Diabetes, Metabolic Syndrome and Obesity

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REVIEW

Interplay of Insulin Resistance, Hyperandrogenism, and Obesity in Polycystic Ovary Syndrome: Pathogenesis and Therapeutic Insights

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Abstract: Polycystic ovary syndrome (PCOS) is a complex disorder of ovarian dysfunction primarily driven by a self-perpetuating pathophysiological cycle. This network centrally involves the interplay of insulin resistance (IR), hyperandrogenism, and obesity. IR stimulates ovarian and adrenal androgen production and can promote increased food intake. The resulting hyperandrogenemia, in turn, exacerbates insulin resistance and contributes to obesity. Furthermore, obesity worsens both IR and hormonal dysregulation through the release of inflammatory cytokines and adipokines, thereby reinforcing the entire cycle. This narrative review aims to critically examine the core pathological interplay between IR, hyperandrogenism, and obesity in PCOS. Building on this foundation, the review systematically explores the rationale and emerging evidence for novel therapeutic strategies that target these key components, moving beyond the established framework of current treatments. Lifestyle interventions, including dietary modification and physical activity, remain the cornerstone of PCOS management, particularly for overweight and obese patients. Current PCOS management primarily relies on oral contraceptives for symptomatic control of hyperandrogenism. Insulin-sensitizing agents form the other pillar of therapy. While metformin is widely used, newer classes of antidiabetic drug—including Dipeptidyl peptidase 4 inhibitors, sodium-glucose co-transporter protein 2 inhibitors, and glucagon-like peptide-1 receptor agonists—have demonstrated potential benefits that extend beyond glycemic control, offering improvements in weight, insulin sensitivity, and androgen levels. The discussion also extends to future perspectives, evaluating investigational approaches such as stem cell therapy and aldo-keto reductase 3 inhibitors, which, though not yet part of clinical practice, may represent future targeted treatment avenues. The management of PCOS is evolving from a symptomatic approach towards a more pathophysiologically-targeted and personalized strategy. A deep understanding of the IR-hyperandrogenism-obesity cycle is crucial for developing and implementing these novel therapies, which hold promise for improving long-term reproductive, metabolic, and cardiovascular outcomes for patients with PCOS. Future research should focus on validating these emerging treatments through robust clinical trials and defining their place within individualized treatment algorithms.

Keywords: obesity, hyperandrogenism, insulin resistance, PCOS, therapy

Introduction

Polycystic ovary syndrome (PCOS) is a reproductive, metabolic, and psychosocial condition that affects all stages of life and affects 5%–18% of women. Recently, the nomenclature of this syndrome has been reevaluated to more accurately reflect its multifaceted nature. A research consortium led by Monash University has put forward a proposal to rename the condition "Polyendocrine Metabolic Ovarian Syndrome" (PMOS), with the aim of highlighting its endocrine and metabolic complications that go beyond ovarian dysfunction. Although the term PCOS continues to be widely employed in both clinical practice and the academic literature, this proposed nomenclature change underscores the systemic nature of the disorder and the need for integrated management approaches that concurrently address reproductive and metabolic health.[1] The etiology of PCOS is complicated and includes factors such as obesity, insulin resistance (IR), androgen overexposure, hypothalamic and ovarian dysfunction, and genetic and epigenetic susceptibility.[2] Within the complex pathophysiological network of PCOS, obesity, insulin resistance, and hyperandrogenism form a self-reinforcing vicious

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cycle. These three factors exacerbate the metabolic and reproductive outcomes of PCOS.[3–5] Based on the phenotype, women with PCOS have a wide range of symptoms that can be divided into the following four groups: 1) androgen excess and ovulatory dysfunction, 2) androgen excess and polycystic-appearing ovarian morphology (PCOM), 3) ovulatory dysfunction and PCOM, and 4) androgen excess, ovulatory dysfunction, and PCOM. These four phenotypes correspond to phenotypes A, B, C, and D, respectively, according to the Rotterdam criteria, reflecting the clinical heterogeneity of PCOS with distinct metabolic and reproductive implications.[6] Current treatment primarily relies on oral contraceptives, which fail to address the individualized needs arising from disease heterogeneity. The complex pathophysiology further complicates therapeutic approaches. Among the complex pathophysiological network of PCOS, we chose to focus specifically on the obesity–insulin resistance–hyperandrogenism axis because this triad forms the central self-perpetuating cycle that underlies most metabolic and reproductive complications of the disease. Moreover, these interconnected mechanisms represent the most promising and actionable therapeutic targets, with emerging interventions directly addressing each component. This focused mechanistic framework allows us to bridge pathophysiology with clinical management more effectively than a comprehensive review covering all aspects of PCOS. Therefore, this review explores novel treatment strategies beyond conventional frameworks by deeply understanding the "obesity-insulin resistance-hyperandrogenism" interaction mechanism (Figures 1 and 2), aiming to provide diversified solutions. While the 2023 international evidence-based guideline systematized and reinforced the traditional treatment framework centered on lifestyle interventions, oral contraceptives, and metformin, this review expands the therapeutic perspective by adopting a forward-looking and critical approach to systematically examine innovative therapies that have moved beyond basic research and are gradually entering the clinical horizon. Specifically, this narrative review provides a critical synthesis of the pathophysiological interplay among insulin resistance, hyperandrogenism, and obesity, evaluates the current evidence for emerging pharmacological interventions, and discusses their potential integration into clinical practice. By bridging mechanistic insights with practical treatment considerations, this review aims to offer a clinically applicable framework for clinicians, researchers, and trainees.

