PATHOPHYSIOLOGICAL SIGNIFICANCE OF INSULIN RESISTANCE IN PCOS AND PREVENTIVE APPROACHES TO MANAGEMENT

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Abstract: Polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic disorder that is widely prevalent among women of reproductive age. This article analyzes the mechanisms underlying the development of the syndrome, with particular emphasis on the role of insulin resistance, as well as its clinical manifestations, diagnostic methods, and approaches to prevention and treatment.Evidence suggests that insulin resistance is one of the key factors in the pathogenesis of PCOS. Through hyperinsulinemia, it enhances androgen synthesis in the ovaries, which leads to disruption of ovulation, infertility, and the development of various metabolic complications. A comprehensive approach, including the adoption of a healthy lifestyle, rational use of pharmacological agents, and early diagnosis, plays a crucial role in reducing PCOS-related disorders.Furthermore, individualized strategies aimed at controlling insulin resistance are effective in improving both reproductive and overall health outcomes.

Keywords Polycystic ovary syndrome, insulin resistance, hyperinsulinemia, ovulatory dysfunction, anovulation, hyperandrogenism, metabolic syndrome, dyslipidemia, obesity, type 2 diabetes mellitus, cardiovascular diseases, prevention, lifestyle, pharmacotherapy

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine and metabolic disorders affecting women of reproductive age and remains a significant challenge in modern medicine. According to recent epidemiological studies, the prevalence of this syndrome ranges from 6% to 20–21%, depending on the diagnostic criteria used (such as the National Institutes of Health criteria and the Rotterdam criteria). This highlights that PCOS is not only an individual health issue but also a matter of global public health importance.The etiology of PCOS is complex and multifactorial, involving genetic predisposition, hormonal imbalances, environmental influences, and lifestyle-related factors. In recent years, scientific research has increasingly emphasized the central role of insulin resistance in the pathogenesis of this syndrome.Insulin resistance is characterized by decreased sensitivity of peripheral tissues to insulin, leading to compensatory hyperinsulinemia. This condition stimulates ovarian androgen production, reduces hepatic synthesis of sex hormone-binding globulin (SHBG), and disrupts the normal functioning of the hypothalamic–pituitary–ovarian axis.According to available data, approximately 50–70% of women with PCOS exhibit insulin resistance. This prevalence is even higher in individuals with obesity. However, insulin resistance can also be present in women with normal body weight, confirming its independent role in the development of the syndrome.

The clinical significance of PCOS extends beyond reproductive dysfunction. Women with this condition have a significantly increased risk of developing metabolic syndrome, type 2 diabetes mellitus, dyslipidemia, and cardiovascular diseases. Research findings indicate that the risk of developing type 2 diabetes mellitus in women with PCOS is several times higher compared to healthy individuals.Moreover, long-term insulin resistance contributes to chronic inflammation, oxidative stress, and endothelial dysfunction, further increasing cardiovascular risk.

Therefore, early detection of insulin resistance and the implementation of preventive strategies aimed at its reduction are essential for effective management of PCOS. Insulin sensitivity can be improved through balanced nutrition, regular physical activity, maintenance of a healthy body weight, and, when necessary, appropriate pharmacological interventions. These measures help alleviate clinical symptoms and reduce the risk of long-term complications.

Objective

The aim of this article is to analyze the pathogenetic and clinical significance of insulin resistance in polycystic ovary syndrome based on scientific literature. Additionally, it seeks to identify and summarize effective preventive strategies aimed at reducing insulin resistance.

MAIN BODY

1. The Role of Insulin Resistance in the Pathogenesis of PCOS

Insulin resistance plays a central role in the pathogenesis of polycystic ovary syndrome (PCOS) and represents a key mechanism linking endocrine and metabolic disturbances associated with the disorder. In this condition, the sensitivity of muscle, liver, and adipose tissues to insulin is reduced, resulting in impaired glucose uptake and the development of compensatory hyperinsulinemia.Hyperinsulinemia directly affects the ovaries by enhancing androgen production in theca cells in synergy with luteinizing hormone (LH). In particular, insulin increases the activity of the enzyme CYP17A1, thereby promoting the synthesis of androgens such as androstenedione and testosterone. At the same time, insulin suppresses hepatic production of sex hormone-binding globulin (SHBG), leading to elevated levels of biologically active free testosterone in circulation. This mechanism contributes significantly to hyperandrogenism, which is a hallmark clinical feature of PCOS.Hyperandrogenism disrupts normal follicular development within the ovaries. As a result, dominant follicle formation is impaired, ovulation does not occur, and anovulatory cycles develop. This process underlies infertility and menstrual irregularities commonly observed in women with PCOS.Insulin resistance also affects central endocrine regulation. At the level of the hypothalamic–pituitary–ovarian (HPO) axis, there is a relative increase in luteinizing hormone secretion and a decrease in follicle-stimulating hormone (FSH). The altered LH/FSH ratio further enhances androgen production and disrupts folliculogenesis.Recent studies highlight the close relationship between insulin resistance and adipose tissue function. Adipose tissue acts as an endocrine organ, producing adipokines such as leptin, adiponectin, and resistin. Dysregulation of these adipokines impairs insulin signaling pathways and increases the production of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). This creates a vicious cycle of chronic low-grade inflammation that further exacerbates insulin resistance.In addition, insulin resistance contributes to increased oxidative stress and endothelial dysfunction. These changes support the concept that PCOS is not merely a

reproductive disorder but a systemic metabolic condition associated with elevated cardiovascular risk.

