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Review Article

Metabolic Dysfunctions in Polycystic Ovary Syndrome

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Abstract:

Polycystic Ovary Syndrome (PCOS) is a condition that involves various metabolic dysfunctions such as insulin resistance (IR), hyperandrogenemia, obesity, dyslipidemia, and steroid hormone irregularities. Although the exact cause of PCOS is still unknown, it is known to cause several hormonal disturbances, including hyperandrogenemia, IR, and hyperinsulinemia. Insulin appears to disrupt all components of the hypothalamic-pituitary-ovarian (HPO) axis, and ovarian tissue insulin resistance results in impaired metabolic signaling. This causes hyperandrogenemia, which is one of the primary causes of the symptoms of PCOS. Androgens may also lead to IR by modifying muscle tissue composition and functionality and increasing levels of free fatty acids, perpetuating the IR-hyperinsulinemia-hyperandrogenemia cycle. Obesity exacerbates hormonal imbalances, and in combination with dyslipidemia, amplifies cardiovascular and cerebrovascular risks. This review discusses the complex risk factors of PCOS, including genetic, epigenetic, and environmental factors. It also discusses the interconnected etiologies of metabolic dysfunctions of PCOS, its effective management, and metabolic consequences such as cardiovascular and cerebrovascular diseases.

Keywords: *Polycystic ovary syndrome; insulin resistance; hyperinsulinemia; hyperandrogenemia; obesity; dyslipidemia.*

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Introduction

Polycystic ovary syndrome (PCOS) is the most common complex and heterogeneous endocrinopathy that affects around 10% of women of reproductive age[1]. It is characterized by a constellation of symptoms and clinical features, which include hyperandrogenism, ovarian dysfunction such as menstrual irregularities, and polycystic ovarian morphology[2]. Different diagnostic criteria for PCOS use various combinations of these clinical traits. The Rotterdam criteria is the most widely used for clinical diagnosis of PCOS, requiring at least two of the three clinical features mentioned above[2]. PCOS is the leading cause of anovulatory infertility, which is why it is often associated with subfertility or infertility[3].

PCOS, although most commonly experienced by women of reproductive age, can also affect prepubescent girls and women in their postmenopausal phase[2]. Symptoms may include premature pubarche in children, early signs of androgenization (such as acne and hirsutism), and menstrual irregularity in adolescents. While hyperandrogenic symptoms may improve during menopause, women with PCOS still face an increased risk for metabolic and cardiovascular comorbidities[2]. It also increases the risk for type 2 diabetes mellitus, gestational diabetes, obstetrical complications, venous thromboembolism, cerebrovascular events, and endometrial cancer[2]. In this review, we discuss the pathogenesis, various risk factors of PCOS, and metabolic dysfunctions and their consequences. We also highlighted the recent treatment briefly.

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Pathogenesis

The pathophysiology and intrinsic mechanisms underlying PCOS are complex. Due to its heterogeneous clinical presentation, several mechanisms are involved in its development and metabolic complications. The interplay between these mechanisms results in and perpetuates the clinical features of PCOS. These are depicted in Figure 1.

Risk Factors

1 *Environmental Factors:* Various environmental elements contribute to PCOS during childhood, including lifestyle choices, unhealthy eating habits, and exposure to environmental chemicals. Physical inactivity and an increased body mass index (BMI), leading to obesity, are crucial factors in the development of PCOS. Additionally, environmental chemicals have the potential to induce epigenetic changes associated with PCOS. The consumption of adulterated, high-sugar foods, particularly those rich in advanced glycation end products (AGEs), significantly contributes to IR and the manifestation of the PCOS phenotype[4].

2 *Genetic Factors:* PCOS has a strong genetic basis, as evidenced by familial clustering and twin studies. Individuals with a family history of PCOS, such as having a mother or sister with the condition, face a 30–50% increased risk of developing PCOS[5-7]. The correlation for PCOS is notably higher between monozygotic twin sisters compared to dizygotic twins, with genetic factors accounting for approximately 66% of the variance, according to the univariate genetic model[8].