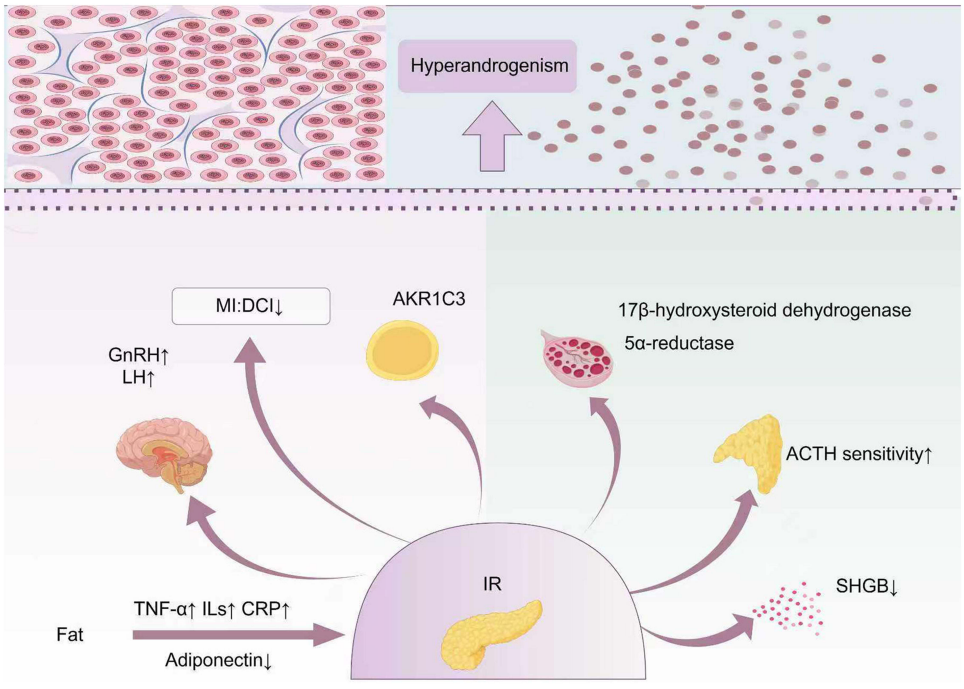


Figure 1 Relationships between insulin resistance, hyperandrogenism, and obesity.
Abbreviations: AKR1C3, aldo-keto reductase 3; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; IR, insulin resistance; SHBG, sex hormone-binding globulin; MI, myo-inositol; DCI, D-chiral inositol; TNF-α, tumor necrosis factor-α; ILs, interleukins; CRP, high-sensitivity C-reactive protein; ACTH,adrenocorticotropic hormone.

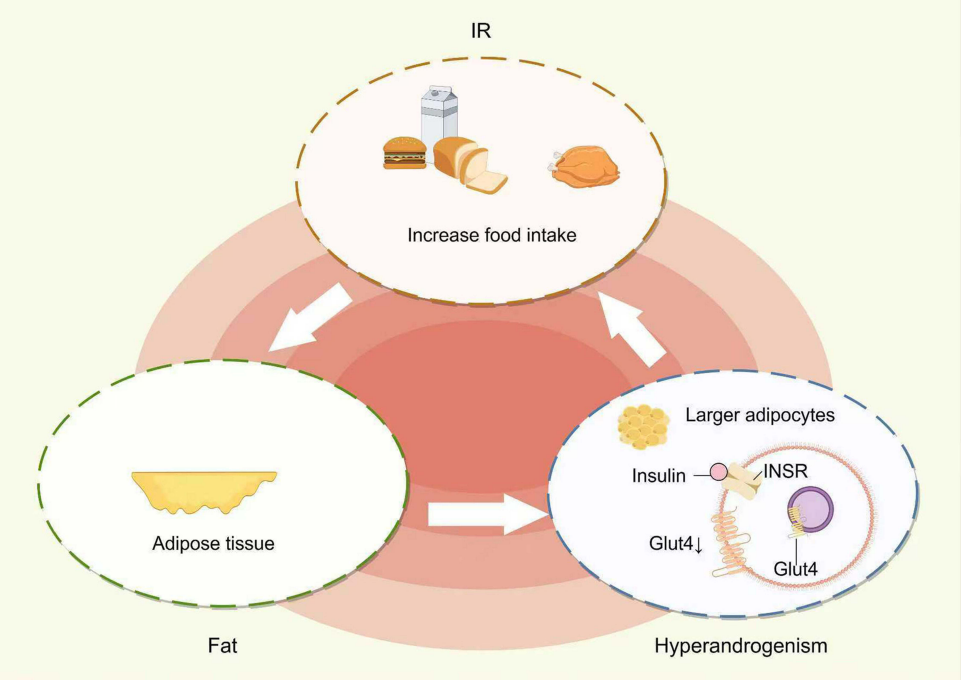


Figure 2 The cycle of insulin resistance, obesity, and hyperandrogenism.
Abbreviations: IR, insulin resistance; Glut4, glucose transporter 4; INSR, insulin receptor.

