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REVIEW

Glycolytic Dysfunction in Granulosa Cells and Its Contribution to Metabolic Dysfunction in Polycystic Ovary Syndrome

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Abstract: Polycystic ovary syndrome (PCOS) is a common endocrine-metabolic disorder in women of reproductive age, marked by hyperandrogenism, ovulatory dysfunction, and insulin resistance, accompanied by significant metabolic disturbances, including glycolytic dysfunction, mitochondrial impairment, and increased oxidative stress. In granulosa cells (GCs), disrupted glycolysis impairs follicular development and compromises oocyte quality, exacerbating reproductive and metabolic abnormalities. At the molecular level, dysregulated energy-sensing pathways, such as AMPK and mTOR, reduce glucose uptake, lower ATP generation, and enhance oxidative stress, fueling disease progression. Epigenetic changes and non-coding RNAs further modulate glycolytic enzyme expression, destabilizing metabolic homeostasis within ovarian follicles. Therapeutically, restoring glycolytic balance using agents like metformin, resveratrol, mogroside V, and nicotinamide mononucleotide (NMN) has shown promise in improving glycolysis, insulin sensitivity, and ovarian function in various models. This review synthesizes current evidence on glycolysis's critical role in PCOS pathophysiology, its influence on follicular energetics and oocyte quality, and highlights metabolic targets for future therapies, offering a foundation for novel mechanism-driven interventions in PCOS management.

Keywords: polycystic ovary syndrome, glycolysis, metabolic dysfunction, insulin resistance, granulosa cells, oxidative stress, metabolic therapy

Introduction

Polycystic Ovary Syndrome (PCOS) is a prevalent endocrine-metabolic disorder that primarily affects women of reproductive age, characterized by menstrual irregularities, ovulatory dysfunction, and hyperandrogenemia. According to the Rotterdam criteria, the diagnosis of PCOS relies on meeting at least two of the following three criteria: polycystic ovarian morphology, ovulatory dysfunction, and clinical or biochemical hyperandrogenism.[1,2] Epidemiological studies indicate that the prevalence of PCOS varies among different populations, with a global incidence ranging from approximately 5% to 10%, predominantly affecting women aged 20 to 35 years.[3] The distribution of PCOS exhibits certain disparities across ethnicities and geographical regions, suggesting that both genetic and environmental factors play a crucial role in its pathogenesis.[3,4]

PCOS not only impacts female reproductive health, leading to infertility and ovarian cyst formation, but is also closely associated with various endocrine disorders. Patients frequently present with elevated androgen levels, abnormal estrogen metabolism, and insulin resistance, manifesting as hirsutism, acne, and adipose tissue deposition.[2,5] Additionally, PCOS significantly increases the risk of developing type 2 diabetes, cardiovascular diseases, and metabolic syndrome.[5,6] These endocrine disturbances impose a substantial physiological burden, exacerbating lipid metabolism dysfunction and impairing blood pressure regulation, thereby elevating cardiovascular risk.[2,5] Moreover, PCOS may contribute to osteoporosis due to its complex interactions within the endocrine system, further complicating disease management and increasing long-term health risks.[5,6]

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Among the pathological mechanisms of PCOS, energy metabolism dysfunction is considered a key characteristic. Glycolysis, a fundamental pathway for cellular energy production, plays a critical role in PCOS pathogenesis.[1,2] This metabolic process converts glucose into pyruvate, generating a limited amount of ATP to meet immediate cellular energy demands.[5,7] Also, evidence shows that mitochondrial bioenergetics are compromised in PCOS ovaries: granulosa-cell mitochondria display a lower membrane potential, diminished oxidative-phosphorylation capacity, and excessive reactive-oxygen-species production.[6,7] This defective mitochondrial state short-circuits ATP output, feeds back to restrain glycolytic flux, and activates redox-sensitive pathways that aggravate insulin resistance and hyper-androgenism, thereby amplifying the metabolic and reproductive derangements characteristic of PCOS.[1,6] In summary, as a complex endocrine-metabolic disorder, the etiology and pathophysiology of PCOS involve multiple biological processes. A deeper understanding of the role of glycolysis and mitochondrial energy metabolism in PCOS is essential for elucidating its pathological mechanisms and developing novel therapeutic strategies.[2,5]

Clinical Manifestations of Polycystic Ovary Syndrome

PCOS is one of the most prevalent disorders among women of reproductive age, with a global prevalence reaching up to 15%.[8] PCOS is a hormonal disorder that manifests through a variety of symptoms, including hair loss, hirsutism (excessive hair growth), pelvic pain, infertility, and irregular menstrual cycles.[9,10] Additionally, it is frequently associated with symptoms such as overweight, fatigue, and acne, which are often linked to hormonal imbalances, particularly elevated testosterone levels. Many women with PCOS exhibit high androgen levels, contributing to hair thinning and acne.[9,11] These symptoms, along with irregular menstrual cycles and ovulatory dysfunction, serve as the clinical foundation for PCOS diagnosis.

In PCOS patients, ovarian structure and function undergo significant alterations. The ovaries often exhibit multiple small cysts, typically measuring 2–9 mm in diameter, which represent immature follicles that fail to undergo normal maturation and ovulation.[12,13] This leads to increased ovarian volume and a characteristic "string of pearls" appearance on ultrasound imaging.[14] Functionally, ovarian activity is disrupted by hormonal imbalances, particularly elevated androgen levels, which impair normal follicular development and ovulation. Disrupted folliculogenesis and anovulation contribute to the irregular menstrual cycles commonly observed in PCOS. Additionally, alterations in ovarian steroidogenesis and androgen levels further impact both ovarian morphology and function (Figure 1).

Moreover, PCOS is frequently associated with insulin resistance and obesity, which contribute to reproductive and metabolic abnormalities across the lifespan, leading to severe conditions such as anovulatory infertility and type 2 diabetes (T2D).[15,16] Despite decades of research, the precise etiology of PCOS remains unclear. Familial clustering suggests that genetic factors play a crucial role in its pathogenesis.[17,18] PCOS typically follows a non-Mendelian inheritance pattern, reflecting a complex genetic architecture similar to that of T2D and obesity, involving interactions between susceptibility genes and environmental factors.[19] Genome-wide association studies