3 *Epigenetic Factors:* Epigenetic factors occurring during fetal development, particularly intrauterine exposure to maternal excess androgen environments, can lead to stable heritable phenotypic changes without alterations in the DNA sequence. These changes are initiated by environmental interactions during fetal and childhood development, potentially contributing to the development of PCOS[9].

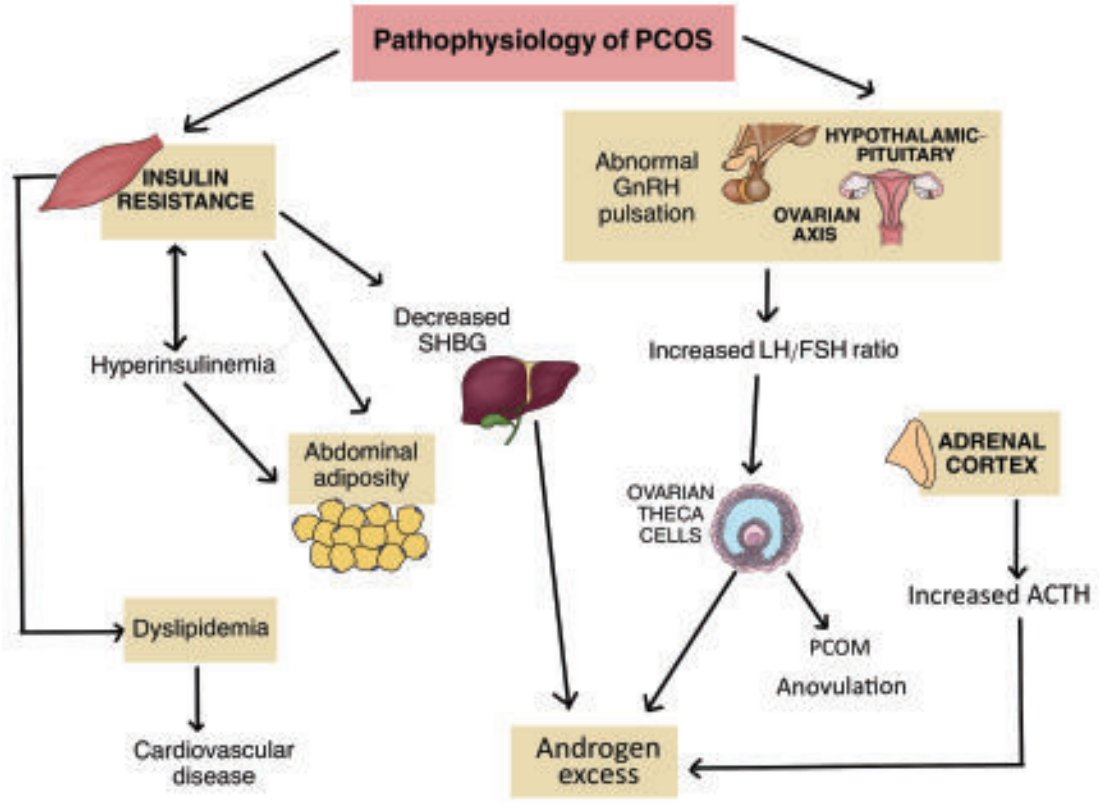

Figure 1. **Pathophysiology of PCOS.** PCOS disrupts the intricate balance of the HPO axis, causing an altered Luteinizing hormone/ Follicular stimulating hormone (LH/FSH) ratio and heightened androgen levels. It also leads to the development of polycystic ovarian morphology (PCOM) and anovulation. The adrenal gland can also contribute to androgen excess. Moreover, IR and obesity further complicate matters by aggravating metabolic syndrome within this complex interplay of factors.

Metabolic dysfunctions in PCOS

The clinical features of PCOS- IR, obesity, dyslipidemia, and hyperandrogenism, can be grouped as metabolic syndrome. Nearly one-third of adolescent teenagers with PCOS and 43% of adult women have metabolic syndrome[10].

