

Effect of Visceral Adipose Tissue on Polycystic Ovary Syndrome: *Review Article*

Hanan Atef Ahmed Ghali, Mohamed Abdel-Moneim Ibrahim Amin, Abdallah Ebrahim Abd Al-Zaher Ahmed, Ahmed Hisham Saleh Radwan

Department of Obstetrics and Gynecology, Faculty of medicine, Zagazig university. Zagazig, Egypt

***Corresponding author: Abdallah Ebrahim Abd Al-Zaher Ahmed**

Abstract

Background: Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders among women of reproductive age, affecting approximately 6–20% of this population worldwide depending on diagnostic criteria. It is characterized by chronic anovulation, hyperandrogenism, and polycystic ovarian morphology. However, beyond the reproductive manifestations, PCOS represents a complex metabolic disorder associated with insulin resistance, obesity, dyslipidemia, and increased cardiovascular risk.

Objective: Understanding the effect of visceral adiposity on PCOS is essential for developing targeted therapeutic interventions that address both reproductive and metabolic outcomes.

Conclusion: Recognizing the importance of visceral adiposity in PCOS underscores the need for comprehensive management approaches that extend beyond symptom control to address underlying metabolic derangements. Lifestyle modification, pharmacologic therapy, and novel interventions targeting adipose tissue biology represent key components of an integrated therapeutic strategy.

Keywords: Polycystic ovary syndrome; visceral adipose tissue; berberine; metformin; insulin resistance; hyperandrogenism.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders among women of reproductive age, affecting approximately 6–20% of this population worldwide depending on diagnostic criteria. It is characterized by chronic anovulation, hyperandrogenism, and polycystic ovarian morphology. However, beyond the reproductive manifestations, PCOS represents a complex metabolic disorder associated with insulin resistance, obesity, dyslipidemia, and increased cardiovascular risk. (Lemaitre et al., 2023)

In recent years, visceral adipose tissue (VAT) has emerged as a crucial determinant of the metabolic disturbances observed in PCOS. Unlike subcutaneous adipose tissue, VAT has unique endocrine and inflammatory properties that profoundly influence systemic metabolism and hormonal balance. Understanding the effect of visceral adiposity on PCOS is essential for developing targeted therapeutic interventions that address both reproductive and metabolic outcomes. (Bril et al., 2024)

The pathophysiology of PCOS is multifactorial, involving genetic, environmental, and endocrine factors. Central to its development is an interplay between hyperandrogenism, insulin resistance, and abnormal gonadotropin secretion. Excessive luteinizing hormone (LH) stimulates theca cells to produce androgens, while inadequate follicle-stimulating hormone (FSH) leads to arrested follicular development. (Y. Zhang et al., 2024)

Hyperinsulinemia, driven by insulin resistance, further amplifies ovarian androgen production and inhibits hepatic synthesis of sex hormone-binding globulin (SHBG), resulting in elevated levels of free circulating androgens. Obesity, particularly visceral obesity, exacerbates these mechanisms through both direct

and indirect pathways, suggesting that adipose tissue dysfunction is integral to the pathogenesis of PCOS. (Kałużna et al., 2021)

Distribution and Function of Adipose Tissue

Adipose tissue is not a uniform storage site for fat but a metabolically active organ that regulates energy homeostasis, immune response, and endocrine signaling. It is broadly classified into subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). SAT is located beneath the skin and primarily functions as an energy reserve, whereas VAT is stored around internal organs such as the liver, intestines, and pancreas.

VAT exhibits higher metabolic activity, greater lipolytic rate, and increased secretion of inflammatory cytokines compared with SAT. This differential behavior means that VAT accumulation contributes disproportionately to insulin resistance and metabolic syndrome. In women with PCOS, this preferential deposition of visceral fat appears to be a major driver of hormonal and metabolic disturbances. (F. Zhang et al., 2022)

Mechanisms Linking Visceral Fat to PCOS

Visceral adipose tissue influences PCOS pathogenesis through several interconnected mechanisms. One of the most significant is insulin resistance. VAT releases free fatty acids (FFAs) into the portal circulation, which directly affect hepatic glucose metabolism and promote insulin resistance. The resulting hyperinsulinemia stimulates ovarian androgen production and reduces SHBG synthesis. Additionally, visceral adipocytes secrete various adipokines and inflammatory mediators such as tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), leptin, and resistin, while adiponectin levels are decreased. These cytokines promote chronic low-grade inflammation, impair insulin signaling, and disrupt hypothalamic-pituitary-ovarian (HPO) axis function. (de Medeiros et al., 2021)

Furthermore, the activity of 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1), an enzyme that converts inactive cortisone to active cortisol, is elevated in visceral fat, leading to increased local cortisol concentrations. This promotes further adipocyte differentiation, lipid storage, and insulin resistance. The interaction between these metabolic and hormonal factors forms a vicious cycle that sustains both visceral obesity and PCOS features.

Visceral Fat and Insulin Resistance in PCOS

Insulin resistance is a hallmark of PCOS and is present even in lean women with the disorder, although it is more pronounced in those who are obese. VAT contributes to systemic insulin resistance by increasing the flux of FFAs to the liver, thereby stimulating gluconeogenesis and impairing hepatic insulin clearance. Additionally, the pro-inflammatory cytokines released from visceral fat interfere with insulin receptor signaling through serine phosphorylation of insulin receptor substrate-1 (IRS-1). (Prabhu et al., 2021). In PCOS, this insulin resistance leads to compensatory hyperinsulinemia, which enhances ovarian androgen synthesis by acting synergistically with LH on theca cells. Hyperinsulinemia also suppresses SHBG production in the liver, further increasing bioavailable androgens. The elevated androgen levels promote abdominal fat deposition, particularly in the visceral region, perpetuating a self-reinforcing cycle between adiposity and hormonal imbalance. This mechanism highlights VAT as both a cause and a consequence of insulin resistance in PCOS. (Micić et al., 2022)