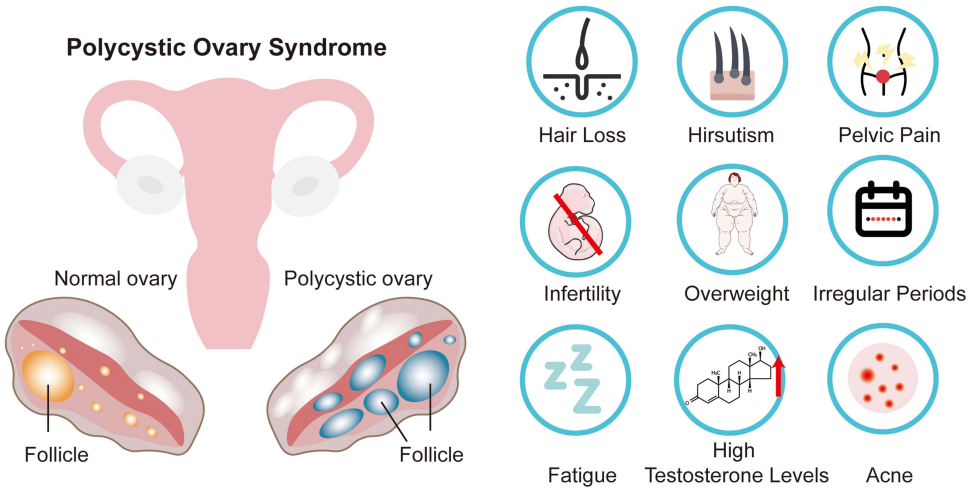

Figure 1 Ovarian changes and clinical symptoms in PCOS patients.

(GWAS) have identified 19 PCOS-associated genetic loci in East Asian and European populations, with 12 of these loci replicated across multiple studies. These loci include genes such as FSHB, LHCGR, FSHR, INSR, and DENND1A, which are involved in gonadotropin secretion, androgen biosynthesis, metabolic regulation, and follicular development.[19–24] Furthermore, genetic correlations between PCOS and various metabolic and reproductive traits, including body mass index (BMI), insulin levels, T2D, high-density lipoprotein (HDL) levels, triglyceride levels, depression, and age at menarche, have been reported.[23,25–29] These findings suggest that BMI and insulin resistance play causal roles in PCOS development, whereas PCOS itself does not directly increase the risk of T2D or cardiovascular diseases.[23,25,27,28,30]

Epigenetic studies have revealed alterations in DNA methylation and gene expression in ovarian granulosa cells, adipose tissue, and skeletal muscle of PCOS patients. These changes may be driven by a combination of genetic variants and environmental exposures.[31–36] Furthermore, PCOS is closely associated with glycolytic dysregulation in granulosa cells, characterized by reduced glucose uptake and utilization due to insulin resistance.[37] Altered expression of glucose transporters (GLUT) further restricts glucose availability,[38] while mitochondrial dysfunction leads to energy deficits and oxidative stress.[1] Transcriptomic sequencing of ovarian granulosa cells and follicular fluid-derived exosomes has revealed significant alterations in the expression of energy metabolism-related genes and non-coding RNAs, suggesting that ovarian cellular metabolism undergoes substantial changes in PCOS.[39]

Glycolysis

Glycolysis is one of the most fundamental and essential metabolic pathways in cells, responsible for converting glucose into pyruvate while generating a small amount of energy in the form of ATP. This process occurs in the cytoplasm and does not require oxygen, making it an anaerobic metabolic pathway. However, under aerobic conditions, glycolysis serves as the initial step in a broader aerobic metabolic network, linking the metabolism of carbohydrates, lipids, and proteins[40,41] (Figure 2).

Glycolysis consists of ten consecutive enzymatic reactions, which can be divided into the energy investment phase and the energy payoff phase. In the energy investment phase, glucose is first phosphorylated by hexokinase (HK) to form glucose-6-phosphate, which then undergoes isomerization to generate fructose-6-phosphate (F6P). Subsequently, phosphofructokinase-1 (PFK-1) catalyzes the conversion of F6P to fructose-1,6-bisphosphate (F1,6BP), a rate-limiting step in glycolysis.[42,43] During the energy payoff phase, F1,6BP is cleaved by aldolase into dihydroxyacetone phosphate and glyceraldehyde-3-phosphate (G3P). G3P then undergoes a series of reactions, leading to its oxidation into 1,3-bisphosphoglycerate (1,3-BPG), ultimately producing pyruvate along with ATP and NADH.[40,41]

The regulation of glycolysis is complex and diverse, primarily achieved through the modulation of enzyme activity. PFK-1, as a key regulatory point of glycolysis, is controlled by various metabolic factors. For instance, AMP and fructose-2,6-bisphosphate act as activators, enhancing PFK-1 activity, whereas ATP and citrate serve as inhibitors, suppressing its function.[42,44] Additionally, pyruvate kinase (PK) is another crucial regulatory enzyme in glycolysis, with its activity positively regulated by acetyl-CoA and F1,6BP, while ATP and pyruvate exert negative feedback inhibition.[41,45]

Beyond its critical role in energy metabolism, glycolysis also plays a significant role in biosynthesis and cellular signaling. The pyruvate produced can enter the mitochondria and participate in the tricarboxylic acid (TCA) cycle and oxidative phosphorylation to generate large amounts of ATP.[41,46] Moreover, glycolytic intermediates such as G3P and 1,3-BPG contribute to the biosynthesis of fatty acids and amino acids, meeting the cellular demand for metabolic precursors.[41,47] Although glycolysis operates under both aerobic and anaerobic conditions, its activity and regulatory mechanisms vary significantly among different cell types and physiological states. Particularly in ovarian granulosa cells and oocytes, glycolytic activity is crucial for oocyte development and maturation, highlighting its essential role in female reproductive physiology.[41,46]

Microenvironment of Polycystic Ovary Syndrome

The disease microenvironment in PCOS displays complex pathological features resulting from the combined effects of insulin resistance, metabolic abnormalities, and chronic low-grade inflammation. These pathological features not only intertwine but also influence each other through various signaling pathways and molecular mechanisms, creating an environment conducive to the onset and progression of PCOS.