Relationship Between IR and Hyperandrogenism

Mechanism of IR Leading to Hyperandrogenism

IR occurs when cells in the body are less sensitive to insulin, and compensatory secretion of excessive insulin leads to hyperinsulinemia. IR and the associated hyperinsulinemia lead to hyperandrogenemia in the body, which plays an important role in the reproductive and endocrine features of PCOS.[7] Insulinemia increases androgen synthesis in ovarian and adrenal tissues. According to Nestler et al, insulin stimulates testosterone synthesis in follicular membrane cells of patients with PCOS by activating its receptor and an inositol glycan-mediated signal transduction system.[8] Insulin controls expression of the gonadotropin-releasing hormone gene through the MAP kinase signaling pathway, which increases the release of luteinizing hormone (LH).[9] Insulin works in concert with LH to promote the generation of androgen by ovarian follicular membrane cells.[10–12] D-chiral inositol (DCI) overload is caused by hyperinsulinemia, which changes the ratio of myo-inositol (MI) to DCI in the follicular fluid of patients with PCOS.[13] MI and DCI are insulin sensitizers and stereoisomers. While DIC functions as an aromatase inhibitor, raising testosterone levels, MI also regulates follicle-stimulating hormone (FSH) signaling, promotes aromatase synthesis, and aids in the conversion of androgens to estrogens.[14] A study showed that through the synergistic interaction of kruppel-like factor 15 and stimulatory protein 1/3, insulin directly increased the expression and activity of 17 β-hydroxysteroid dehydrogenase and accelerated the conversion of androstenedione to testosterone in the ovarian and adrenocortical reticular zones.[15] Insulin appears to increase the sensitivity of the adrenal cortex to adrenocorticotropic hormone activation in women with PCOS, which accelerates the synthesis of androgens.[16] Insulin boosts aldo-keto reductase 3 (AKR1C3) activity, which drives androstenedione production of testosterone in adipose tissue, as shown by in vitro and in vivo investigation of adipose androgen production in PCOS.[17] The growth factor effect of hyperinsulinemia is further enhanced at the tissue level by promoting tissue 5 α-reductase activity, which raises the conversion of testosterone to its more physiologically active metabolite, dihydrotestosterone.[10] By directly lowering sex hormone-binding globulin (SHBG) concentrations in women with obesity and PCOS, hyperinsulinemia also indirectly contributes to hyperandrogenemia by increasing the tissue availability of circulating testosterone concentrations.[10]

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Mechanisms of IR Due to Hyperandrogenism

Antiandrogen medication partially corrects the peripheral IR associated with hyperandrogenism in patients with hirsutism and/or PCOS. Hyperandrogenism in women can also result in IR. Hyperandrogenism in women negatively affects the physiological function of insulin in the body.[18] According to Chen et al, hyperandrogenism may contribute to IR by attenuating insulin signaling, which is caused by a decrease in the amount of the insulin receptor substrate, glucose transporter 4.[19] Adipocyte hypertrophy is another effect of hyperandrogenism,[20] and the emergence of IR is associated with larger adipocytes.[21] Additionally, an in vitro study showed that IR resulted from androgen-induced suppression of adiponectin synthesis in 3T3-L1 adipocytes.[22] Adenosine monophosphate-dependent kinase, peroxisome proliferator-activated receptor-alpha, and other potentially unidentified signaling pathways are activated when the insulin-sensitizing hormone adiponectin binds to its receptors AdipoR 1 and AdipoR 2, which increases insulin sensitivity.[23–25]

Relationship Between IR and Obesity

Mechanisms of IR Due to Obesity

One of the factors contributing to IR in women with PCOS is the inverse relationship between obesity and insulin sensitivity.[26,27] The precise processes involved are unclear, but they might be related to altered adipokine secretion and enhanced lipolysis.[26] IR is associated with retinol-binding proteins, visceral adiponectin, adiponectin, leptin, and adipokines.[20] Using adiponectin as an example, obesity results in impaired insulin sensitivity because obesity abnormally reduces adiponectin production in adipocytes[28] and is negatively correlated with adiponectin concentrations.[29] Furthermore, obesity increases inflammation-associated genes, such as the inflammation-associated gene, tumor necrosis factor-α (TNF-α).[30] The presence of inflammation is suggested by higher concentrations of TNF-α, interleukins (ILs), and high-sensitivity C-reactive protein in the blood of patients with PCOS.[31,32] Inflammation can be due to hyperandrogenism and obesity. Therefore, whether the disease or hyperandrogenism or obesity is the primary cause of chronic inflammation in patients with PCOS needs to be investigated.

Mechanisms of IR Leading to Obesity

Insulin activity in the hypothalamus causes anorexia and weight loss,[33] and circulating insulin concentrations are positively associated with body weight and obesity.[34] Proopiomelanocortin (POMC) of the hypothalamic melanocortin system can be regulated by insulin through the insulin receptor substrate-phosphatidylinositol 3-kinase-Akt pathway.[35,36] The cleavage product of POMC, β-melanocyte-stimulating hormone, acts on downstream target neurons to decrease food intake.[37] In contrast, IR has the opposite effect, resulting in obesity. By sympathetically enhancing uncoupling protein action, the nigrostriatal system can affect energy expenditure and control obesity in addition to regulating energy intake.[38] Furthermore, through a sequence of cascade reactions, insulin binds to receptors in the hypothalamus and influences the binding of the transcription factor FoxO1 to DNA, lowering neuropeptide Y (NPY) levels.[39] NPY is a neurotransmitter that functions as a neurotransmitter in the brain and can mediate appetite-stimulating effects through multiple NPY G protein-coupled receptors.[36] Leptin plays a major role in energy regulation. Leptin primarily acts in the hypothalamic arcuate nucleus to inactivate neurons that contain pro-appetite NPY and agouti-related peptide. Furthermore, cellular IR disrupts the ability of leptin to regulate hypothalamic neurons.[40] Beyond these peripheral and hypothalamic mechanisms, the dopamine (DA) system—which originates in the ventral tegmental area (VTA) and extends to the medial prefrontal cortex, amygdala, hippocampus, and nucleus accumbens—provides an important link between metabolic status and motivated behaviors such as eating. DA dysfunction has been closely associated with IR and obesity, and in the context of PCOS, this interconnection may contribute to aberrant eating behaviors and weight gain that reinforce the vicious cycle. The DA system is involved in the production of motivated behaviors such as eating. DA neurons in the VTA are important substrates for the incentive, reinforcement, and motivational components of food intake, and they react to cues that predict reward, among other factors. By decreasing the excitatory drive to VTA DA neurons, insulin may reduce the motivational drive of food-related stimuli. By decreasing the excitatory drive to VTA DA neurons, insulin may reduce the motivational drive of food-related stimuli. Even in a situation of sufficient energy,