Inflammatory Role of Visceral Adipose Tissue

A key distinguishing feature of visceral adiposity is its pro-inflammatory state. Visceral fat exhibits an increased infiltration of macrophages and T lymphocytes that produce pro-inflammatory cytokines. This chronic low-grade inflammation contributes to insulin resistance and ovarian dysfunction in PCOS. Elevated levels of TNF- α and IL-6 have been correlated with markers of hyperandrogenism and menstrual irregularity. (de Medeiros et al., 2021)

Moreover, inflammatory cytokines alter the secretion of gonadotropin-releasing hormone (GnRH) and disrupt normal follicular maturation. They also impair endothelial function, increasing cardiovascular risk. This inflammatory milieu generated by visceral adiposity extends beyond metabolic dysfunction, affecting reproductive tissues directly and thereby worsening PCOS symptoms. In summary, inflammation serves as a mechanistic bridge linking visceral adiposity with both the endocrine and metabolic manifestations of PCOS. (Bril et al., 2024)

Adipokines and Their Impact on Ovarian Function

Adipose tissue acts as an endocrine organ through the secretion of bioactive peptides known as adipokines. Among them, leptin, adiponectin, resistin, and visfatin have significant roles in PCOS pathophysiology. Leptin levels are typically elevated in obese women with PCOS, reflecting leptin resistance. High leptin levels may impair ovarian folliculogenesis and oocyte quality. Conversely, adiponectin, which enhances insulin sensitivity and has anti-inflammatory properties, is decreased in women with PCOS, especially those with visceral obesity. Low adiponectin levels correlate with insulin resistance, dyslipidemia, and hyperandrogenism. (Lemaitre et al., 2023)

Resistin and visfatin, both of which are secreted predominantly by visceral adipocytes, contribute to insulin resistance and chronic inflammation. Their elevated levels in PCOS further promote metabolic disturbances and ovarian dysfunction. These alterations in adipokine profiles illustrate how visceral fat acts as an endocrine disruptor that drives both systemic metabolic dysfunction and local ovarian pathology. (Y. Zhang et al., 2023)

Visceral Adiposity and Hyperandrogenism

Hyperandrogenism is a central feature of PCOS, manifesting as hirsutism, acne, and alopecia. VAT contributes to hyperandrogenism through several pathways. First, increased insulin levels derived from VAT-induced insulin resistance stimulate ovarian androgen synthesis. Second, VAT expresses higher levels of enzymes involved in steroid metabolism, such as aromatase and 17 β -hydroxysteroid dehydrogenase, which can alter the balance between androgens and estrogens. Third, the release of inflammatory mediators from VAT stimulates the hypothalamic-pituitary axis to secrete more LH, thereby enhancing androgen production. (Lonardo et al., 2024). Moreover, androgens themselves promote visceral fat accumulation, leading to a bidirectional relationship. This reciprocal interaction between androgens and visceral fat reinforces the metabolic and reproductive dysfunction in PCOS. Clinical studies consistently show that women with PCOS have higher visceral fat-to-subcutaneous fat ratios than BMI-matched controls, even when total body fat is similar. (Bai et al., 2023)

Cardiometabolic Consequences of Visceral Adiposity in PCOS

The accumulation of visceral adipose tissue in PCOS has profound cardiometabolic implications. It predisposes affected women to metabolic syndrome, type 2 diabetes mellitus, dyslipidemia, and hypertension. The combination of insulin resistance, inflammation, and endothelial dysfunction increases the risk of atherosclerosis and cardiovascular disease later in life. (Başar Gökçen et al., 2021)

Visceral fat contributes to an atherogenic lipid profile characterized by elevated triglycerides, low high-density lipoprotein (HDL) cholesterol, and small dense low-density lipoprotein (LDL) particles. These metabolic abnormalities often appear in early adulthood and may persist even after normalization of menstrual function or fertility treatment. Thus, visceral adiposity not only exacerbates PCOS symptoms but also represents a key determinant of long-term health risks in this population. (Jurczewska et al., 2023)

Diagnostic Assessment of Visceral Fat in PCOS

Accurate assessment of visceral fat is essential for understanding its role in PCOS and guiding therapeutic strategies. Conventional anthropometric measurements such as body mass index (BMI) and waist-to-

hip ratio provide only indirect estimates of fat distribution. Imaging modalities, including magnetic resonance imaging (MRI), computed tomography (CT), and dual-energy X-ray absorptiometry (DEXA), offer more precise quantification of visceral fat compartments. However, their use is limited by cost and accessibility. (Y. Zhang et al., 2022)

Ultrasound-based measurement of intra-abdominal fat thickness has emerged as a practical and non-invasive alternative for evaluating VAT in clinical and research settings. Studies have shown strong correlations between ultrasonographic VAT measurements and metabolic markers of insulin resistance in women with PCOS. Hence, assessing visceral fat distribution can provide valuable insight into disease severity and help tailor individualized management approaches (Q. Zhang et al., 2022), also diagnosed by Waist-to-height ratio (WHtR). $WC/H > 0.5$ is indicative of visceral obesity. (Valeria et al., 2021). To calculate (WHtR), WC needs to be measured precisely by measuring the waist midway between the bottom of the ribs and the top of the hips with natural breath. WC and height need to be measured in the same units, and the calculation method of WHtR is to divide WC by height measurement (ZHANG et al., 2024).