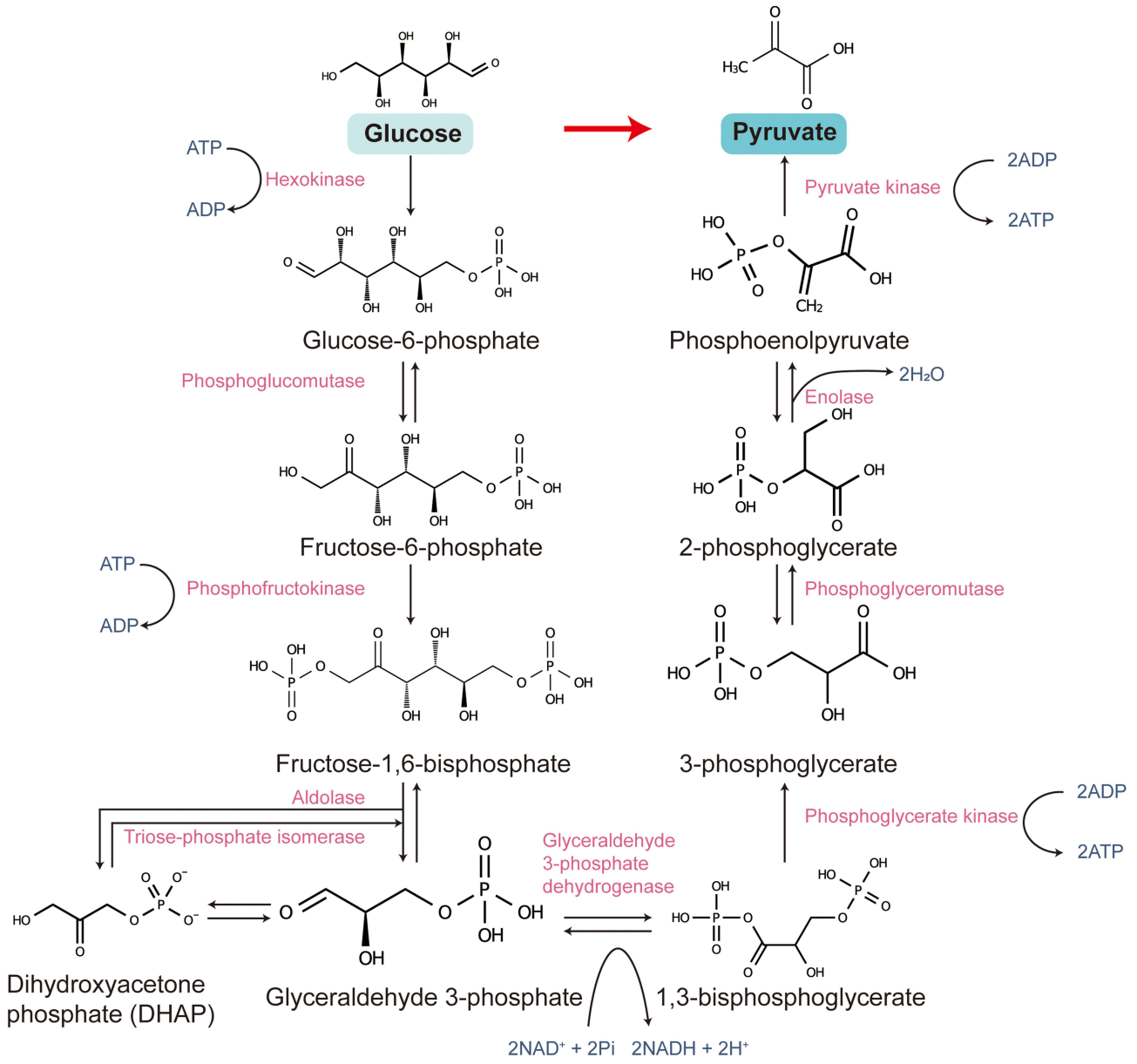

Figure 2 Biochemical pathway of glycolysis.

PCOS patients are often accompanied by hyperandrogenism and insulin resistance, which not only disrupt the hormonal balance within the ovaries but also directly affect the function of granulosa cells and the support provided to oocytes. Specifically, BMP15 and GDF9 secreted by oocytes normally activate the TGFβ signaling pathway, promoting granulosa cell proliferation, differentiation, and functional maintenance, thereby supporting oocyte maturation and normal follicular development.[48–50] However, in the PCOS microenvironment, the expression of these growth factors may be suppressed or dysfunctional, leading to increased granulosa cell apoptosis, which weakens their support for oocytes.[51] Additionally, the expression and function of gap junction proteins such as Cx43 in granulosa cells of PCOS follicles may be negatively regulated by elevated androgen levels. This not only weakens the nutrient and signaling exchange between oocytes and granulosa cells but also hinders normal metabolic processes and gene expression in oocytes, thus affecting their maturation.[52,53] Furthermore, the elevated androgen levels in the PCOS microenvironment may directly act on granulosa cells, altering their hormone secretion profile, increasing androgen secretion while suppressing estrogen synthesis, disrupting the hormonal balance within the follicle. This hormonal imbalance not only

suppresses the action of FSH but also interferes with the expression of FSH receptors, hindering the transformation of follicles from primordial to secondary and dominant stages.[54–56] Additionally, under insulin resistance, abnormalities in the insulin and IGF signaling pathways further affect granulosa cell proliferation and function, leading to impaired follicular development and reduced oocyte quality.[57,58]

In the follicular fluid (FF) of PCOS patients, the levels of inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNFα) are significantly elevated, while the levels of the anti-inflammatory cytokine interleukin-10 (IL-10) are reduced. This imbalance in inflammatory cytokines leads to the formation of a pro-inflammatory and immune-suppressive microenvironment within the follicle, which in turn affects follicular development and oocyte quality.[59–61] Among these, IL-6 not only plays a key role in the inflammatory response but also regulates cell proliferation and differentiation within the follicle. IL-1β, by activating the inflammasome, promotes the maturation and secretion of pro-inflammatory cytokines, further exacerbating the local inflammatory state. In addition, overexpression of TNFα can lead to increased cell apoptosis, inhibiting the expression of follicular development-related genes, ultimately affecting oocyte maturation and quality.[62,63] Moreover, inflammasomes and their products IL-1β and IL-18 are significantly elevated in the FF of PCOS patients, suggesting that inflammasomes may play an important role in the pathogenesis of PCOS.[62,63] Inflammasomes are intracellular multi-protein complexes that primarily promote the maturation and secretion of IL-1β and IL-18 through the activation of caspase-1, thereby enhancing the inflammatory response. In PCOS patients, excessive activation of inflammasomes may result in prolonged inflammation within the follicular microenvironment, further disrupting normal follicular development and oocyte maturation. Additionally, inflammasome activation may induce cell apoptosis and autophagy, further damaging the cellular structure and function within the follicle, leading to a decline in oocyte quality and limited embryonic developmental potential.[62,63] Therefore, the role of inflammasomes in PCOS is not limited to promoting the secretion of pro-inflammatory cytokines but also directly or indirectly affects follicular development and oocyte function through various pathways. This pro-inflammatory environment not only directly acts on oocytes but also affects the function of granulosa cells and surrounding support cells, leading to impaired follicular development and ovulation disorders.

Insulin resistance, as one of the core pathological features of PCOS, further exacerbates the disruption of inflammation. Elevated insulin levels not only promote androgen synthesis but also interfere with glucose metabolism pathways within the follicle, disrupting the energy supply and maturation process of oocytes.[64] Specifically, insulin resistance leads to hyperinsulinemia, and elevated insulin levels increase androgen production by promoting the expression of androgen synthesis enzymes in ovarian granulosa cells. These excess androgens not only directly affect follicular development but also activate downstream signaling pathways by binding to androgen receptors, further exacerbating metabolic and inflammatory disruptions. Furthermore, insulin resistance also activates inflammatory pathways, such as the NF-κB signaling pathway, further promoting the expression of pro-inflammatory cytokines and exacerbating the inflammatory state within the follicle.[63,65] NF-κB, as a key transcription factor, can lead to the overexpression of various pro-inflammatory genes with sustained activation, further enhancing local inflammation, creating a vicious cycle, and ultimately leading to abnormal follicular development and oocyte dysfunction.