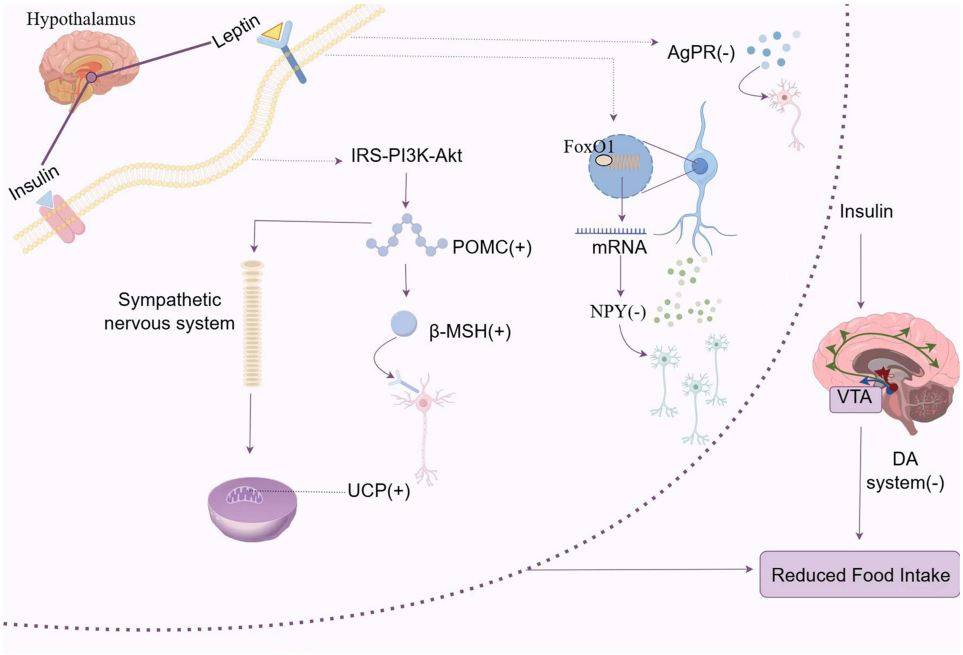


Figure 3 Insulin causes weight reduction by acting on the hypothalamus and VTA.
Abbreviations: DA, dopamine; NPY, neuropeptide Y; β-MSH, β-melanocyte-stimulating hormone; POMC, proopiomelanocortin; VTA, ventral tegmental area; UCP, uncoupling protein; IRS-PI3K-Akt, insulin receptor substrate-phosphatidylinositol 3-kinase-Akt pathway; AgPR, agouti-related peptide; +, activation; -, inhibition.

insulin may not prevent the VTA from receiving information on food-related signals in hyperinsulinemia. This information could encourage additional food-seeking and increase weight and obesity[41] (Figure 3).

Relationship Between Hyperandrogenism and Obesity

Although how obesity and hyperandrogenism are related to each other in women with PCOS is unknown, research suggests that excess adiposity and hyperandrogenism are related.[26] Reduced SHBG concentrations are associated with women's obesity-induced increase in androgen production.[42] Furthermore, obesity increases androgen production and the conversion of androstenedione to testosterone in adipose tissue, and human adipose tissue contains 17 β-hydroxysteroid oxidoreductase.[43] According to Tosi et al, IR appears to play a major role in explaining the association between body fat and hyperandrogenism.[26] Adiponectin decreases insulin-induced progesterone and androstenedione synthesis, and insulin-like growth factor-1-induced gene expression of *CYP11A1*, *CYP17A1*, and *LH* receptors in follicular membrane cells, according to studies conducted in bovine ovarian cell cultures.[44] Therefore, lowering lipocalin concentrations in patients with PCOS may encourage the production of androgens in the ovaries.

Additionally, women with PCOS or ultrasound who have PCOS have a higher likelihood of engaging in bulimic behavior, in part because of elevated androgens, which suppress impulse control and enhance appetite.[45] To provide logical therapeutic strategies for individuals with PCOS who have metabolic diseases, such as obesity and hyperandrogenism, further research is required to understand the association between androgens and obesity and the mechanisms involved.

Therapy

Non-Pharmacological Therapy

Diet plays a very important role in the clinical manifestations and laboratory findings of PCOS.[46] Very low-calorie ketogenic diet[47] very-low-calorie diet, moderate energy deficit diet[48] and Mediterranean diet[49] have all been observed to positively impact patients with polycystic ovary syndrome. The Mediterranean diet is thought by some to be the best dietary treatment for PCOS.[50] The Mediterranean diet is characterized by a high intake of fruits, vegetables, whole

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grains, legumes, and olive oil, with moderate consumption of fish and poultry, and limited intake of red meat and processed foods. However, despite the well-recognized benefits of the Mediterranean diet, the prevalence of PCOS remains high in Mediterranean regions. For example, a study by Amini et al reported a PCOS prevalence of 8.8% among Iranian women, suggesting that although lifestyle modifications such as dietary control and exercise can play an important role in PCOS management, the success of these interventions critically depends on patient adherence. Notably, obese PCOS patients often experience greater difficulty in achieving weight loss through exercise compared with their lean counterparts.[51] For PCOS patients who are overweight or obese, exercise improves lipid levels, insulin resistance, and fasting blood glucose.[52] High-intensity interval training has also been shown in small-sample studies to enhance reproductive results, cardiovascular metabolism, and mental wellness.[53,54] It is advised to perform 75 minutes of vigorous-intensity aerobic exercise or at least 150 minutes of moderate-intensity physical activity every week. Additionally, at least two non-consecutive days each week should be dedicated to muscle-strengthening exercises like resistance or flexibility training.[55]