Therapeutic Implications: Targeting Visceral Adiposity

Given its pivotal role in PCOS pathophysiology, targeting visceral adiposity offers a promising therapeutic avenue. Lifestyle modification, including dietary intervention and regular physical activity, remains the cornerstone of management. Caloric restriction and aerobic exercise preferentially reduce visceral fat stores and improve insulin sensitivity. Even modest weight loss (5–10%) has been shown to restore ovulation and reduce androgen levels in obese women with PCOS. (Hurayb et al., 2024)

Pharmacological interventions such as metformin and thiazolidinediones improve insulin sensitivity and may reduce visceral fat accumulation. Anti-obesity agents like orlistat and glucagon-like peptide-1 (GLP-1) receptor agonists have also demonstrated beneficial effects on body composition and reproductive outcomes. In addition, bariatric surgery has been associated with significant reductions in visceral fat and improvement in PCOS manifestations in morbidly obese women. Future therapies targeting adipokine signaling and inflammatory pathways may provide further benefits by directly addressing visceral fat dysfunction.

Berberine: Origin and Pharmacological Profile

Berberine is a plant-derived isoquinoline alkaloid found in species of *Berberis*, *Coptis*, and *Phellodendron*. It has been used for thousands of years in traditional Chinese medicine to treat gastrointestinal infections, diarrhea, and metabolic disorders. In recent decades, extensive pharmacological research has revealed that berberine exerts pleiotropic effects on glucose and lipid metabolism, inflammation, and oxidative stress. (Rondanelli et al., 2021)

Berberine has poor oral bioavailability, but it demonstrates high tissue distribution and a long half-life due to its active metabolites. It acts through multiple molecular pathways, including activation of adenosine monophosphate-activated protein kinase (AMPK), modulation of gut microbiota, and regulation of insulin signaling cascades. These mechanisms underpin its therapeutic effects in metabolic diseases and have attracted attention for its potential use in PCOS management. (He et al., 2024)

Mechanisms of Action of Berberine in PCOS

Berberine exerts its beneficial effects in PCOS through multiple mechanisms that target the core pathophysiological abnormalities of the syndrome.

1. Improvement of Insulin Sensitivity

Insulin resistance is central to PCOS pathophysiology, and berberine has shown potent insulin-sensitizing effects. It activates AMPK, a cellular energy sensor that regulates glucose and lipid metabolism. AMPK activation enhances glucose uptake in skeletal muscle, promotes fatty acid oxidation, and suppresses hepatic gluconeogenesis. These actions collectively reduce circulating glucose and insulin levels. Clinical studies have

demonstrated that berberine decreases fasting plasma glucose, fasting insulin, and HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) in women with PCOS, comparable to the effects of metformin. (Yu et al., 2021)

2. Regulation of Lipid Metabolism

Women with PCOS often exhibit dyslipidemia characterized by elevated triglycerides and low high-density lipoprotein (HDL) levels. Berberine improves lipid profiles by upregulating low-density lipoprotein receptor (LDLR) expression and promoting cholesterol clearance. Moreover, it reduces triglyceride synthesis and very low-density lipoprotein (VLDL) secretion in the liver. By ameliorating lipid abnormalities, berberine mitigates cardiovascular risks associated with PCOS and improves overall metabolic health. (X. Zhang et al., 2025)

3. Reduction of Androgen Excess

Hyperandrogenism is a defining feature of PCOS, and berberine has been shown to reduce serum testosterone and androstenedione levels. This effect is mediated partly by improved insulin sensitivity, which diminishes insulin's stimulatory effect on ovarian androgen production. Additionally, berberine directly modulates steroidogenic enzyme activity within the ovary, reducing androgen biosynthesis. Some studies also suggest that berberine may increase SHBG production, thereby reducing free circulating androgens. (Usulkar et al., 2024)

4. Anti-inflammatory and Antioxidant Effects

PCOS is associated with chronic low-grade inflammation and oxidative stress, contributing to metabolic and reproductive dysfunction. Berberine exhibits potent anti-inflammatory properties by inhibiting nuclear factor-kappa B (NF- κ B) signaling and suppressing the release of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α). It also enhances the activity of antioxidant enzymes, including superoxide dismutase and catalase, thereby reducing oxidative damage in ovarian and metabolic tissues. (Ochyra et al., 2022)

5. Modulation of Gut Microbiota

Emerging evidence suggests that gut dysbiosis may play a role in the development of insulin resistance and systemic inflammation in PCOS. Berberine beneficially modulates gut microbiota composition by increasing short-chain fatty acid-producing bacteria and reducing endotoxin-producing species. These microbiome changes improve intestinal barrier integrity and metabolic function, offering an additional mechanism for berberine's efficacy in PCOS. (Mirzaee et al., 2021)