1 Insulin Resistance *PCOS is commonly associated with IR. It is caused by specific molecular defects at the post-receptor level in target tissues, which result in an inability of insulin to mediate its metabolic functions (Figure 2). This ultimately leads to ovulatory dysfunction, endometrial disorder, and infertility. Insulin binds to cell surface receptors and initiates a series of intracellular events that lead to insulin signal transduction. This process involves the activation of specific proteins such as glycogen synthase kinase-3 (GSK-3) and insulin-responsive glucose transporter-4 (GLUT-4). In IR the insulin signaling process is disrupted due to increased serine phosphorylation and decreased tyrosine phosphorylation of insulin receptors and insulin receptor substrate 1/2 (IRS1/2). This results in post-binding defects that prevent the cells from effectively using insulin to regulate glucose uptake[2,11,12].*

New information regarding IR in PCOS has emerged in recent years. For instance, microRNA alterations have been found in PCOS, as shown by Dong et al.[13] Moreover, Zhang et al. discovered that abnormal autophagy can impair insulin sensitivity in peripheral tissues by increasing the high mobility group box (HMGB1), a damage-associated molecular pattern molecule[14]. Dysbiosis in PCOS, due to endotoxemia, chronic inflammatory response, and abnormal metabolites, can also be a potential cause of IR[15].

A systematic review and meta-analysis found that lifestyle modification combined with metformin resulted in a greater reduction of BMI in PCOS women than lifestyle modification alone[16].

2 Hyperandrogenemia *Hyperandrogenemia is a crucial diagnostic criterion for PCOS, indicating the abnormal synthesis and accumulation of androgens. This condition has a multifactorial origin, primarily linked to the ovary, with significant contributions from the adrenal glands and, to a lesser extent, adipose tissue (Figure 3).*

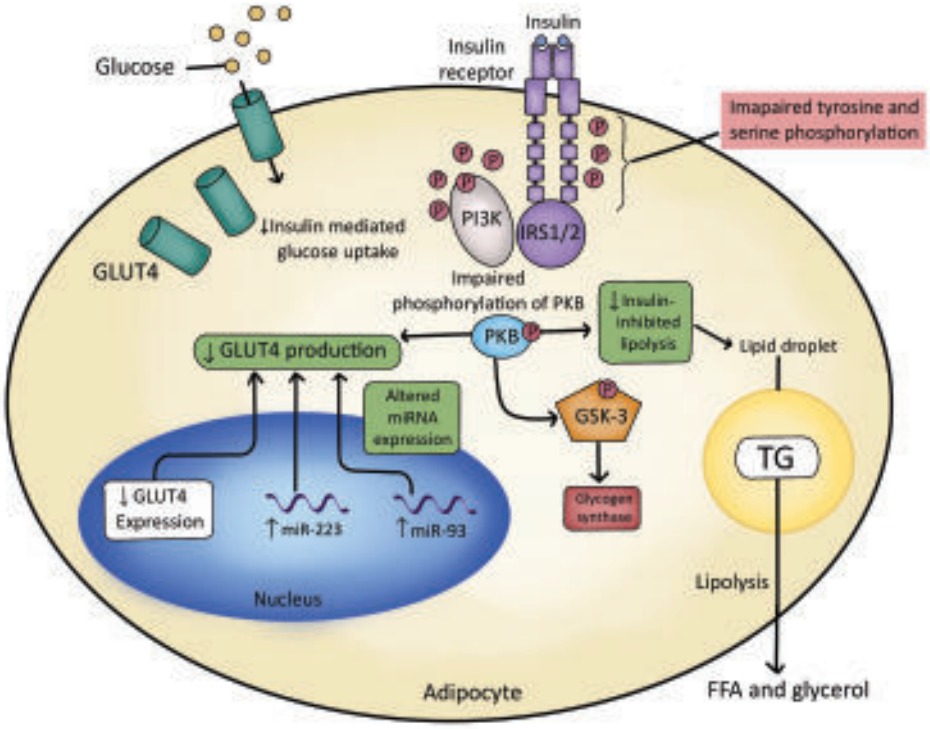

Figure 2. Molecular basis of insulin resistance in PCOS. The main mechanism of insulin resistance is due to defects in the post-binding such as excessive serine phosphorylation and decreased tyrosine phosphorylation, disrupting the normal insulin signaling process. As a result, there is impaired phosphorylation of protein kinase B(PKB) which in turn causes reduced insulin-dependent glucose uptake, inactivation of glycogen synthase kinase-3(GSK-3) leading to increased activation of glycogen synthase, and increased lipolysis.