Overall, insulin resistance serves as a central link integrating hormonal, metabolic, and inflammatory mechanisms in PCOS, thereby determining both the development and severity of the disease.

2. Clinical Implications and Complications of Insulin Resistance in PCOS

Insulin resistance is one of the major determinants of the clinical manifestations of PCOS, exerting complex effects on reproductive, metabolic, and endocrine systems. Its clinical significance is primarily associated with hyperandrogenism and ovulatory dysfunction.Under normal physiological conditions, insulin exerts its effects by binding to insulin receptors with intrinsic tyrosine kinase activity located on the cell membrane. This triggers receptor autophosphorylation and intracellular signaling through insulin receptor substrates (IRS). However, in insulin resistance, these processes are impaired due to receptor downregulation, decreased tyrosine kinase activity, or increased serine/threonine phosphorylation. As a result, intracellular signaling is disrupted, leading to metabolic dysfunction.One of the most prominent clinical manifestations is menstrual irregularity, typically presenting as oligomenorrhea or amenorrhea. These disturbances are directly related to anovulation and often result in infertility. Chronic anovulation remains the primary cause of infertility in women with PCOS.Hyperandrogenism manifests clinically as hirsutism, acne, and androgenic alopecia. These symptoms not only affect reproductive health but also have a significant psychological impact, contributing to decreased self-esteem, anxiety, and depression.One of the most serious consequences of insulin resistance is the development of metabolic syndrome. Women with PCOS frequently exhibit abdominal obesity, hypertension, dyslipidemia, and impaired glucose tolerance. Together, these factors markedly increase the risk of cardiovascular disease.Disturbances in lipid metabolism, particularly elevated levels of free fatty acids, also play a crucial role in the progression of insulin resistance. In conditions of obesity and visceral fat accumulation, increased free fatty acids accumulate in muscle and liver tissues, causing lipotoxicity. This process enhances serine phosphorylation of IRS-1, disrupts mitochondrial function, and further impairs insulin signaling.Mitochondrial dysfunction leads to reduced energy production and impaired fatty acid oxidation, thereby exacerbating insulin resistance. Studies indicate that women with PCOS have a significantly higher risk of developing type 2 diabetes mellitus compared to healthy individuals, reflecting the long-term metabolic consequences of insulin resistance. Additionally, impaired glucose tolerance and prediabetic states are more prevalent in this population.Insulin resistance and hyperinsulinemia also negatively affect the cardiovascular system. A state of chronic low-grade inflammation develops, mediated by cytokines such as TNF-α and interleukin-6, which inhibit insulin signaling pathways and further reduce insulin sensitivity. This establishes a self-perpetuating pathological cycle in which insulin resistance and inflammation reinforce each other.Endothelial dysfunction, oxidative stress, and inflammation contribute to the development of atherosclerosis. Therefore, PCOS should be considered not only a gynecological condition but also a systemic metabolic disorder with significant cardiovascular risk.Psychological disturbances, including anxiety and depression, are also more common among women with PCOS. These are associated with hormonal imbalances, body image concerns, and the chronic nature of the disease.At the hepatic level, insulin resistance impairs

the ability of insulin to suppress gluconeogenesis, resulting in continued glucose production and elevated fasting blood glucose levels. This contributes to hyperglycemia and further hyperinsulinemia. Chronic hyperinsulinemia, in turn, reduces receptor sensitivity in peripheral tissues and exacerbates hormonal imbalances in both the ovaries and the liver.

In summary, insulin resistance broadens the clinical spectrum of PCOS, transforming it from a purely reproductive disorder into a complex multisystem disease.

3. Prevention and Clinical Management of Insulin Resistance in PCOS

In polycystic ovary syndrome (PCOS), insulin resistance represents a key pathogenetic mechanism, and preventive strategies aimed at its reduction have a direct impact on clinical outcomes. Clinical studies demonstrate that even a modest reduction in body weight (5–10%) significantly improves insulin sensitivity, increases the likelihood of ovulation, and reduces androgen levels.Physical activity is one of the most effective interventions for reducing insulin resistance. Aerobic exercise performed for 150–300 minutes per week enhances glucose utilization in muscle tissue and activates insulin signaling pathways, leading to an improvement in insulin sensitivity by approximately 20–40%.Dietary management also plays a crucial role in PCOS treatment. A low glycemic index diet helps prevent rapid increases in blood glucose and insulin levels. This dietary approach reduces androgen synthesis and improves ovulatory function. Additionally, a fiber-rich diet combined with restriction of simple carbohydrates contributes to the stabilization of insulin response.A significant proportion of women with PCOS exhibit visceral obesity, which is closely associated with increased production of adipokines and pro-inflammatory mediators that exacerbate insulin resistance. Therefore, weight reduction is of fundamental pathogenetic importance. Evidence suggests that a 5–10% reduction in body weight not only improves insulin sensitivity but also normalizes menstrual cycles and restores ovulation.Metformin is one of the most commonly used insulin-sensitizing agents in PCOS management. It reduces hepatic gluconeogenesis and improves glucose utilization through activation of the AMP-activated protein kinase (AMPK) pathway. Clinical studies have shown that metformin therapy results in:

- a 20–40% reduction in insulin resistance,
- increased ovulation frequency,
- decreased androgen levels.