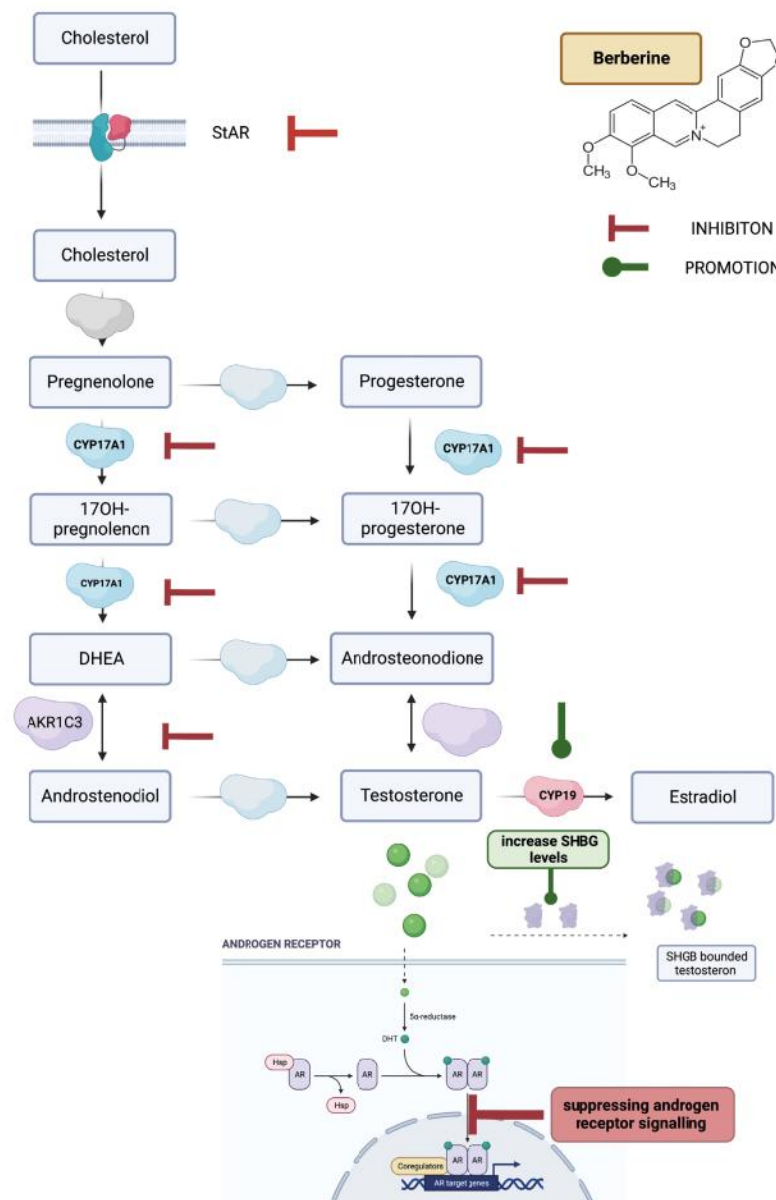


Fig. (1). The mechanism of berberine's action in polycystic ovary syndrome (PCOS).

Clinical Evidence of Berberine Use in PCOS

Several clinical studies have investigated the effects of berberine in women with PCOS, often comparing its efficacy to that of metformin.

A landmark randomized controlled trial compared berberine, metformin, and placebo in women with PCOS undergoing in vitro fertilization (IVF). The study found that berberine significantly improved insulin sensitivity, reduced androgen levels, and enhanced lipid profiles. Interestingly, women receiving berberine exhibited higher pregnancy rates compared to the metformin group, suggesting additional reproductive benefits beyond metabolic improvement. (He et al., 2024)

Another clinical trial demonstrated that berberine reduced body mass index (BMI) and waist-to-hip ratio in obese women with PCOS. These improvements were accompanied by decreased fasting insulin and testosterone levels. Importantly, berberine was associated with fewer gastrointestinal side effects compared to metformin, highlighting its better tolerability. (Rondanelli et al., 2021)

In a meta-analysis of randomized controlled trials, berberine was shown to significantly lower fasting glucose, fasting insulin, total cholesterol, and testosterone levels in women with PCOS. Moreover, the combination of berberine with lifestyle modification or metformin produced additive effects, further enhancing metabolic and hormonal outcomes. These findings position berberine as a promising alternative or adjunct therapy for PCOS management. (Jin et al., 2024)

Berberine and Ovulatory Function

Restoration of ovulation and fertility remains a key goal in PCOS treatment. Studies indicate that berberine can improve ovulatory frequency and menstrual regularity. This is primarily attributed to the reduction in insulin resistance and androgen levels, which normalize the hypothalamic–pituitary–ovarian axis. By improving follicular maturation and oocyte quality, berberine enhances natural conception rates and outcomes in assisted reproduction. Some evidence also suggests that berberine may improve endometrial receptivity, facilitating successful implantation and pregnancy. (Mishra et al., 2022)

Comparative Efficacy: Berberine vs. Metformin

Metformin has long been considered the cornerstone of pharmacologic therapy for insulin resistance in PCOS. However, berberine has emerged as a comparable agent with additional advantages. Both agents activate AMPK and improve glucose metabolism, but berberine exerts broader effects on lipid regulation and inflammation. Clinical studies have shown that berberine achieves similar reductions in fasting glucose, insulin, and HOMA-IR values as metformin but with a superior impact on lipid parameters. (Mirzaee et al., 2021)

Furthermore, berberine appears to cause fewer gastrointestinal side effects, such as diarrhea and nausea, which often limit metformin adherence. The dual action of berberine on metabolic and reproductive axes suggests that it may offer a more holistic approach to PCOS management, especially in patients with significant dyslipidemia or intolerance to metformin. (Ochyra et al., 2022)

Berberine in Combination Therapy

Combination therapy is increasingly being explored to maximize the therapeutic benefits of berberine. Co-administration with metformin has shown synergistic effects in improving insulin sensitivity and hormonal balance. Similarly, the addition of berberine to oral contraceptives or anti-androgenic medications can enhance metabolic outcomes without compromising reproductive benefits. In some trials, combining berberine with myo-inositol or D-chiro-inositol improved ovulatory function more effectively than either agent alone, indicating potential additive or complementary mechanisms. (He et al., 2024)

Safety and Tolerability of Berberine

Berberine is generally well-tolerated, with few adverse effects reported in clinical studies. The most common side effects include mild gastrointestinal discomfort, constipation, or nausea, which are typically transient. Unlike metformin, berberine does not cause lactic acidosis or severe hypoglycemia. However, its use during pregnancy and lactation remains inadequately studied, and caution is advised in women attempting conception. Long-term safety data are still limited, and further large-scale trials are warranted to assess its chronic use in reproductive-age women. (Jin et al., 2024)

Limitations of Current Evidence

Despite promising results, several limitations exist in the current evidence regarding berberine's role in PCOS. Most clinical trials have been conducted in Asian populations, raising questions about generalizability to other ethnic groups. Moreover, sample sizes in many studies are relatively small, and study durations are often short. There is also considerable variability in berberine formulations, dosages, and treatment durations, complicating comparisons across studies. Standardization of berberine supplements and well-designed, multicenter randomized controlled trials are necessary to establish definitive efficacy and safety profiles. (Mishra et al., 2022)