In terms of metabolism, the levels of branched-chain amino acids (BCAAs), such as leucine, isoleucine, and valine, are significantly elevated in the FF of PCOS patients, which is closely related to insulin resistance, hyperandrogenism, and menstrual irregularities.[66] Moreover, glucose metabolism in PCOS patients is significantly affected, with reduced glucose levels in the FF and complex changes in lactate and pyruvate levels, reflecting impaired glycolysis and abnormal regulation of gluconeogenesis.[64,66] Specifically, glucose is the main energy source for both oocytes and granulosa cells, and pyruvate and lactate from glycolysis are crucial metabolic products for oocyte energy supply. However, in PCOS patients, due to insulin resistance and abnormal activation of the mTOR pathway, glycolysis is inhibited, leading to reduced glucose utilization efficiency, which subsequently affects the energy supply and maturation of oocytes. In addition, the abnormal regulation of gluconeogenesis may lead to an imbalance of intracellular glucose metabolites, further exacerbating metabolic stress and cellular dysfunction.[64,66] This metabolic disorder not only affects the energy supply of oocytes but also alters the balance of intracellular metabolic products, affecting cellular signaling and gene expression, ultimately leading to abnormal follicular development and a decline in oocyte quality. Furthermore, oxidative stress levels are significantly elevated in the FF of PCOS patients, as indicated by an increase in reactive oxygen species

(ROS) products such as malondialdehyde (MDA) and 8-oxodeoxyguanosine (8-OHdG), while the activities of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) are significantly reduced.[67,68] Oxidative stress is caused by excessive ROS generation and a decline in antioxidant defense system function, leading to an imbalance in the cellular redox state. In PCOS patients, excessive ROS not only directly damages the cellular structure and DNA of oocytes but also activates multiple signaling pathways, inducing cell apoptosis and autophagy, which further reduce oocyte survival and developmental potential. Additionally, oxidative stress is closely linked to inflammation, as ROS can act as signaling molecules to promote the expression of inflammatory cytokines and the recruitment of inflammatory cells, exacerbating the local inflammatory state.[69–71] Specifically, ROS promote the secretion of pro-inflammatory cytokines such as IL-6 and TNFα by activating NF-κB and other pro-inflammatory transcription factors, creating a vicious cycle of inflammation and oxidative stress that further disrupts the follicular microenvironment, leading to a decline in oocyte quality and impaired embryonic.

Abnormal Glycolysis in PCOS

During follicular development, the glycolytic activity in granulosa cells is crucial (Figure 3). The enhancement of glycolysis in granulosa cells can promote the activation of primordial follicles via the mTOR signaling pathway.[72]

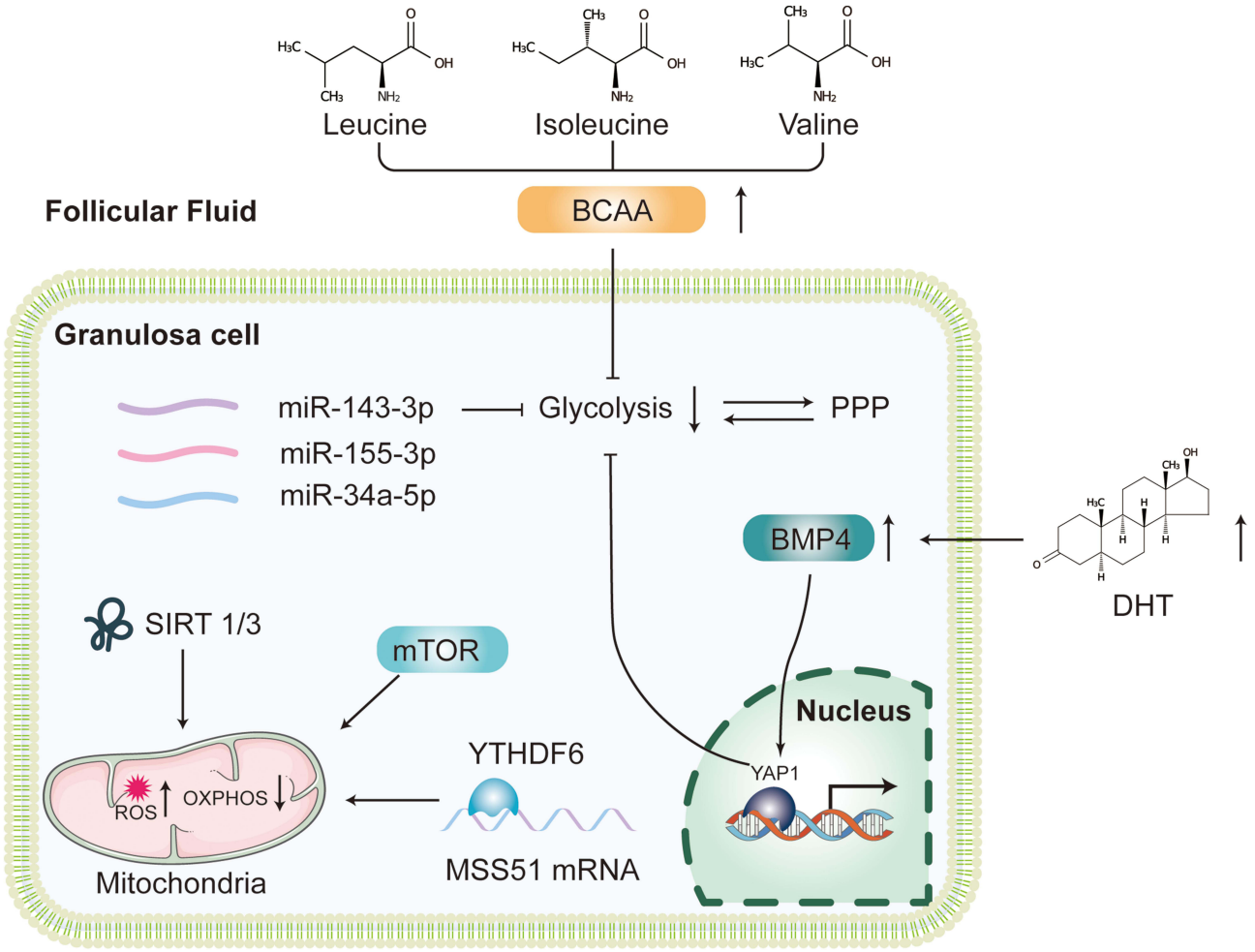

Figure 3 How the disruption of the ovarian microenvironment in PCOS patients affects the glycolytic activity of granulosa cells: Increased DHT levels in follicular fluid may affect the changes in BMP4 levels within granulosa cells, thereby influencing the transcriptional activity of YAP1 and inhibiting glycolytic activity. Fluctuations in BCAA levels significantly inhibit glycolytic activity and oxidative phosphorylation in granulosa cells, shifting towards the pentose phosphate pathway. Additionally, during PCOS, the reduced activity of the mTOR pathway, decreased levels of deacetylases SIRT1/3 in granulosa cells, and the binding of YTHDF6 with MSS51 mRNA significantly increase mitochondrial ROS accumulation and decrease oxidative phosphorylation levels. Furthermore, granulosa cell-derived (miR-143-3P, miR-155-3P) and exosome-derived (miR-34a-5p) miRNAs may epigenetically suppress the expression of glycolysis-related genes, thereby affecting glycolytic activity.