Oral Contraceptives

The most popular medication for treating PCOS is the combined oral contraceptive pill, which enhances SHBG concentrations and suppresses folliculogenesis and pituitary gonadotropin secretion.[56] Although there are no specific recommended medications to treat PCOS, recommendations from the 2023 international evidence-based guideline for the assessment and management of PCOS recommend combined oral contraceptives as first-line treatments for hyperandrogenism and irregular menstruation. Medications with fewer side effects and lower ethinylestradiol dosages are preferred.[55] The combined ethinylestradiol/cyproterone acetate regimen may be better than the conventional combined oral contraceptive pill in reducing hyperandrogenism, body mass index (BMI), and hirsutism, according to a recent meta-analysis that included 19 randomized, controlled trials. However, the general population is at a higher risk of venous thrombotic events, and combining cyproterone acetate with natural or low-dose estrogen may be a good option in the future.[57] Balancing of the advantages and disadvantages, including venous thromboembolism, is required for using ethinylestradiol/cyproterone acetate and other compounded oral contraceptives as second-line therapy.[55]

Antiandrogenic Drugs

A major contributing factor to PCOS is hyperandrogenism, which causes issues, such as hirsutism, acne, and hair loss. However, there are currently insufficient data to justify treating hyperandrogenism in patients with PCOS on antiandrogenic drugs rather than contraceptives.[58] The 2023 evidence-based guideline recommends treating PCOS with antiandrogenic agents in conjunction with effective contraception if women's hirsutism does not improve after at least 6 months of oral contraceptives and/or cosmetic procedures, such as laser hair removal and intense pulsed light.[55] The current most effective treatments for hirsutism include flutamide, spironolactone, and the 5α-reductase inhibitor finasteride. These medications also improve hirsutism more than insulin sensitizers, and pregnant women should not take antiandrogenic medications because of the possibility of feminization of the fetus.[59]

Antidiabetic Drugs

Metformin

Metformin is a medication that can improve IR and is typically used to treat type 2 diabetes. Metformin has also been shown to be effective in patients with PCOS, and it greatly improves androgen concentrations, BMI, IR, and menstrual patterns.[60] For obese PCOS patients with fertility needs, metformin can improve clinical pregnancy and ovulation rates, though it is less effective than clomiphene.[61] Metformin may serve as one treatment strategy for obese PCOS patients of reproductive age. Patients with PCOS may benefit directly or indirectly from metformin, although the processes underlying its effects on metabolism and reproduction are not fully understood, and the indications for its use have not been established. The combination of metformin and spironolactone is more effective than metformin alone in lowering BMI and serum androgen concentrations. When the course of treatment is ≥ 6 months, combination therapy is more effective than metformin alone in reducing fasting glucose and improving insulin resistance.[62] A recent review suggested that the combination of metformin with birth control pills improves hyperandrogenism, insulin concentrations, and IR more

effectively than the use of birth control pills alone.[63] In adolescents with PCOS and hyperinsulinemia, low-dose metformin combined with oral contraceptives has also been found to improve insulin sensitivity and androgen profiles. This combination therapy can also reduce ovarian volume. Benefits persist after discontinuation of treatment.[64] Polycystic ovarian morphology is often observed during adolescence as part of normal ovarian maturation. An increased stromal-to-ovarian area ratio in the early postmenarcheal phase may serve as an early indicator of PCOS development.[65] Early detection and prompt intervention with metformin may form part of a management strategy for adolescents with PCOS. To assess and further define the most effective course and efficacy of the metformin combination, more high-quality research is required.

Glucagon-Like Peptide-1 Receptor Agonists

Enteric insulin analogs known as glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RAs) slow stomach emptying, raise satiety, reduce glucagon release, and enhance glucose-dependent insulin secretion. An emerging treatment option for PCOS may be GLP-1 RAs, which considerably improve blood glucose concentrations, reduce body weight, moderately lower blood pressure, and ameliorate hyperlipidemia.[66] A meta-analysis of patients with overweight/obesity and PCOS showed that liraglutide and metformin improved total testosterone, free testosterone, and SHBG concentrations similarly.[67] Additionally, the combination of these two drugs was more effective than metformin in improving PCOS, but the incidence of gastrointestinal side effects was much higher. In a clinical pilot trial, 68 patients with obesity or overweight and PCOS were studied (NCT04876027).[68] Although dulaglutide was not substantially different from the control dietary treatment, this trial showed that dulaglutide led to more effective weight loss and, when paired with a calorie-restricted dietary intervention, improved insulin concentrations and the menstrual cycle. GLP-1 RAs can be taken orally and are helpful for people with obesity (NCT05051579)[69] and those with diabetes (NCT02692716 and NCT02906930).[70,71] A clinical trial of an oral formulation in teenage girls with obesity and PCOS has not yet produced core results (NCT03919929).[72] In summary, GLP-1 RAs lower the risk of IR, metabolic diseases, and the ensuing cardiovascular disease in women with PCOS. Additionally, an improvement in these metabolic profiles can affect hyperandrogenism and ovulatory abnormalities.[73] The most common adverse reactions associated with GLP-1 RAs include upper gastrointestinal symptoms such as diarrhea, nausea, abdominal bloating, and vomiting.[74] GLP-1 RAs pose a financial burden for lower-income groups, and individuals in economically disadvantaged areas are less likely to receive GLP-1 RAs treatment.[75] Side effects and cost concerns may hinder the widespread adoption of GLP-1 RAs in PCOS patients. Clinical trials of GLP-1 RAs in PCOS patients are limited, with insufficient long-term data available. Additional evidence is needed to support the metabolic benefits of GLP-1RAs in obese PCOS patients.