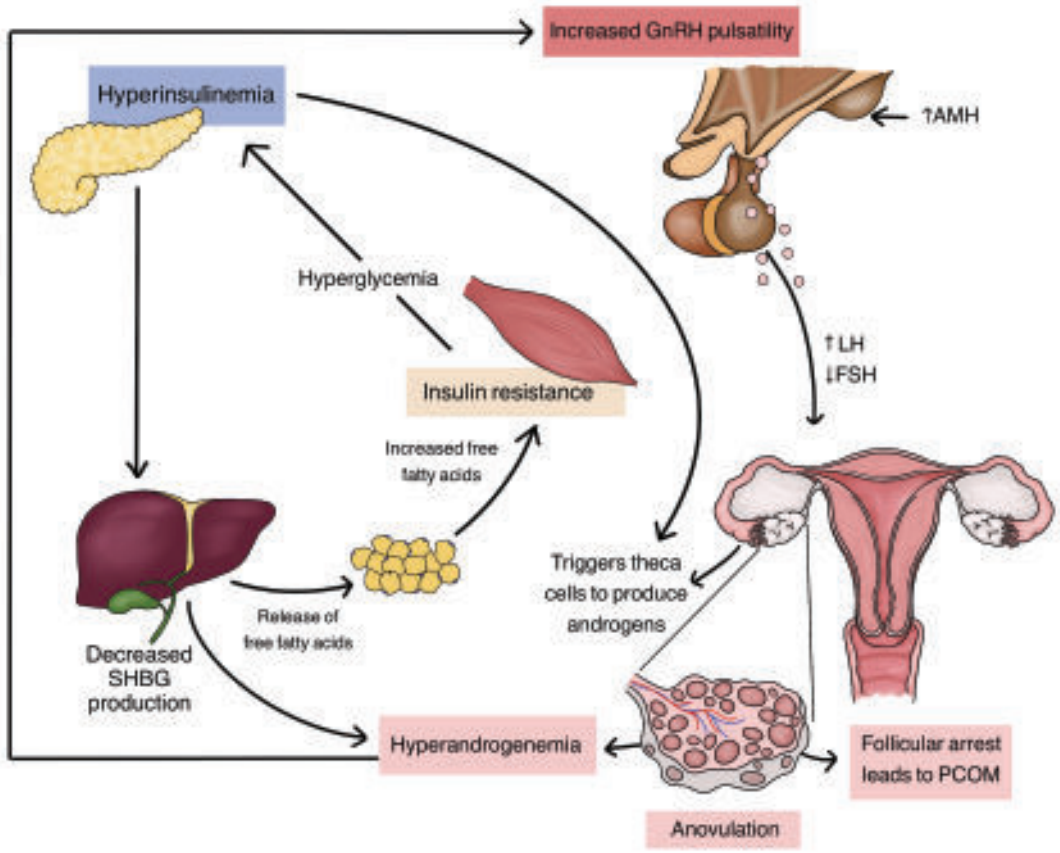

Figure 3. Hyperandrogenemia in PCOS. Hyperandrogenemia has a multifactorial origin. Due to increased gonadotropin-releasing hormone (GnRH) pulsatility, an increase in LH and a decrease in FSH occurs, leading to follicular arrest, PCOM, anovulation, and hyperandrogenemia. Hyperinsulinemia contributes by directly triggering theca cells to produce androgens. It also decreases (sex hormone-binding globulin) SHBG production, increasing the circulating testosterone.