Correspondingly, during the transition of primordial follicles to primary follicles in mice, the levels of glycolysis-related proteins in granulosa cells, such as GLUT 4, HK 1, PFKL, and PKM 2, are significantly increased.[72] However, in granulosa cells (GCs) of PCOS patients, significant metabolic changes occur, with decreased mTOR pathway activity and reduced Akt phosphorylation levels.[72,73] Granulosa cells also show notable changes in mitochondrial morphology, quantity, and localization, accompanied by reduced membrane potential, decreased ATP synthesis, increased mitochondrial ROS and oxidative stress, insufficient oxidative phosphorylation (OXPHOS), and reduced glycolysis.[74]

Studies indicate that the low expression of HIF-1α and the reduction in glycolysis levels in granulosa cells may be important factors contributing to the lower oocyte quality in PCOS.[1] In vitro studies show that glycolytic activity in granulosa cells is time-dependently inhibited by DHT stimulation.[73]

Direct metabolic profiling of follicular fluid has shown that the levels of pyruvate and lactate are significantly decreased during the development of PCOS.[75] However, the exact reasons for the altered metabolic profile in granulosa cells of PCOS patients remain unclear. During the development of PCOS, the levels of branched-chain amino acids (BCAAs) in both plasma and follicular fluid are significantly elevated.[66,76,77] Studies on female mice with a Ppm1k deficiency have shown increased BCAA levels and PCOS-like characteristics, and these changes are linked to the conversion of glycolysis to the pentose phosphate pathway and the inhibition of mitochondrial oxidative phosphorylation (OXPHOS).[66]

In granulosa cells of PCOS patients, significant changes in acetylation levels are observed, mainly in the form of increased lysine acetylation modifications. These changes are associated with abnormal expression of acetyltransferases and deacetylases. Several sirtuin family proteins, including Sirt1-3, show significant alterations in expression during PCOS development, with SIRT3 expression being notably decreased.[74] As a mitochondrial-localized deacetylase, SIRT3 removes acetyl groups from mitochondrial proteins, regulating mitochondrial function and metabolic homeostasis. The downregulation of SIRT3 leads to reduced mitochondrial membrane potential, increased ROS levels, and decreased OXPHOS efficiency. These changes not only impair cellular energy production but also exacerbate oxidative stress, further inhibiting glycolytic activity.[74,78] Moreover, multiple studies have shown that manipulating Sirt2 in granulosa cells can effectively improve insulin resistance and activate glycolytic pathways, promoting lactate metabolism in granulosa cells.[79,80] This is consistent with earlier studies indicating that Sirt2 expression is related to glycolytic activity in cells. Inhibition of SIRT2 using small-molecule inhibitors like AGK2 significantly decreases lactate levels and increases pyruvate accumulation.[79,81]

Similarly, SIRT1 expression is significantly downregulated in PCOS, resulting in decreased expression of downstream genes like PGC1α and mtTFA, which impairs mitochondrial function and energy metabolism. The reduction in SIRT1 inhibits AMPK activity, further suppressing glycolysis and leading to insufficient energy supply and metabolic imbalance. These changes exacerbate oxidative stress and mitochondrial dysfunction, ultimately affecting granulosa cell survival and follicular development.[82,83] The expression of SIRT1 in granulosa cells may be influenced by advanced glycation end-products (AGEs), while the expression of ACAT1 (Acetyl-CoA Acetyltransferase 1) is significantly upregulated.[84] This upregulation is accompanied by significant changes in acetylation levels across glycolysis, fatty acid degradation, the TCA cycle, tryptophan metabolism, and BCAA degradation pathways, which correlate negatively with oocyte quality and embryo development efficiency.[84]

Transcriptome sequencing of granulosa cells and follicular fluid exosomes has revealed changes in the levels of various non-coding RNAs during the development of PCOS.[85,86] These changes may significantly impact the glycolytic activity in granulosa cells. While the roles of some non-coding RNAs in PCOS are still not fully understood,[87] studies have found that miR-143-3p and miR-155-5p exhibit differential expression in exosomes from granulosa cells of PCOS patients.[85,88] Specifically, the upregulation of miR-143-3p significantly inhibits glycolytic activity in granulosa cells by directly or indirectly targeting key enzymes in the glycolysis pathway, reducing the production of pyruvate and lactate. In contrast, silencing miR-155-5p weakens the activation of glycolysis, suggesting that miR-155-5p plays a positive role in promoting glycolysis.[85,88] Non-coding RNAs in follicular fluid exosomes may also play a communicative role in PCOS pathogenesis. Studies have shown that miR-34a-5p directly targets lactate dehydrogenase A, inhibiting glycolysis and promoting granulosa cell apoptosis,[88] thus affecting GC proliferation and follicular growth and development.

Additionally, studies suggest that the regulation of glycolytic activity in granulosa cells may be influenced by transcriptional and post-translational modifications. Bone Morphogenetic Protein 4 (BMP4) expression is significantly

upregulated in a high androgen environment.[89] BMP4 regulates glycolysis and autophagy pathways in granulosa cells by affecting the nuclear translocation of Yes-associated protein 1 (YAP1).[89] Furthermore, the expression of YTHDF2 (YTH N6-methyladenosine RNA binding protein 2) is significantly upregulated in granulosa cells of PCOS patients.[90] YTHDF2 regulates the stability and translation efficiency of MSS51 mRNA, leading to decreased MSS51 protein expression, which in turn affects the assembly and function of mitochondrial respiratory chain complexes and reduces the expression of glycolysis-related genes such as LDHA, PFKP, and PKM.[90]

Glycolytic Dysregulation and Metabolic Pathway Alterations in PCOS

AMPK Pathway

AMPK (AMP-activated protein kinase) plays a central role in regulating cellular energy balance, metabolism, proliferation, and apoptosis. Its role in PCOS (Polycystic Ovary Syndrome) has been widely studied, as it is a key enzyme that responds to the energy status of cells. Research indicates that AMPK activity is significantly reduced in PCOS patients, leading to metabolic imbalance, which in turn affects ovarian and uterine function.[91] In PCOS animal models, silencing AMPK exacerbated polycystic ovarian changes and disrupted ovulation.[91] AMPK regulates metabolism by sensing cellular energy levels, and its reduced activity leads to abnormal glycolysis in granulosa cells, disrupting cellular energy metabolism.