Dipeptidyl Peptidase 4 Inhibitors

By preventing GLP-1 from becoming inactive, dipeptidyl peptidase 4 (DPP-4) inhibitors raise the amount of active GLP-1, while also increasing insulin secretion and decreasing glucagon secretion, which lowers blood glucose concentrations.[76] As a hypoglycemic drug, this inhibition might be a novel treatment for PCOS. By reducing the quantity of transforming growth factor-β1/Smad2/3 signaling pathway components, the DPP-4 inhibitor sitagliptin improves ovulation in rats with PCOS, reduces fasting blood glucose concentrations, ameliorates the hyperandrogenic state, and postpones the onset of ovarian fibrosis.[77] Devin et al showed that sitagliptin helped patients with PCOS lose visceral fat. However, there were no changes in the clinical signs or symptoms and androgen levels of women with PCOS.[78] In obese women with PCOS who previously had liraglutide treatment, sitagliptin also reduced weight regain.[79] Studies have shown that short-term saxagliptin treatment improves BMI, waist circumference, the free androgen index, insulin sensitivity, and menstruation in the pre-diabetic population with PCOS.[80] When saxagliptin was combined with extended-release metformin, the combination produced better clinical and metabolic benefits than metformin alone.[80] Currently, most studies on DPP-4 inhibitors for the treatment of PCOS are small-scale, short-term, single-center clinical trials or observational studies. These studies cannot evaluate the long-term reproductive and metabolic outcomes of DPP-4 inhibitors in PCOS patients, and data on long-term medication safety are lacking. The evidence level is low, preventing their recommendation in clinical guidelines.

Sodium-Glucose Co-Transporter Protein 2 Inhibitors

Sodium-glucose co-transporter protein 2 (SGLT2) has cardioprotective and renoprotective actions. SGLT2 prevents glucose blockage at SGLT2 receptors in the proximal tubules of the kidney and prevents urine glucose reabsorption.[81] In PCOS, SGLT2 has not been well studied. Javed et al showed that 12 weeks of empagliflozin medication resulted in a lower body weight, BMI, and total body fat than metformin treatment, but there was no difference in the effects of empagliflozin on hormonal or metabolic markers.[82] In a licogliflozin (LIK066) experiment, dual inhibition of SGLT1/2 reduced hyperinsulinemia and hyperandrogenemia in women with PCOS.[83] In another study of patients with PCOS, dapagliflozin reduced weight, improved IR, and reduced hyperandrogenism, and the benefit was amplified when combined with exenatide.[84] Canagliflozin improved menstrual pattern, and decreased body weight and total fat mass.[85] Canagliflozin is more successful in lowering dehydroepiandrosterone sulphate concentrations than metformin in patients with IR and PCOS.[85] Generally, SGLT2 inhibitors are beneficial for weight gain, hyperandrogenism, IR, and the menstrual cycle in patients with PCOS. In women with obesity or overweight and PCOS who do not respond to metformin treatment, SGLT2 inhibitors can be a novel alternative therapy.[86] SGLT2 inhibitors are primarily indicated for type 2 diabetes. Their application for PCOS treatment constitutes "off-label use", which has resulted in limited motivation for large-scale clinical research. Consequently, small-scale studies currently dominate the existing body of evidence.

Weight Loss Drugs

Although weight reduction medications, such as GLP-1 RAs, orlistat, phentermine, topiramate, naloxone/bupropion, and lorcaserin, are not authorized for use in PCOS, their effects on IR and weight loss suggest that they are important medications for PCOS treatment in the future.[87] The effects of phentermine, topiramate, naloxone/bupropion, and lorcaserin (anti-obesity medications) have not been documented in women with PCOS. Additionally, the function of GLP-1 RAs as a weight loss medication has been described above. Panda et al investigated the effects of orlistat on weight loss and concentrations of testosterone, serum total cholesterol, and triglycerides.[88] They concluded that orlistat is a more effective medication than metformin and should be the medication of choice for weight loss in patients with obesity and PCOS. In a meta-analysis, orlistat and metformin showed similar benefits in lowering BMI, homeostasis model assessment index, testosterone concentrations, and insulin concentrations in women with overweight/obesity and PCOS.[89] This meta-analysis included three prospective, non-randomized studies and six randomized, controlled trials. To increase ovulation and conception rates in patients with PCOS, orlistat needs to be further investigated. Table 1 describes the pharmacological interventions in PCOS.

Table 1 Summary of Pharmacologic Interventions in PCOS

Classification	Representative Drug	Findings	Year
Oral contraceptives	Ethinylestradiol/cyproterone	Hyperandrogenism↓, BMI↓, hirsutism↓	2023[57]
Antiandrogenic drugs	Flutamide, spironolactone, and the 5α-reductase inhibitor finasteride	Hirsutism↓	2014[59]
Metformin	Metformin	Androgen concentrations↓, BMI↓, IR↓, menstrual patterns↑	2023[60]
GLP-1 RAs	Liraglutide	Blood glucose concentrations↓, body weight↓, blood pressure↓, hyperlipidemia↓,	2017[66]
DPP-4 inhibitors	Saxagliptin	BMI↓, waist circumference↓, the free androgen index↓, insulin sensitivity↑, menstruation↑	2017[80]
SGLT2 inhibitors	Dapagliflozin	Weight↓, IR↑, hyperandrogenism↓	2021[84]
Weight loss drugs	Orlista	Weight↓, concentrations of testosterone↓, total cholesterol, and triglycerides↓	2018[88]

Abbreviations: GLP-1 RA, Glucagon-like peptide-1 receptor agonists; DPP-4, dipeptidyl peptidase 4; SGLT2, sodium-glucose co-transporter protein 2; BMI, body mass index; IR, insulin resistance; ↓,reduce; ↑, improve.