Ovarian-steroidogenic dysregulation in PCOS is believed to involve hyperinsulinemia, luteinizing hormone (LH), and inherent upregulating defects. Insulin, compensatory to insulin resistance, may directly stimulate ovarian androgen production or inhibit the hepatic synthesis of SHBG, increasing bioavailable testosterone. Insulin also potentiates adrenal androgen production and accentuates LH-stimulated ovarian steroidogenesis. Insulin sensitivity within physiological levels is observed in ovarian steroidogenesis, despite the peripheral IR[17,18].

In PCOS, ovarian responsiveness to LH/hCG is exaggerated, potentially intensified by elevated LH levels [19-20]. Abnormal LH secretion is attributed to a defect in the hypothalamic-pituitary axis, with impaired GnRH feedback inhibition due to excessive androgens[19,22-24]. Treatment with naltrexone has been shown to inhibit pulsatile GnRH and results in reduced LH and testosterone levels. The same results were achieved with GnRH antagonist use[23,25]. Recent data also suggests that FSH administration may enhance androgen production via granulosa-theca cell paracrine mechanisms.[26].

Obesity is prevalent in the PCOS population and is associated with more severe hyperandrogenism[27-30]. Weight loss has been shown to decrease androgen levels[2130-35]. Central adiposity, even in lean women with PCOS, is linked to intraabdominal visceral fat accumulation[36,37]. Adrenal androgen excess is found in 20–36% of PCOS patients, possibly due to increased zonae reticularis mass, altered P450c17alpha activity, or increased peripheral cortisol metabolism[38-40]. The contribution of adrenal function to PCOS hyperandrogenism is limited.

3 Obesity: *Obesity is a major component of metabolic dysfunction in PCOS. It is caused by a long-term energy imbalance, where energy consumption exceeds expenditure resulting in chronic inflammation in the adipose tissue. This inflammation occurs when adipocytes increase in number or size, triggering an inflammatory response when they reach their storage capacity. This leads to IR and hyperglycemia due to serine phosphorylation of IRS-1[41].*

Obesity has a significant impact on female fertility because it affects the HPO axis. Obese individuals typically have higher insulin levels in their blood, leading to increased ovarian androgen production that is converted to estrogen by adipose tissue[42]. This negatively affects the HPO axis, reducing gonadotropin production, and ultimately resulting in ovulatory dysfunction and menstrual irregularities[43]. Furthermore, women with PCOS and obesity have more visceral fat deposition, which accentuates IR and hyperinsulinemia, fueling this vicious cycle[44] (Figure 4). The effects of adipose tissue are mediated by molecules such as leptin, adiponectin, tumor necrosis factor a (TNFa), interleukin 6 (IL-6), and plasminogen activator inhibitor-1, which are altered in women with PCOS[45].

Studies indicate that obese women with PCOS express higher levels of lipogenic enzymes and lower levels of lipolysis in their omental adipose tissue compared to obese women without hyperandrogenism[46]. Another study found that obese women with PCOS had significantly lower levels of SHBG than non-obese women, indicating higher levels of free androgens in the former[46-47].

Different drugs have been approved for weight loss purposes. One of them is orlistat, which is a lipase inhibitor that reduces the absorption of fat in the intestines. It helps reduce BMI in women with PCOS. However, there is still debate about whether it affects insulin sensitivity or not[2].

4 Dyslipidemia: *While dyslipidemia is not a diagnostic criterion of PCOS, it is still considered an important metabolic phenotype. According to the National Cholesterol Education Program (NCEP) guidelines, approximately 70% of PCOS patients exhibit abnormal serum lipid levels[48]. Studies have shown that women with PCOS typically have higher levels of total cholesterol, triglycerides, and low-density lipoprotein (LDL), and lower levels of high-density lipoprotein (HDL)[49] (Figure 5). In a study by Wekker et al., it was revealed that PCOS women have a more adverse lipid profile and are at a higher risk for non-fatal cerebrovascular disease events[50].*

Hyperandrogenism promotes adipogenesis and inhibits fat decomposition, leading to obesity in PCOS[51-56]. Obesity further worsens the disorder of endocrine hormones, causing abnormal glucose and lipid metabolism in PCOS patients by increasing protein kinase A (PKA)- hormone-sensitive lipase (HSL) complex activity in visceral fat cells.