AMPK pathway dysfunction in PCOS is primarily linked to altered glycolytic activity, which impacts downstream signaling pathways such as mTOR and Akt. Specifically, the reduction in AMPK activity contributes to abnormal androgen levels, which further impairs follicular development.[92] Additionally, AMPK activity is suppressed by abnormal glucose metabolism and mitochondrial dysfunction, particularly in the ovaries and granulosa cells of PCOS patients.[74] AMPK also regulates autophagy through SIRT1, and disruption of AMPK signaling in PCOS can lead to autophagic dysfunction, further compromising ovarian function and fertility.[91,92] The relationship between AMPK and glycolysis in PCOS is central to metabolic disturbances, particularly in granulosa cells. Disruption of glycolysis and oxidative phosphorylation (OXPHOS) impairs AMPK signaling. Glycolysis, being a core metabolic pathway, directly influences ATP synthesis and energy status within the cell. AMPK, as an energy sensor, activates under energy stress to regulate metabolic pathways, including enhancing glycolysis and inhibiting fatty acid synthesis to restore energy balance.[92] However, in PCOS, changes in glycolysis hinder AMPK activation. When glycolysis is impaired, ATP levels decrease, activating AMPK. Yet, due to the continued suppression of glycolysis, AMPK's activity cannot be effectively restored, creating a vicious cycle that exacerbates metabolic dysfunction in PCOS.[92]

Conversely, increasing glycolysis may help improve metabolic abnormalities in PCOS by enhancing AMPK activation. Studies show that short-term pyruvate deprivation can increase glycolytic protein levels in mouse ovaries and activate the AMPK pathway, promoting the restoration of ovarian energy metabolism.[72] By enhancing glycolysis, AMPK activation can normalize energy balance and regulate downstream mTOR signaling to promote granulosa cell proliferation and follicular development.[72] Additionally, AMPK activation can increase the expression of glycolytic enzymes like LDHA and PKM2, further promoting glycolysis and correcting metabolic dysregulation in PCOS.[91]

mTOR Pathway

The mTOR (mechanistic target of rapamycin) pathway plays a significant role in the regulation of follicular development, and its relationship with glycolysis is particularly relevant during the transition of primordial follicles to primary follicles. Studies on mice have shown that glycolysis-related proteins such as GLUT4, HK1, PFKL, and PKM2 are significantly upregulated in granulosa cells during this process, indicating a positive correlation between glycolytic activity and mTOR signaling.[72] Acute fasting and pyruvate deprivation in vivo and in vitro increase glycolytic gene and protein expression in the ovaries, decrease AMPK activity, and enhance mTOR activation, which in turn leads to elevated phosphorylation of downstream proteins like Akt and FOXO3a, promoting primordial follicle activation.[72] Blocking glycolysis with 2-deoxyglucose significantly inhibits the mTOR pathway activation caused by pyruvate deprivation, while KIT inhibitor ISCK03 does not affect the communication between granulosa cells and oocytes, further reducing mTOR activity.[72] However, the relationship between PCOS and the mTOR pathway is complex and contradictory. For example, in the DHEA-induced PCOS mouse model, phosphorylation levels of mTOR (ser2448 and ser2481) in granulosa cells are significantly increased

compared to normal mice, suggesting activation of mTORC1/2. However, downstream kinase S6K1 expression is reduced.[93] Conversely, in granulosa cells during the luteal phase of PCOS patients, although basal mTOR protein levels are similar to those of healthy women, insulin stimulation leads to a marked decrease in mTOR expression,[94] along with downregulation of downstream kinase S6K1. This suggests that PCOS may be associated with reduced mTOR pathway activity in granulosa cells. Meanwhile, aberrant Akt/mTOR pathway regulation in PCOS granulosa cells affects their proliferation and apoptosis.[94] At the same time, studies have shown that short-term administration of the mTOR inhibitor rapamycin not only fails to protect DHEA-induced non-cyclical and PCO morphology, but also hinders DHEA-induced mouse follicle development and increased serum testosterone levels, which is related to the inhibition of Hsd3b1, Cyp17a1 and Cyp19a1 expression and the effect on mitochondrial function,[95] This also shows the complexity of the mTOR pathway in the pathogenesis of PCOS, so precise regulation may be crucial for the treatment of PCOS. Several studies have indicated that activation of the PI3K/Akt/mTOR pathway is crucial for ovarian function,[96] and inactivation of this pathway is linked to inhibited granulosa cell proliferation and increased apoptosis[97] Table 1.

Potential Strategies for Targeting Glycolysis in PCOS Treatment

Metformin, a classic drug for treating polycystic ovary syndrome (PCOS), has been widely used. Additionally, adolescent PCOS patients, especially those who are overweight or obese, often face a higher risk of metabolic syndrome.[98,99] The use of metformin (1700 mg/day for 6 months) in these patients can improve menstrual cycles and promote ovulation. Moreover, metformin can reduce patients' body mass index (BMI) and symptoms of hyperandrogenism, such as hirsutism and acne, while also lowering total testosterone, androstenedione, and free testosterone levels.[100,101] The regulatory effects of metformin on hormone and metabolic status in PCOS patients are closely related to improvements in ovulation, pregnancy rates, and hyperandrogenism symptoms.[102] The primary mechanism of action of metformin is the improvement of insulin resistance. It is believed that metformin improves ovulation and hormone changes by activating the AMPK/SIRT1 signaling pathway in the ovaries.[103] Dysfunction of the AMPK/SIRT1 signaling pathway in granulosa cells is associated with insulin resistance and hyperandrogenemia. By activating the AMPK/SIRT1 pathway, metformin