Other Therapies

AKR1C3

In addition to insulin catalyzing the production of testosterone and 5α-dihydrotestosterone in peripheral tissues and activating the androgen receptor (AR), insulin stimulates AKR1C3 in adipocytes. Insulin also preferentially converts adrenal-sourced 11β-hydroxy-Δ4-androstene-3.17-dione and 11-keto-delta-4-androstene-3.17-dione to 11-ketotestosterone, which helps women with PCOS develop a hyperandrogenic profile.[90] AKR1C3 also stimulates fatty acid synthase to support lipid excess by stabilizing AR when androgens are not present.[91] Bifunctional inhibitors may be able to alleviate cardiometabolic problems in women with PCOS by targeting AKR1C3. Currently, AKR1C3 is a target that is being studied mostly in drug resistance and tumors, such as liver, breast, and prostate cancers.[92] Research on AKR1C3 in the field of PCOS remains confined to basic research. However, repurposing AKR1C3 inhibitors from oncology for PCOS treatment represents a highly promising direction. A major challenge is ensuring the drug acts solely on the ovaries and spares other tissues that express AKR1C3. Additionally, systemic inhibition of AKR1C3 could interfere with normal hormonal metabolism in other organs, leading to unforeseen side effects.

Inositol

Inositol supplementation appears to improve glycemic parameters, such as fasting glucose concentrations, insulin concentrations, and IR, increase ovulation rates and the menstrual cycle frequency, and decrease total androgens, serum testosterone concentrations, and dehydroepiandrosterone concentrations. Inositol also increases SHBG concentrations in women with PCOS.[93] In a prospective trial involving 90 patients, after 6 months of oral inositol, 68% of patients with PCOS returned to normal menstruation, with a decrease in LH concentrations, the LH/FSH ratio, serum insulin concentrations, and homeostatic modeling of IR.[94] New therapeutic approaches need to be further investigated in non-hyperandrogenic patients because inositol does not improve the clinical features of all PCOS phenotypes. Hyperandrogenic phenotypes of PCOS are strongly associated with decreased testosterone concentrations, the LH/FSH ratio, blood glucose concentrations, and the HOMA index, as well as increased SHBG concentrations.[95] According to Gref et al and Gudović et al, inositol had a non-inferior effect to metformin on testosterone, androstenedione, and SHBG concentrations.[96,97] While inositol may be a viable substitute for metformin, it is still unknown if the two drugs work well together. Ovarian volume and anti-Mullerian hormone concentrations are considerably affected by inositol, which is better than oral contraceptives at lowering androgen concentrations.[98] In addition to inositol improving IR and androgen and cholesterol concentrations, combination with oral contraceptives may be a more successful long-term therapeutic strategy for managing PCOS symptoms.[99] In hyperinsulinemic patients with obesity and PCOS, small doses of DCI can normalize hormonal patterns and restore insulin sensitivity, and DCI administered in conjunction with MI may have even more positive benefits.[100] Clinical and animal research have shown that patients with PCOS benefit the most from a DCI: MI ratio of 40:1.[101,102] With small sample sizes and few pertinent studies, the available evidence for the use of inositol in treatment for PCOS is weak and inconclusive. To strengthen the body of evidence and gain a better understanding of the potential role of inositol in managing PCOS, more research and clinical trials are required.[103]

Mesenchymal Stem Cells

Recent studies have demonstrated the therapeutic effects of mesenchymal stem cells (MSCs) in PCOS. MSCs can migrate to damaged tissues and secrete a variety of bioactive mediators, such as growth factors, cytokines, and extracellular vesicles. These mediators have immunosuppressive, anti-apoptotic, anti-fibrotic, angiogenic, and anti-inflammatory effects.[104] Adipose MSCs, umbilical cord MSCs, bone marrow MSCs (BMMSCs), and others are examples of MSCs.[105] BMMSCs or their secretome suppresses the growth, inflammation, and androgen production of androgen-secreting cells (H295R) in human adrenocortical carcinoma. BMMSCs also improve metabolic and reproductive dysfunction by secreting IL-10, which restores impaired fertility and suppresses androgen synthesis and angiogenicity in letrozole-induced PCOS mouse models.[106] BMMSC overexpression in IL-10 may represent a unique therapeutic strategy for the treatment of PCOS. A study showed that H295R cell proliferation, androgen production, androgen synthesis gene expression, and inflammatory gene expression were inhibited by the overexpression of bone morphogenetic protein-2 (BMP-2).[104] BMP-2 is secreted by BMMSCs and is also a novel approach for stem cell therapy. In

Table 2 Emerging Therapies for PCOS and Level of Evidence

Category	Mechanism	Evidence Level
GLP-1 RAs	GLP-1 RAs slow stomach emptying, raise satiety, reduce glucagon release, and enhance glucose-dependent insulin secretion.	1b
DPP-4 inhibitors	DPP-4 inhibitors raise the amount of active GLP-1.	2b
SGLT2 inhibitors	SGLT2 prevents glucose blockage at SGLT2 receptors in the proximal tubules of the kidney and prevents urine glucose reabsorption.	2b
AKR1C3	AKR1C3 drives androstenedione production of testosterone in adipose tissue	5
Inositol	MI regulates follicle-stimulating hormone signaling, promotes aromatase synthesis, and aids in the conversion of androgens to estrogens	1b
Mesenchymal stem cells	Mesenchymal stem cells can migrate to damaged tissues and secrete a variety of bioactive mediators, such as growth factors, cytokines, and extracellular vesicles.	5

Notes: Levels of evidence are based on the Oxford Centre for Evidence-Based Medicine criteria. Level 1b: Individual randomized controlled trial with a narrow confidence interval. Level 2b: Individual cohort study or low-quality RCT. Level 5: Expert opinion without explicit critical appraisal, or based on physiology, bench research, or animal studies.