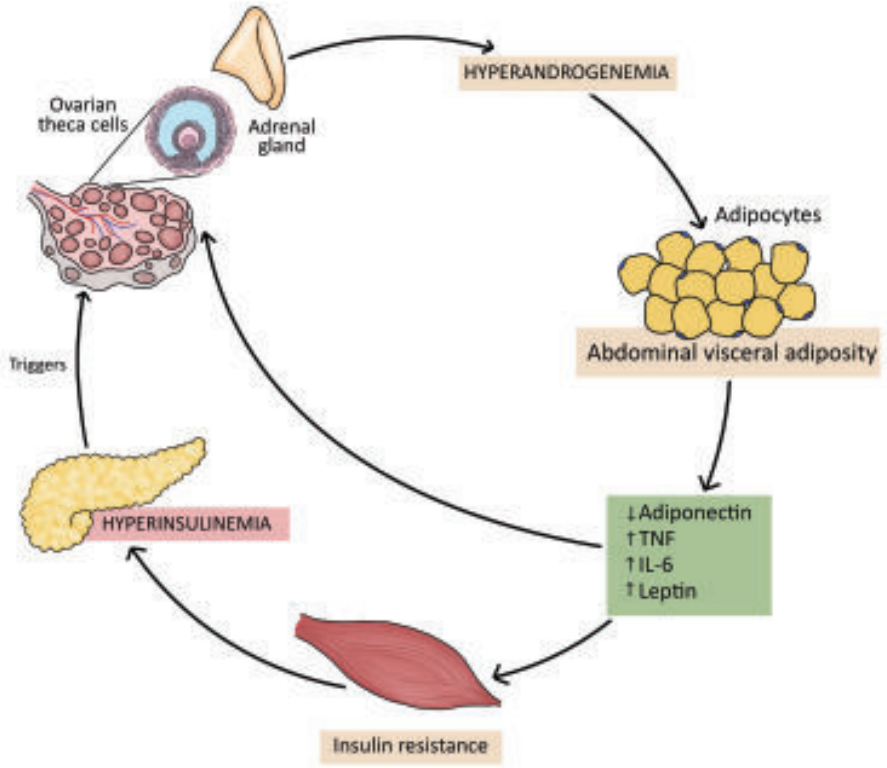

Figure 4. The interplay of PCOS and abdominal adiposity seems to establish a harmful loop where an excess of androgens drives the buildup of visceral abdominal fat. This, in turn, amplifies the surplus of androgens from the ovaries and/or adrenal glands. Multiple mediators, like reduced adiponectin and heightened levels of TNF, IL 6, and leptin, act through autocrine, paracrine, and endocrine routes. Alternatively, they indirectly contribute by instigating IR and hyperinsulinism.