Table 1 Potential Drugs Targeting Glycolysis for the Treatment of PCOS

Drug	Glycolysis-Based Targets	Dose	Pharmacological Effect	Reference
Metformin	Activation of AMPK/SIRT1 signaling pathway, increased expression of LDH-A, PKM2, and SIRT1, inhibition of mTOR signaling pathway	1700 mg/day	Improvement of menstrual cycle, promotion of ovulation, reduction of body mass index (BMI) and hyperandrogenism symptoms, regulation of hormone levels, improvement of ovulation, pregnancy rate, and androgen symptoms	[100,101]
Resveratrol	Upregulation of LDHA, HK2, PKM2 expression, increase in lactate and ATP levels, suppressing pro-inflammatory cytokines	20 mg/kg/day	Improvement of menstrual cycle irregularities, reduction of hair loss, inhibition of serum testosterone levels, increase in adiponectin levels, regulation of ovarian function.	[109]
Mogroside V	Upregulation of LDHA, HK2, PKM2 expression, improvement of ovarian microenvironment	Not yet specified	Restoration of glycolysis and glucose metabolism, improvement of metabolic disorders, promotion of follicular development, reduction of ovarian apoptotic factors and inflammatory cytokine expression.	[110]
Nicotinamide mononucleotide(NMN)	Upregulation of LDHA expression, regulation of NAD+ synthesis	Not yet specified	Restoration of glycolytic processes, increased lactate production, improvement of ovarian function, promotion of follicular development, enhancement of fertility, regulation of NAD+ synthesis	[78,111]

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effectively regulates insulin resistance and improves hormonal status.[104,105] Furthermore, by activating AMPK, metformin inhibits the mTOR signaling pathway and reduces the expression of MMP-2 and MMP-9 in PCOS animal models.[106] Recent studies have also revealed that metformin improves the metabolic state and ovarian function of PCOS patients by activating the AMPK/SIRT1 signaling pathway and regulating the expression of glycolytic enzymes. Glycolysis is a crucial metabolic pathway in cellular energy metabolism, and its dysfunction plays a key role in the metabolic disturbances of PCOS.[80,83] Metformin can restore energy balance by activating AMPK, inhibit the mTOR signaling pathway, and repair the glycolytic dysfunction, improving the physiological state of the ovaries. Studies have shown that metformin significantly increases the expression of lactate dehydrogenase A (LDH-A), pyruvate kinase M2 (PKM2), and SIRT1 in the ovaries of PCOS rats.[80,83] LDH-A and PKM2 are key rate-limiting enzymes in the glycolytic pathway, and their increase not only promotes the glycolytic reaction but also improves the follicular development defects caused by abnormal glucose metabolism in PCOS patients.[80,83] Recent studies have shown that metformin, by activating the AMPK–SIRT2 axis, restores the expression of key glycolytic enzymes suppressed by insulin, thereby enhancing glycolytic flux in ovarian granulosa cells.[107] At the same time, metformin downregulates insulin-like growth factor 1 (IGF-1) and upregulates its receptor (IGF-1R), further ameliorating insulin resistance and hyperandrogenism to collectively correct the energy metabolic imbalance characteristic of polycystic ovary syndrome (PCOS).[107] Moreover, combination therapy of metformin with other agents has been reported to improve glycolytic activity and overall metabolic function in granulosa cells from PCOS models.[108] The therapeutic effects of metformin also manifest in its ability to inhibit the mTOR signaling pathway, reduce excessive energy accumulation in the ovaries, restore ovarian function, and improve follicle quality and fertility.[92] Through these mechanisms, metformin effectively alleviates the metabolic disturbances and ovarian dysfunction of PCOS, providing significant therapeutic benefits for PCOS patients. However, it is worth noting that, although metformin is generally well-tolerated in the treatment of PCOS and no serious adverse events or hepatic or renal dysfunction were observed during the clinical period, the most commonly reported side effects are short-term gastrointestinal disturbances—including nausea, bloating, and diarrhea—with roughly one quarter of adult participants experiencing these symptoms yet continuing the medication, and a small number of adolescents discontinuing treatment after gastrointestinal reactions persisted for more than two weeks.[100,101]

Resveratrol is a natural polyphenolic compound widely found in grape skins, berries, and peanuts. Its antioxidant and anti-inflammatory properties make it a potential treatment for PCOS. In rat experiments, resveratrol (20 mg/kg/day) combined with metformin (300 mg/kg/day) significantly reduced the levels of LH, LH/FSH ratio, TNF-α, and AMH in the ovaries of PCOS rats.[109] Additionally, resveratrol possesses anti-inflammatory, antioxidant, and anti-apoptotic properties. Several studies have shown that resveratrol can modulate the NF-κB pathway by inhibiting IκB kinase activity,[112] suppressing pro-inflammatory cytokines.[113,114] Clinical studies have demonstrated that resveratrol can improve menstrual cycle irregularities in PCOS and reduce hair loss in PCOS patients.[115] In combination with myo-inositol (1000 mg twice daily for 12 weeks), resveratrol significantly reduced serum testosterone levels, increased adiponectin levels, and resulted in a decrease in serum LH and FSH levels as well as ovarian volume.[116] From the perspective of glycolysis, resveratrol can restore the glycolytic process by upregulating the expression of key enzymes (such as LDHA, HK2, and PKM2), significantly increasing lactate and ATP levels, and thus improving cellular energy metabolism.[80] The mechanism of action of resveratrol primarily involves activating the AMPK/SIRT2 signaling pathway, promoting normal glucose metabolism. AMPK is a key kinase for cellular energy sensing, and its activation helps regulate metabolic balance within cells, restoring ovarian dysfunction caused by glucose metabolism disorders in PCOS patients.[80] In PCOS rat models, resveratrol significantly improved insulin resistance and regulated the expression of glycolytic enzymes by enhancing AMPK activity, suggesting its potential in the treatment of PCOS.[80] These studies suggest that resveratrol, as a natural glycolysis regulator, can alleviate metabolic disturbances in PCOS and may improve ovarian function and fertility. However, clinical studies indicate that resveratrol's teratogenicity remains controversial, often leading to an increased abortion rate in assisted reproduction.[117] Clinical studies have shown that, although combination therapy with resveratrol does not present obvious side effects and is generally well tolerated, a double-blind trial demonstrated an increase in fat mass and a decrease in lean body mass after 3 months ($p = 0.03$ and 0.004),[116] and previous research indicates that high-dose resveratrol treatment may be associated with elevated TSH levels and an increased risk of thyroid enlargement.[118]

Mogroside V (MV) is a natural compound extracted from the fruit of Siraitia grosvenorii, known for its antioxidant and anti-inflammatory properties, making it a promising drug for the treatment of PCOS. MV regulates the glycolytic pathway to protect ovarian function in PCOS rats. Studies have shown that after MV treatment in PCOS rats, the levels of D-glucose-6-phosphate, lactate, and GTP were significantly increased, while pyruvate levels were reduced, indicating that MV can improve metabolic disturbances in PCOS patients by restoring glycolysis and glucose metabolism.[110] Glycolysis is one of the important pathways for cellular energy production, and a normal glycolytic process can effectively provide ATP for cellular metabolism, improving cellular energy supply. In PCOS patients, the ovaries often exhibit glycolytic insufficiency, which leads to impaired follicular development.[72] MV enhances the expression of rate-limiting enzymes in glycolysis, such as LDHA, hexokinase 2 (HK2), and PKM2, increasing lactate and ATP production, thereby improving the ovarian microenvironment, promoting follicular development and ovulation.[110] These effects suggest that MV can not only improve ovarian function by regulating the glycolytic pathway but also support follicular development by providing energy, and it may reduce the expression of ovarian stress factors (NLRP3, Caspase-1, GSDMD) and inflammatory cytokines (IL-1β, IL-18), thereby lowering insulin resistance and apoptotic markers.[119] However, the clinical research on MV for the treatment of PCOS is still lacking.