In some cases, myo-inositol and D-chiro-inositol are also used to improve insulin signaling and restore reproductive function. Furthermore, GLP-1 receptor agonists are increasingly applied, particularly in obese patients with PCOS, to improve metabolic parameters.Given the high risk of metabolic disturbances in PCOS patients, regular laboratory monitoring is essential. Measurements of fasting glucose, insulin levels, the HOMA-IR index, and oral glucose tolerance tests enable early detection of metabolic abnormalities. Statistical data indicate that 30–40% of PCOS patients exhibit impaired glucose tolerance, while 10–15% may develop type 2 diabetes mellitus.

Early correction of insulin resistance significantly reduces long-term complications. In particular, the risk of developing type 2 diabetes mellitus can be reduced by 40–60%, while cardiovascular risk is also markedly decreased. Therefore, PCOS should be considered not merely a reproductive disorder but a complex metabolic syndrome requiring a comprehensive and systematic approach.

4. Integrative Role of Insulin Resistance in PCOS Pathophysiology

The pathogenesis of PCOS is multifactorial, involving complex interactions between hormonal, metabolic, and genetic mechanisms. Within this framework, insulin resistance acts as a central integrative factor, expanding both the endocrine and clinical spectrum of the disorder.Research indicates that insulin resistance is present not only in obese individuals with PCOS but also in patients with normal body weight. This finding supports the concept that insulin resistance is not merely a secondary phenomenon but an independent component of PCOS pathogenesis.

Moreover, hyperandrogenism and insulin resistance in PCOS operate through a mutually reinforcing mechanism. Hyperinsulinemia enhances androgen production, while elevated androgen levels promote visceral fat accumulation and further decrease insulin sensitivity. This results in the formation of a pathological "vicious cycle," contributing to the chronic progression of the disease.Literature data suggest that components of metabolic syndrome are 2–3 times more prevalent in women with PCOS compared to the healthy population. In particular, the risk of impaired glucose tolerance and type 2 diabetes mellitus is significantly increased, further emphasizing the clinical importance of insulin resistance.Recent studies also highlight the need to redefine PCOS as a "reproductive–endocrine–metabolic syndrome," as it involves not only ovarian dysfunction but also systemic disturbances in metabolic homeostasis.The effectiveness of preventive strategies can also be explained by this integrative mechanism. Combined approaches, including lifestyle modification and pharmacological therapy, reduce insulin resistance, restore reproductive function, and significantly decrease the risk of long-term metabolic complications.

Therefore, the management of PCOS requires a comprehensive, multidisciplinary approach involving gynecological, endocrinological, and metabolic monitoring.

CONCLUSION

Polycystic ovary syndrome (PCOS) is a common endocrine–metabolic disorder among women of reproductive age, characterized by a complex and multifactorial pathogenesis. The findings presented in this article demonstrate that insulin resistance is one of the key pathogenetic mechanisms underlying the development of PCOS. It plays a crucial role in the formation of hormonal imbalances, particularly hyperandrogenism and ovulatory dysfunction.Hyperinsulinemia stimulates theca cells in the ovaries, enhancing androgen production, which in turn disrupts follicular maturation, leading to anovulation and infertility. In addition to its effects on the reproductive system, insulin resistance exerts significant adverse effects on overall metabolism. It increases the risk of dyslipidemia, obesity, impaired glucose tolerance, and type 2 diabetes mellitus, as well as cardiovascular diseases.Therefore, PCOS should be regarded not only as a gynecological condition but also as a systemic metabolic syndrome. Control of insulin resistance is a cornerstone of effective PCOS management. Improving insulin sensitivity helps restore hormonal balance, normalize ovulation, and enhance reproductive outcomes. Moreover, it significantly reduces the risk of long-term complications such as diabetes and cardiovascular disease.Preventive strategies—including the adoption of a healthy lifestyle, balanced nutrition, regular physical activity, and weight management—remain the most effective and safest approaches to reducing insulin resistance. Early diagnosis and regular screening in high-risk individuals are essential for timely intervention and prevention of severe complications.In conclusion, effective management of PCOS requires a comprehensive and individualized approach. Integration of preventive

strategies, early diagnosis, and modern therapeutic interventions aimed at reducing insulin resistance can significantly improve reproductive health, overall well-being, and quality of life in affected individuals.

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