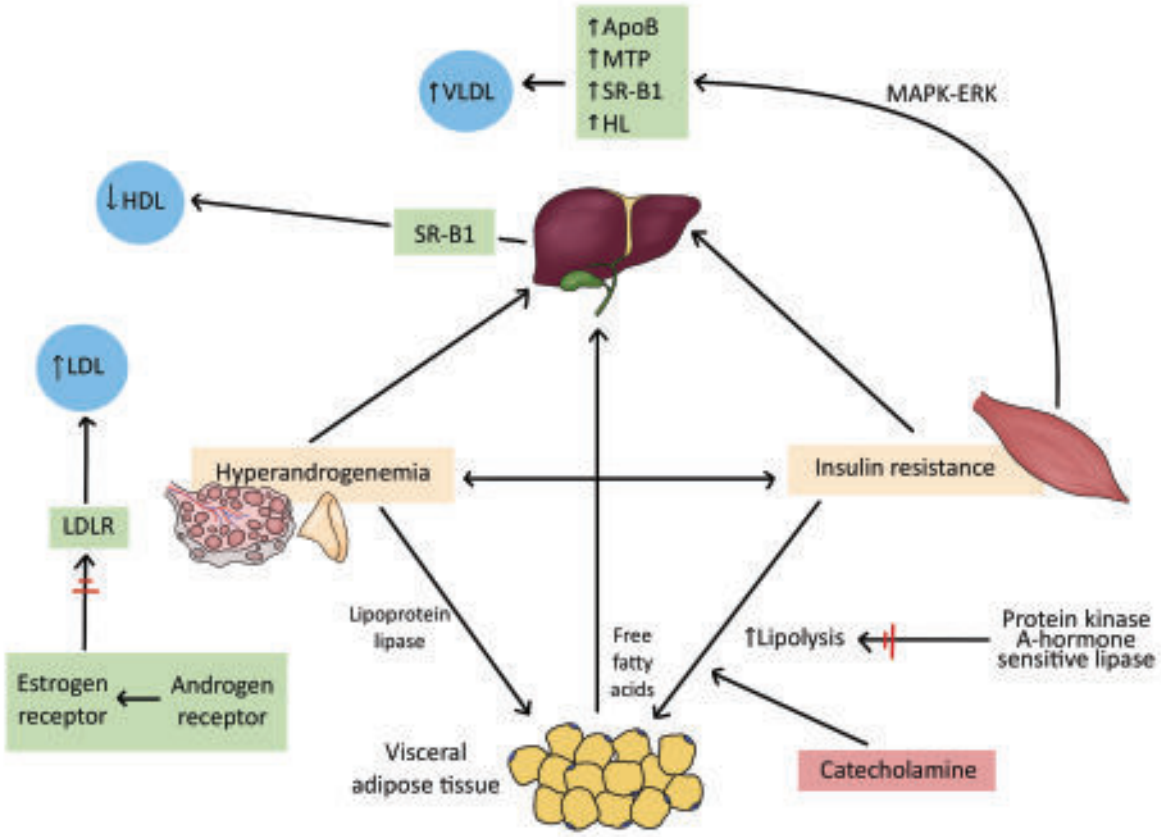

Figure 5. Pathogenesis of dyslipidemia in PCOS. In adipocytes, the combination of insulin resistance and hyperandrogenemia leads to heightened catecholamine-triggered lipolysis, prompting the release of fatty acids into the bloodstream. This increased flow of free fatty acids toward the liver stimulates the formation and discharge of VLDL, consequently causing elevated levels of triglycerides in the blood. Moreover, microsomal triglyceride protein (MTP) causes the excessive production of apoB-containing VLDL by the liver and appears to be a critical link between insulin resistance and heightened triglyceride levels. Additionally, the scavenger receptor, class B type 1 (SR-B1) plays a pivotal role in selectively absorbing HDL lipids in the liver. Androgens hinder the breakdown of LDL by diminishing estrogen receptor (ER)-mediated enhancement of low-density lipoprotein receptor (LDLR) activity.

In addition, overexpression of SR-B1 resulted in a dramatic reduction of HDL[57]*. ER-mediated induction of LDLR activity is significantly reduced leading to a decrease in catabolic removal of LDL when androgens interact with the AR*[58]*. ApoB is a potential risk factor for atherosclerosis*[59]*. Additionally, women with PCOS often suffer from hyperinsulinemia and insulin resistance, which further increase their risk of dyslipidemia. One of the suggested mechanisms linking IR and hypertriglyceridemia is the overproduction of apoB-containing VLDL by the liver*[28]*. MTP plays a crucial role in the secretion of apoB and the subsequent production of VLDL. Overexpression of MTP may be involved in insulin resistance-associated VLDL overproduction*[60]*.*

Lifestyle modification, including diet and exercise, is the first-line therapy for all women with PCOS and is particularly important for those with dyslipidemia. PCOS women receiving statins showed a significant decrease in testosterone, free androgen index, C-reactive protein, and IR[61-63].