Pathophysiology of PCOS and the Role of Insulin Resistance

Insulin resistance is a fundamental pathogenic mechanism in PCOS and occurs in both obese and lean phenotypes. Defects in insulin receptor signaling, increased serine phosphorylation of insulin receptor substrates, and enhanced lipolysis contribute to peripheral insulin resistance. To compensate, pancreatic β -cells secrete higher amounts of insulin, resulting in hyperinsulinemia.(Xu et al., 2022)

Hyperinsulinemia has several deleterious effects in PCOS. It stimulates theca cells in the ovaries to produce excessive androgens and suppresses hepatic production of sex hormone-binding globulin (SHBG), thereby increasing free androgen levels. Elevated androgens disrupt follicular development, leading to chronic anovulation and the formation of polycystic ovaries. In addition, insulin resistance contributes to dyslipidemia and promotes visceral adiposity, which further aggravates metabolic and hormonal imbalances. Consequently, therapies that improve insulin sensitivity, such as metformin, have been considered central to managing PCOS, particularly in women with metabolic features.(Ma et al., 2021)

Pharmacology of Metformin

Metformin belongs to the biguanide class of oral hypoglycemic agents. It exerts its action primarily by decreasing hepatic glucose production and enhancing peripheral glucose uptake in skeletal muscle and adipose tissue. Unlike other antidiabetic agents, metformin does not cause hypoglycemia or weight gain, making it suitable for long-term use in women with PCOS.(Huang et al., 2023)

Metformin is absorbed mainly in the small intestine and is not metabolized by the liver. It is excreted unchanged by the kidneys. The drug's bioavailability ranges from 40% to 60%, and it has a half-life of approximately 4–6 hours. Common side effects include gastrointestinal discomfort such as nausea, diarrhea, and abdominal cramping, which can often be minimized by gradual dose titration or the use of extended-release formulations. The risk of lactic acidosis, though frequently cited, is exceedingly rare in patients with normal renal function.(Miao & Zhou, 2022)

Molecular Mechanisms of Metformin Action

The primary mechanism of metformin is the activation of adenosine monophosphate-activated protein kinase (AMPK), a cellular energy sensor that regulates lipid and glucose metabolism. Activation of AMPK leads to inhibition of hepatic gluconeogenesis, increased glucose uptake in peripheral tissues, and reduced lipid synthesis. This shift in energy metabolism decreases hepatic glucose output and improves insulin sensitivity.(Melin et al., 2024)

Metformin also inhibits mitochondrial respiratory chain complex I, leading to a mild reduction in intracellular ATP levels. This energy deficit stimulates AMPK activation and suppresses hepatic gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase. Moreover, metformin enhances insulin receptor tyrosine kinase activity, thereby improving insulin signaling.(Saadati et al., 2025)

Beyond its metabolic effects, metformin exerts direct ovarian actions. It reduces theca cell androgen production by lowering insulin and LH stimulation, decreases expression of steroidogenic enzymes such as cytochrome P450c17 α , and may improve follicular maturation. Metformin's anti-inflammatory and antioxidant properties further contribute to restoring ovarian and metabolic homeostasis in PCOS.(Yen et al., 2021)

Metformin and Insulin Sensitivity in PCOS

Metformin significantly improves insulin sensitivity in women with PCOS. Clinical studies have demonstrated reductions in fasting insulin levels, glucose tolerance, and HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) scores after 8–12 weeks of therapy. These improvements are more pronounced in obese and insulin-resistant subgroups but can also benefit lean women with biochemical evidence of insulin resistance.(Meng & Zhu, 2021)

Enhanced insulin sensitivity decreases hyperinsulinemia, which in turn reduces ovarian androgen production and increases SHBG levels. This leads to an overall reduction in circulating free testosterone. The improvement in insulin dynamics also promotes weight stabilization and reduces the risk of developing metabolic syndrome and type 2 diabetes in PCOS patients.(Nowak et al., 2024)

Effects of Metformin on Ovarian Function and Ovulation

One of the most significant benefits of metformin in PCOS is the restoration of ovulatory function. By improving insulin sensitivity and lowering androgen levels, metformin reestablishes the hormonal milieu necessary for normal follicular development and ovulation. Several studies have shown that metformin therapy results in the resumption of regular menstrual cycles and spontaneous ovulation in up to 40–60% of women with PCOS.(Abdalla et al., 2022)

Metformin can be used as monotherapy or in combination with ovulation-inducing agents such as clomiphene citrate or letrozole. The combination of metformin and clomiphene has demonstrated superior efficacy compared with either drug alone, especially in women who are clomiphene-resistant. Furthermore, pre-treatment with metformin before assisted reproductive techniques such as in vitro fertilization (IVF) can reduce the risk of ovarian hyperstimulation syndrome and improve ovulatory response.(Melin et al., 2023)

Metformin and Hyperandrogenism

Hyperandrogenism is a defining feature of PCOS and manifests clinically as hirsutism, acne, and alopecia. Metformin reduces serum androgen concentrations by multiple mechanisms. The drug decreases insulin levels, thereby reducing insulin-stimulated androgen synthesis in theca cells. It also indirectly increases hepatic SHBG production, resulting in lower levels of bioavailable testosterone.(Xing et al., 2022)

In addition, metformin's anti-inflammatory and metabolic effects may suppress ovarian expression of enzymes responsible for androgen biosynthesis. Clinical trials have consistently shown that metformin lowers total and free testosterone levels and improves hyperandrogenic symptoms. However, the magnitude of improvement in hirsutism and acne may take several months to become clinically evident due to the slow turnover of hair follicles.(Shamim et al., 2022)