Nicotinamide mononucleotide (NMN) is a precursor molecule that can regulate cellular energy metabolism by supplementing NAD+. NAD+ is an important coenzyme in cellular metabolism, involved in glycolysis, oxidative phosphorylation, and many other metabolic pathways. The levels of NAD+ and the NAD+/NADH ratio in granulosa cells (GC) decrease in response to LPS-induced PCOS, while NMN can mitigate LPS-induced GC inflammation. NMN supplementation restores NAD+ levels in GCs and significantly reduces the expression of pro-inflammatory markers at both mRNA and protein levels, downregulates pro-apoptotic markers such as Caspase-3, Caspase-9, and Bax, and upregulates anti-apoptotic markers like Bcl-2 to reduce GC apoptosis.[120] Moreover, NMN intervention can alleviate hyperandrogenemia, ovarian abnormalities, and bile acid reduction.[111] Studies have shown that NMN can restore the glycolytic pathway in granulosa cells, promote follicular development, and improve fertility.[78] NMN activates the glycolytic process in the ovaries, increasing lactate production and enhancing LDHA expression, improving ovarian function in PCOS rats.[78] Normalizing the glycolytic pathway provides sufficient energy to support follicular development and maturation, thus improving fertility in PCOS patients. NMN also enhances the NAD+ synthesis pathway, improving cellular energy metabolism and promoting normal ovarian function.[78] These studies suggest that NMN has potential in the treatment of PCOS, especially in improving ovarian function and follicular development. Meanwhile, research indicates that NMN supplementation may address the decline in NAD+ levels associated with PCOS in skeletal muscle, normalizing insulin sensitivity and preventing compensatory hyperinsulinemia associated with obesity and hepatic lipid deposition.[121] However, clinical studies on NMN for PCOS treatment are still lacking.

Conclusion

PCOS remains a complex endocrine disorder with a multifaceted pathophysiology, involving reproductive and metabolic dysfunctions. Among the key features of PCOS, the aberrant regulation of energy metabolism, particularly glycolysis, plays a pivotal role in the disease's progression. Glycolysis, a fundamental metabolic pathway responsible for converting glucose into pyruvate while generating ATP, is crucial for ovarian cell function and follicular development. In PCOS, the glycolytic pathway is disrupted, leading to reduced glucose utilization, altered mitochondrial function, and compromised energy supply in granulosa cells and oocytes, which are vital for follicular growth and oocyte maturation. These metabolic disturbances contribute to the hallmark features of PCOS, including insulin resistance, hyperandrogenism, and impaired ovarian function. As such, glycolytic dysregulation is a central feature of PCOS pathogenesis and a potential therapeutic target.

Recent research has underscored the significance of glycolysis in PCOS, particularly in granulosa cells, where changes in the expression of key enzymes like HK2, LDHA, and PKM2 can impact cellular energy metabolism. These enzymes are critical for the proper functioning of glycolysis and its relationship with mitochondrial function. A marked reduction in glycolytic activity, often due to altered signaling pathways like AMPK, mTOR, and insulin signaling, results in decreased ATP production, contributing to follicular dysfunction and impaired oocyte quality. In particular, the interaction between glycolysis and AMPK activation is crucial for maintaining metabolic homeostasis in ovarian cells. Reduced AMPK activity, commonly observed in PCOS, disrupts glycolysis and further exacerbates the metabolic abnormalities associated with the syndrome.

Given the critical role of glycolysis in PCOS pathophysiology, therapeutic interventions targeting metabolic pathways offer promising treatment strategies. Drugs that modulate glycolytic activity and improve cellular energy balance may provide significant benefits to PCOS patients. Metformin, a widely used drug for managing insulin resistance in PCOS, has shown efficacy in improving metabolic profiles and restoring ovarian function. By activating AMPK and regulating glycolysis-related enzymes, metformin enhances energy metabolism, reduces hyperandrogenism, and improves follicular development, thereby addressing both the metabolic and reproductive aspects of PCOS. Moreover, natural compounds like resveratrol, which modulate glycolysis via AMPK and SIRT1 pathways, have also demonstrated potential in improving metabolic dysfunction in PCOS. These treatments highlight the therapeutic potential of targeting glycolytic pathways and energy metabolism to ameliorate the symptoms and underlying causes of PCOS.

Other emerging therapies, such as NMN (Nicotinamide Mononucleotide), have shown promise in restoring NAD+ levels and improving energy metabolism in granulosa cells. NMN supplementation has been demonstrated to enhance glycolysis and mitochondrial function, offering a novel approach for addressing the metabolic dysregulation in PCOS. Similarly, natural compounds like Mogroside V (MV), which have antioxidant and anti-inflammatory properties, can improve glycolytic activity and metabolic homeostasis in the ovaries, potentially improving ovulatory function and fertility outcomes in PCOS patients. Despite these promising therapeutic options, much remains to be understood regarding the precise mechanisms linking glycolysis to PCOS and how these metabolic alterations can be effectively targeted for therapeutic intervention. Future research should focus on further elucidating the molecular pathways that regulate glycolysis and energy metabolism in PCOS. In particular, the role of non-coding RNAs, epigenetic modifications, and metabolic enzymes in the pathogenesis of PCOS warrants further investigation. Additionally, clinical trials are needed to validate the therapeutic potential of drugs and natural compounds that target glycolysis and energy metabolism in improving the reproductive and metabolic health of PCOS patients.

In conclusion, glycolysis is central to the pathophysiology of PCOS, and understanding its regulation and dysfunction in ovarian cells could provide key insights into novel therapeutic approaches. As research continues to unfold, targeted metabolic therapies, including those focused on enhancing glycolytic pathways, may offer new hope for patients with PCOS, particularly in addressing the complex interplay between metabolic and reproductive dysfunctions that define this disorder.

Data Sharing Statement

The current study was based on the results of relevant published studies.

Author Contributions

Zhenzhen Cao contributed to the study conception and manuscript drafting. Qin Zhou assisted in data interpretation and critical revision. Jie An participated in data collection and manuscript editing. Xiaojing Guo contributed to reference management and formatting. Yuena Qiu assisted in data acquisition. XiaoFang Jia supervised the study and finalized the manuscript. All authors made a significant contribution to the work reported, took part in drafting, revising, or critically reviewing the article; 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

The authors declared that they have no competing interests in this work.

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