5 Other metabolic consequences of PCOS

5.1 Cardiovascular and cerebrovascular disease

Women with PCOS have an increased prevalence of cardiovascular disease (CVD) indicators, mediated mostly by insulin resistance, as well as hormonal and metabolic imbalances (Figure 6). Some of these indicators, such as vascular calcification and vascular wall thickness, suggest a heightened CVD risk in women with PCOS compared to controls. However, demonstrating an increased occurrence of actual cardiovascular events has proven challenging[64]. Notably, women with PCOS exhibit a higher prevalence of

significant coronary calcification and greater intimal layer thickness of the carotid wall than healthy controls. Aortic calcification incidence and arterial stenosis prevalence are also elevated in this population[65-68].

Conflicting data exists regarding cardiovascular events, such as myocardial infarctions, in PCOS. While the general population experiences a substantial rise in CVD incidence after 50 years of age, a similar increase is expected post-menopause in women with PCOS[69]. Some studies report an elevated risk of myocardial infarction in patients with PCOS[69-71].

Regarding cerebrovascular events, older women with PCOS exhibit a slightly increased incidence compared to the general population (Figure 6)[72-73]. The risk of venous thromboembolisms is elevated in PCOS, with a twofold increase in those taking oral contraceptive pills compared to the general population[74-76]. Overall, the understanding of cardiovascular risks in PCOS remains nuanced, with conflicting evidence and various factors influencing study outcomes.

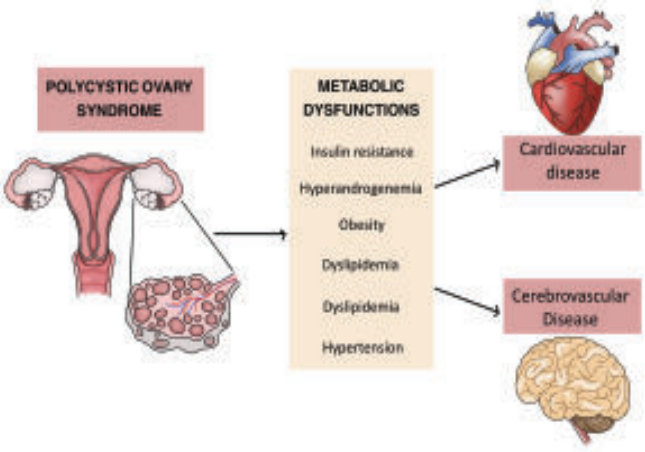

Figure 6. Metabolic consequences of PCOS. PCOS can lead to cardiovascular and cerebrovascular disease as a result of the insult generated by insulin resistance, excess androgens, obesity, dyslipidemia, and hypertension.

Unresolved issues in PCOS

Although significant progress has been made in understanding PCOS, much remains to be discovered. To better comprehend the molecular and genetic causes of metabolic dysfunction underlying PCOS, further research is needed, especially in other tissues such as fat and muscle. Additionally, we need to understand how metabolic dysfunction is related to the other clinical features of the disorder such as ovarian dysfunction. Prospective studies of at-risk children can provide a better understanding of this relationship. It is important to develop preventive therapies to minimize obesity in peripubertal and adolescent girls to avoid PCOS development in the future. There is also a need for more precise information on the impact of metabolic dysfunction on cardiovascular and cerebrovascular complications associated with PCOS, and whether controlling metabolic complications could help reduce the risk of these complications.

Conclusions

PCOS is a common endocrine and reproductive disorder that affects women and is associated with several factors, including genetic, environmental, epigenetic, and developmental factors. The metabolic symptoms of PCOS are interrelated, and hyperandrogenism triggers a cycle of metabolic disorders in patients with PCOS. This cycle is initiated by hyperinsulinemia and insulin resistance, which lead to the accumulation of visceral adipose tissue, causing an increase in androgen production in the adrenal glands and ovaries. Thus, a vicious cycle is formed, a possible mechanism for steroidogenesis defects. These endocrine-metabolic alterations may lead to the development of additional comorbidities, both metabolic, cardiovascular, and cerebrovascular, further complicating the management of PCOS. By understanding the metabolic implications of PCOS, we can take more targeted and effective measures to manage this condition.

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