgen excess should be included in the current guidelines for the management of type 1 diabetes in women.

Therapeutic management

Since one of the basic disorders in PCOS is insulin resistance and the co-existing hyperinsulinaemia, combating this phenomenon constitutes one of the fundamental goals in the treatment of polycystic ovary syndrome.

Improvement of the insulin sensitivity may produce several benefits in the treatment of PCOS. This leads to a decrease in the insulin and androgen levels and an improvement of co-existing metabolic disorders [22].

In treatment it is important to elicit lifestyle changes, such as dietary modification and exercise [23].

So as to reduce insulin resistance, pharmacotherapy is made use of, too. The drug of choice is metformin, but in obese patients orlistat, GLP1 agonists are used, as well [24].

A report has been issued recently on the beneficial effects of saxagliptin (dipeptidyl peptidase-4 inhibitor) and metformin on the glycemic control and the β-cell function in the new onset type 2 diabetes patients with PCOS [25].

An interesting report about the application of adjunctive therapies to the insulin treatment for the management of type 1 diabetes in pediatric patients has been communicated by Naciu and Pozzilli [26].

It seems that this solution may be considered for application in adolescent patients with type 1 diabetes, insulin resistance, and PCOS.

Wu., *et al.* suggested that the metformin and pioglitazone combination therapy demonstrated great efficacy in ameliorating PCOS through regulating the AMPK/PI3K/JNK (5'adenosine monophosphate-activated protein kinase/phosphoinositide-3 kinase/c-Jun N-terminal kinase) pathway [27].

Conclusions

Although the aetiology of the syndrome is not completely understood yet, PCOS is considered a multifactorial disorder with various genetic, endocrine, and environmental abnormalities. Moreover, PCOS patients have a higher risk of metabolic and cardiovascular diseases and their related morbidity, if compared to the general population.

The choice of hormonal drugs depends on multiple factors and must be individually determined for each patient.

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