Metformin and Weight Management

Obesity and visceral adiposity are common in women with PCOS and contribute to worsening insulin resistance and hormonal disturbances. Metformin exerts modest but clinically meaningful effects on weight reduction. It decreases appetite by influencing hypothalamic neuropeptides and enhances fat oxidation through AMPK activation. Although weight loss achieved with metformin alone is generally moderate (2–4 kg), it can be significant when combined with lifestyle modification.(Nowak et al., 2024)

Importantly, metformin reduces visceral rather than subcutaneous fat stores, leading to improved metabolic outcomes. Reduction of visceral adiposity is associated with better insulin sensitivity, decreased inflammation, and improved reproductive function. Therefore, metformin represents a valuable adjunct in comprehensive weight management strategies for PCOS.(Yen et al., 2021)

Metformin and Lipid Profile

Women with PCOS often present with dyslipidemia characterized by elevated triglycerides, low HDL cholesterol, and increased small dense LDL particles. Metformin has been shown to improve these lipid abnormalities through both direct and indirect mechanisms. By activating AMPK and reducing hepatic lipogenesis, metformin decreases triglyceride synthesis and VLDL secretion. The improvement in insulin sensitivity further normalizes lipid metabolism.

Metformin in Combination Therapy

While metformin monotherapy provides significant benefits, combination therapy with other agents often yields superior outcomes. The combination of metformin with clomiphene citrate or letrozole enhances ovulation rates and pregnancy outcomes in infertile women. When combined with lifestyle interventions such as diet and exercise, metformin amplifies weight loss and metabolic improvement.(Abdalla et al., 2022)

Recent studies have explored metformin's combination with oral contraceptives, anti-androgens, and GLP-1 receptor agonists. In combination with oral contraceptives, metformin helps mitigate the adverse metabolic effects of estrogen-progestin therapy. Pairing metformin with GLP-1 agonists produces synergistic effects on weight loss, insulin sensitivity, and ovulatory function, representing an emerging area of interest in PCOS treatment optimization.(Nowak et al., 2024)

Safety and Tolerability of Metformin

Metformin is generally safe and well tolerated. Gastrointestinal side effects, including nausea, diarrhea, and abdominal discomfort, are the most common and usually transient. These can be minimized by initiating therapy with a low dose (e.g., 500 mg once daily) and gradually increasing to the target dose of 1500–2000 mg per day or by using extended-release formulations.(Meng & Zhu, 2021)

Metformin should be used cautiously in patients with renal impairment, hepatic dysfunction, or conditions predisposing to hypoxia. Regular monitoring of renal function is advised. The incidence of lactic acidosis is extremely low in the absence of contraindications. Long-term use may be associated with reduced vitamin B12 levels, warranting periodic assessment and supplementation when necessary.(Yen et al., 2021)

Limitations of Metformin Therapy

Despite its wide utility, metformin is not a universal solution for PCOS. Its efficacy varies among individuals depending on the degree of insulin resistance and metabolic dysfunction. Some women may not achieve adequate ovulatory response with metformin alone and may require additional ovulation-inducing agents. Moreover, metformin's effects on weight reduction are modest compared to newer pharmacological agents targeting obesity.(Saadati et al., 2025). There is also variability in treatment response related to genetic factors and ethnicity. Long-term adherence may be affected by gastrointestinal side effects, and discontinuation can lead to relapse of symptoms. Thus, metformin should be considered part of a multifaceted management plan rather than a standalone therapy.(Miao & Zhou, 2022)

Conclusion

Visceral adipose tissue plays a central role in the development and progression of polycystic ovary syndrome. Through its effects on insulin resistance, inflammation, adipokine secretion, and steroid metabolism, VAT acts as a metabolic hub that links obesity to reproductive dysfunction. The disproportionate accumulation of visceral fat in women with PCOS not only exacerbates hyperandrogenism and anovulation but also increases long-term cardiometabolic risks. (Lemaitre et al., 2023)

Recognizing the importance of visceral adiposity in PCOS underscores the need for comprehensive management approaches that extend beyond symptom control to address underlying metabolic derangements. Lifestyle modification, pharmacologic therapy, and novel interventions targeting adipose tissue biology represent key components of an integrated therapeutic strategy. Continued research into the molecular mechanisms of visceral fat dysfunction will be crucial for developing more effective and individualized treatments for women suffering from PCOS. (Bril et al., 2024).

Berberine represents a promising natural therapeutic option for the management of Polycystic Ovary Syndrome. Through multifaceted mechanisms—including the activation of AMPK, improvement of insulin sensitivity, reduction of androgen excess, regulation of lipid metabolism, and attenuation of inflammation—berberine addresses both the metabolic and reproductive aspects of PCOS. Clinical studies have demonstrated

its efficacy in improving hormonal balance, ovulatory function, and metabolic parameters, often with comparable or superior outcomes to metformin. (Ionescu et al., 2023)

Its favorable safety profile and additional lipid-lowering and anti-inflammatory effects make it an attractive alternative or adjunct to conventional pharmacotherapy. Nevertheless, further large-scale, long-term studies are needed to confirm its efficacy, standardize dosing regimens, and evaluate its impact on fertility and metabolic outcomes. In conclusion, berberine offers a natural, well-tolerated, and mechanistically comprehensive approach to managing PCOS, bridging the gap between traditional herbal medicine and modern evidence-based therapy. (Jurgiel et al., 2024).

Metformin remains a cornerstone in the management of polycystic ovary syndrome due to its multifaceted effects on metabolism, reproduction, and endocrine function. By improving insulin sensitivity, reducing hyperinsulinemia, and mitigating hyperandrogenism, metformin addresses the root metabolic disturbances underlying PCOS. It restores ovulatory cycles, improves fertility outcomes, enhances metabolic health, and reduces long-term cardiovascular risk. (Huang et al., 2023)

Although not universally effective in all phenotypes, metformin's favorable safety profile, affordability, and pleiotropic benefits make it an indispensable therapeutic option. Optimal management of PCOS requires an individualized, multidisciplinary approach integrating lifestyle modification, pharmacologic therapy, and regular follow-up. As new research continues to uncover additional mechanisms and potential synergistic therapies, metformin's role in PCOS will remain central to bridging reproductive and metabolic medicine. (Yen et al., 2021).