Abbreviations: GLP-1 RA, Glucagon-like peptide-1 receptor agonists; DPP-4, dipeptidyl peptidase 4; SGLT2, sodium-glucose co-transporter protein 2.

addition, the expression of testosterone synthesis genes was increased in H295R cells treated with the BMMSC secretome in the presence of anti-BMP-2 antibody or H295R cells treated with BMP-2 knockdown.[104] In a letrozole-induced mouse model of PCOS, increased ovarian BMP-2 expression was associated with the restoration of ovulation and normal levels of androgen steroid gene expression in the ovary following implantation of BMMSCs. This finding suggests that BMP-2 is a potential molecule for the treatment of PCOS. Certain proteins released by BMMSCs have an effect on androgen synthesis by suppressing the expression of the *CYP11A1*, *CYP17A1*, and *DENND1A* genes. These proteins interact with the MAPK pathway to suppress CYP17A1 and its target.[107] In a rat model of PCOS, adipose MSCs and the exosomes they release greatly reduce the phenotypes of dehydroepiandrosterone-induced PCOS, such as infertility, polycystic ovaries, and metabolic abnormalities. MiR-21-5p, which stimulates the insulin receptor substrate-1/AKT pathway and hepatic glucose homeostasis through BTG 2 regulation, is at least partially responsible for the positive effects of adipose MSCs and the exosomes they release.[108] According to recent research, the phosphatidylinositol 3-kinase-AKT pathway primarily mediates the protective effects of adipose MSC transplantation in rats with PCOS.[109] Treatment with umbilical cord MSCs also markedly reduces local and systemic inflammatory responses and improves pathological alterations in the ovarian and uterus of mice with PCOS.[110] These alterations include polycystic ovaries, a disrupted motility cycle, uterine congestion, edema, and tissue fibrosis. The mechanism of action of MSCs from various sources needs to be better investigated. MSC transplantation has received little attention in the field of PCOS, and there are limited data to support its therapeutic benefit in PCOS. Mesenchymal stem cells therapy for PCOS remains in a very early exploratory stage and is not a mature, standard, or recommended treatment option. Its mechanism of action in PCOS is unclear, the cost-effectiveness ratio is extremely low, and its long-term safety is unknown. Table 2 summarises the emerging treatments for PCOS And level of evidence.

Conclusion

In summary, IR and altered steroidogenesis are two of the many mechanisms that contribute to the pathophysiology of PCOS. IR, obesity, and hyperandrogenism interact with each other in PCOS, creating a vicious cycle. A thorough comprehension of the underlying mechanisms can aid in the development of tailored medicines and the accurate management of patients with PCOS. The current main treatment is anti-androgen therapy with oral contraceptives. However, strong medical evidence is still required to support the controversial use of metformin in patients with PCOS without diabetes. Additionally, evidence is required to support the potential use of weight-loss medications such as GLP-1 agonists to treat metabolic disorders in PCOS in the future.[111] SGLT2 inhibitors are a novel strategy for future cardiometabolic complications in PCOS. Furthermore, DPP-4 inhibitors and SGLT2 inhibitors are glucose-lowering medications that have demonstrated some antiandrogenic effects, improved insulin concentrations, and weight reduction

effects that may be useful in the treatment of PCOS. Based on the current evidence, clinical uncertainty regarding the use of inositol for treating PCOS should be taken into account. More research on AKR1C3 and MSCs needs to be performed, and their potential for treating PCOS has not yet been established. Translating these novel strategies into safe, effective treatments for PCOS requires a concerted effort. First, large-scale, rigorous randomized controlled trials are needed to confirm their efficacy and advantage over standard care. Second, long-term follow-up studies must prioritize reproductive and metabolic outcomes. The safety of long-term medication use also requires assessment. Only then can the promise of basic research be fully realized in the clinic. Looking ahead, the integration of emerging therapies into existing PCOS management guidelines will require careful consideration of several practical factors beyond efficacy. Cost-effectiveness remains a critical barrier, particularly for newer agents such as GLP-1 receptor agonists and SGLT2 inhibitors, which may impose significant financial burdens on patients and healthcare systems. Accessibility, including regional availability and healthcare infrastructure, will also determine the real-world applicability of these novel treatments. Furthermore, long-term safety profiles must be firmly established through extended follow-up studies before these agents can be widely recommended. Future guideline updates should therefore incorporate not only clinical efficacy data but also these pragmatic considerations to ensure that novel therapies translate into equitable and sustainable improvements in patient care. In the future, the management of PCOS is poised to enter a new era of individualized and multi-targeted precision medicine. This paradigm shift will rely not only on the established and emerging pharmaceutical agents discussed previously but also on a deeper understanding of the disease's complex network.

Future Directions

Future therapeutic strategies are expected to encompass multiple cutting-edge approaches, ranging from neuroendocrine regulation (eg, kisspeptin, GABA), immunomodulation and adrenal androgen control (eg, prednisolone), to direct ovarian intervention (eg, Anti-Müllerian Hormone therapy).[112] Concurrently, optimizing the nutritional and metabolic micro-environment is increasingly recognized as an indispensable component of comprehensive management. Growing evidence supports the value of specific minerals (eg, calcium, zinc, selenium, chromium picolinate), vitamins (eg, B12, D, E, K, folate), and dietary supplements (eg, omega-3 fatty acids, probiotics, cinnamon).[113] Together, these diverse targets paint a promising future picture: crafting the most suitable therapeutic regimen tailored to the unique pathophysiological characteristics of each PCOS patient by integrating pharmaceuticals, nutrients, and lifestyle interventions.

Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analyzed in this study.

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Author Contributions

Conceptualization: Weiying Guo; funding acquisition: Weiying Guo; Investigation: Fanfan Bao; visualization: Fanfan Bao, Lin Sun; writing-original draft: Weiying Guo,Fanfan Bao, Lin Sun; writing-review & editing: Fanfan Bao, Lin Sun, Weiying Guo. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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