References

1. **Abdalla, M. A., Shah, N., Deshmukh, H., Sahebkar, A., Östlundh, L., Al-Rifai, R. H., Atkin, S. L., & Sathyapalan, T. (2022).** Impact of metformin on the clinical and metabolic parameters of women with polycystic ovary syndrome: a systematic review and meta-analysis of randomised controlled trials. *Therapeutic Advances in Endocrinology and Metabolism*, 13, 20420188221127144.
2. **Bai, X., Ma, J., Wu, X., Qiu, L., Huang, R., Zhang, H., Huang, H., & Chen, X. (2023).** Impact of visceral obesity on structural and functional alterations of gut microbiota in polycystic ovary syndrome (PCOS): a pilot study using metagenomic analysis. *Diabetes, Metabolic Syndrome and Obesity*, 1–14.
3. **Başar Gökçen, B., Akdevelioğlu, Y., Canan, S., & Bozkurt, N. (2021).** Evaluation of the relationship between serum ferritin and insulin resistance and visceral adiposity index (VAI) in women with polycystic ovary syndrome. *Eating and Weight Disorders-Studies on Anorexia, Bulimia and Obesity*, 26(5), 1581–1593.
4. **Bril, F., Ezech, U., Amiri, M., Hatoum, S., Pace, L., Chen, Y.-H., Bertrand, F., Gower, B., & Azziz, R. (2024).** Adipose tissue dysfunction in polycystic ovary syndrome. *The Journal of Clinical Endocrinology & Metabolism*, 109(1), 10–24.
5. **de Medeiros, S. F., de Medeiros, M. A. S., Barbosa, B. B., & Yamamoto, M. M. W. (2021).** The role of visceral adiposity index as predictor of metabolic syndrome in obese and nonobese women with polycystic ovary syndrome. *Metabolic Syndrome and Related Disorders*, 19(1), 18–25.
6. **Dong, H., Zhao, Y., Zhao, L., & Lu, F. (2013).** The Effects of Berberine on Blood Lipids: A Systemic Review and Meta-Analysis of Randomized Controlled Trials. *Planta Medica*, 79, 437–446. <https://doi.org/10.1055/s-0032-1328321>
7. **Feng, Y., Li, M., Li, X., Tang, Q., Li, X., Ji, X., ... & Zhang, H. (2024).** Characteristics of different obesity metabolic indexes and their correlation with insulin resistance in patients with polycystic ovary syndrome. *Reproductive Sciences*, 31(9), 2829–2835.
8. **Hurayb, N. H., Alshammari, G. M., Al-Khalifa, A. S., Alafif, N., Aljaroudi, D. H., Mohammed, M. A., Yagoub, A. E. A., & Yahya, M. A. (2024).** A Comparative Study of Food Intake and Adipose Tissue Distribution in Saudi Women with Polycystic Ovarian Syndrome. *Healthcare*, 12(3), 369.

9. **Ionescu, O. M., Frincu, F., Mehedintu, A., Plotogea, M., Cirstoiu, M., Petca, A., ... & Mehedintu, C. (2023).** Berberine—a promising therapeutic approach to polycystic ovary syndrome in infertile/pregnant women. *Life*, 13(1), 125.
10. **Jin, R., Chen, A., Ye, Y., Ren, Y., Lu, J., Xuan, F., & Zhou, W. (2024).** Effect of berberine combined with metformin on autophagy in polycystic ovary syndrome by regulating AMPK/AKT/mTOR pathway. *Molecular Reproduction and Development*, 91(8), e23768.
11. **Jurczewska, J., Ostrowska, J., Chelchowska, M., Panczyk, M., Rudnicka, E., Kucharski, M., Smolarczyk, R., & Szostak-Węgierek, D. (2023).** Abdominal obesity in women with polycystic ovary syndrome and its relationship with diet, physical activity and insulin resistance: a pilot study. *Nutrients*, 15(16), 3652.
12. **Jurgiel J., Graniak A., Opyd P., Zawodny T., Lis M., (2024).** The role of berberine in polycystic ovary syndrome — a summary of knowledge. *Ginekologia Polska* 95(4), 276–284.
13. **Kaluźna, M., Czapka-Matyasik, M., Bykowska-Derda, A., Moczko, J., Ruchala, M., & Ziemnicka, K. (2021).** Indirect predictors of visceral adipose tissue in women with polycystic ovary syndrome: a comparison of methods. *Nutrients*, 13(8), 2494.
14. **Lemaitre, M., Christin-Maitre, S., & Kerlan, V. (2023).** Polycystic ovary syndrome and adipose tissue. *Annales d'endocrinologie*, 84(2), 308–315.
15. **Levate, G., Wang, Y., McCredie, R., Fenwick, M., Rae, M. T., Duncan, W. C., & Siemienowicz, K. J. (2025).** Insights into the effects of sex and tissue location on the evolution of adipocyte dysfunction in an ovine model of polycystic ovary syndrome (PCOS). *Molecular and Cellular Endocrinology*, 595, 112416.
16. **Lonardo, M. S., Cacciapuoti, N., Guida, B., Di Lorenzo, M., Chiurazzi, M., Damiano, S., & Menale, C. (2024).** Hypothalamic-ovarian axis and adiposity relationship in polycystic ovary syndrome: physiopathology and therapeutic options for the management of metabolic and inflammatory aspects. *Current Obesity Reports*, 13(1), 51–70.
17. **Melin, J., Forslund, M., Alesi, S., Piltonen, T., Romualdi, D., Spritzer, P. M., Tay, C. T., Pena, A., Witchel, S. F., & Mousa, A. (2024).** Metformin and combined oral contraceptive pills in the management of polycystic ovary syndrome: a systematic review and meta-analysis. *The Journal of Clinical Endocrinology & Metabolism*, 109(2), e817–e836.
18. **Melin, J., Forslund, M., Alesi, S., Piltonen, T., Romualdi, D., Spritzer, P. M., Tay, C. T., Pena, A., Witchel, S. F., & Mousa, A. (2023).** The impact of metformin with or without lifestyle modification versus placebo on polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. *European Journal of Endocrinology*, 189(2), S38–S64.
19. **Mellott, E. N., Sharon, E., & Hensley, T. (2018).** Efficacy of metformin use to induce ovulation in women with polycystic ovarian syndrome. *Obstet Gynecol Int J*, 9(6), 465–469. Mishra, N., Verma, R., & Jadaun, P. (2022). Study on the Effect of Berberine, Myoinositol, and Metformin in Women with Polycystic Ovary Syndrome: A Prospective Randomised Study. *Cureus*, 14(1), e21781. <https://doi.org/10.7759/cureus.21781>
20. **Meng, J., & Zhu, Y. (2021).** Efficacy of simvastatin plus metformin for polycystic ovary syndrome: A meta-analysis of randomized controlled trials. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 257, 19–24.
21. **Miao, K., & Zhou, H. (2022).** Effect of statins combined or not combined with metformin on polycystic ovary syndrome: A systematic review and meta-analysis. *Journal of Obstetrics and Gynaecology Research*, 48(7), 1806–1815.
22. **Mičić, B., Teofilović, A., Djordjevic, A., Veličković, N., Macut, D., & Vojnović Milutinović, D. (2022).** AMPK activation is important for the preservation of insulin sensitivity in visceral, but not in subcutaneous adipose tissue of postnatally overfed rat model of polycystic ovary syndrome. *International Journal of Molecular Sciences*, 23(16), 8942.
23. **Mirzaee, F., Razmjouei, P., Shahrahmani, H., Vafisani, F., Najaf Najafi, M., & Ghazanfarpour, M. (2021).** The effect and safety of Berberine on polycystic ovary syndrome: A systematic review. *Journal of Obstetrics and Gynaecology*, 41(5), 684–689.

24. **Mishra, N., Verma, R., & Jadaun, P. (2022).** Study on the effect of berberine, myoinositol, and metformin in women with polycystic ovary syndrome: a prospective randomised study. *Cureus*, 14(1).
25. **Nowak, K., Olejarz, Z., Drygala, Z., Wyrwał, J., Zielińska, Z., Slowik, M., Nieć, M., Gierlach, K., & Krasuska, M. (2024).** Role of metformin in polycystic ovary syndrome. *Journal of Education, Health and Sport*, 52, 131–144.
26. **Ochyra, Ł., Łopuszyńska, A., Pawlicki, M., & Piecewicz-Szczęsna, H. (2022).** Berberine in the treatment of polycystic ovary syndrome. *Journal of Education, Health and Sport*, 12(4), 309–314.
27. **Prabhu, Y. D., Borthakur, A., Vellingiri, B., & Gopalakrishnan, A. V. (2021).** Increased pro-inflammatory cytokines in ovary and effect of γ -linolenic acid on adipose tissue inflammation in a polycystic ovary syndrome model. *Journal of Reproductive Immunology*, 146, 103345.
28. **Rondanelli, M., Riva, A., Petrangolini, G., Allegrini, P., Giacosa, A., Fazia, T., Bernardinelli, L., Gasparri, C., Peroni, G., & Perna, S. (2021).** Berberine Phospholipid Is an Effective Insulin Sensitizer and Improves Metabolic and Hormonal Disorders in Women with Polycystic Ovary Syndrome: A One-Group Pretest–Post-Test Explanatory Study. *Nutrients*, 13(10), 3665. <https://www.mdpi.com/2072-6643/13/10/3665>
29. **Rondanelli, M., Riva, A., Petrangolini, G., Allegrini, P., Giacosa, A., Fazia, T., ... & Perna, S. (2021).** Berberine Phospholipid Is an Effective Insulin Sensitizer and Improves Metabolic and Hormonal Disorders in Women with Polycystic Ovary Syndrome: A One-Group Pretest-Post-Test Explanatory Study. *Nutrients*, 13, Article No. 3665.
30. **Shamim, H., Jean, M., Umair, M., Muddaloor, P., Farinango, M., Ansary, A., Dakka, A., Nazir, Z., White, C. T., & Habbal, A. B. (2022).** Role of metformin in the management of polycystic ovarian syndrome-associated acne: a systematic review. *Cureus*, 14(8).
31. **Usulkar, S., Sutar, K. P., Biradar, P., Patil, V., & Jadhav, V. (2024).** Innovative berberine nanoethosomal vaginal in situ gel: Unraveling polycystic ovary syndrome treatment on female Wistar rats. *International Journal of Pharmaceutics*, 663, 124564.
32. **Wang, Z., Nie, K., Su, H., Tang, Y., Wang, H., Xu, X., & Dong, H. (2021).** Berberine improves ovulation and endometrial receptivity in polycystic ovary syndrome. *Phytomedicine*, 91, 153654. <https://doi.org/https://doi.org/10.1016/j.phymed.2021.153654>
33. **Xing, C., Zhao, H., Zhang, J., & He, B. (2022).** Effect of metformin versus metformin plus liraglutide on gonadal and metabolic profiles in overweight patients with polycystic ovary syndrome. *Frontiers in Endocrinology*, 13, 945609.
34. **Yen, H., Chang, Y.-T., Yee, F.-J., & Huang, Y.-C. (2021).** Metformin therapy for acne in patients with polycystic ovary syndrome: a systematic review and meta-analysis. *American Journal of Clinical Dermatology*, 22(1), 11–23.