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Review

Breaking the Metabolic–Inflammatory Vicious Cycle in Polycystic Ovary Syndrome: A Comparative Review of Ketogenic and High-Fat Diets

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Abstract: Polycystic ovary syndrome (PCOS) is a multifactorial metabolic–endocrine disorder in women of reproductive age in which lipid metabolism disorders and chronic low-grade inflammation reinforce and amplify each other. Recently, the ketogenic diet (KD), which is a high-fat, very-low-carbohydrate dietary intervention, has drawn attention because of its metabolic regulation and anti-inflammatory properties. This review integrates current evidence to elucidate how aberrant fatty acid turnover, adipose tissue dysfunction, and adipokine imbalance trigger convergent proinflammatory pathways, thus forming an "inflammatory hub" that links insulin resistance, hyperandrogenemia, impaired folliculogenesis, and heightened cardiovascular risk in PCOS. We then delineate how strict carbohydrate restriction promotes fatty acid β-oxidation

and hepatic ketogenesis, thereby reprogramming cellular metabolism. The principal ketone body, β-hydroxybutyrate, directly suppresses the nucleotide-binding oligomerization domain–like receptor family pyrin domain containing 3 inflammasome, remodels the gut microbiota, and attenuates nuclear factor kappa-light-chain-enhancer of activated B cells signaling, thus yielding multitarget anti-inflammatory effects. Unlike isocaloric high-fat diets, which lead to obesity, inflammation, and insulin resistance, the KD lowers triacylglycerols and the proportion of small, dense low-density lipoprotein particles; enhances whole-body insulin sensitivity; and mitigates systemic inflammation. Collectively, the KD offers a multidimensional intervention that couples metabolic correction with immune modulation and holds promise for improving PCOS trajectories and long-term complications. Nevertheless, its long-term safety profile, lipid subclass optimization, and biomarker-driven personalization require further investigation.

Keywords: ketogenic diet; polycystic ovary syndrome; lipid metabolism; chronic inflammation

1. Introduction

Polycystic ovary syndrome (PCOS) is the most common reproductive–endocrine disorder in women of reproductive age; it is often accompanied by significant metabolic dysfunction, including insulin resistance, obesity, dyslipidemia, and a low-grade chronic inflammatory state. In recent years, the incidence of PCOS has shown a significant upward trend [1]. Since 1990, the age-standardized prevalence and annual incidence of PCOS have increased by 30.4% and 29.5%, respectively [2]. The global prevalence of PCOS under different diagnostic criteria has a wide range of 5%–20% [3]; according to the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine, the prevalence can be as high as 15%–20% [4]. This situation not only reflects the high prevalence of PCOS in the population but also reveals the problem of heterogeneity due to differences in diagnostic criteria, which in turn results in a significant percentage of patients not being diagnosed and managed in a timely manner. This high prevalence and difficulty in diagnosis indicates that PCOS has become a public health

challenge that requires urgent attention in the field of women's health; furthermore, it emphasizes the need for in-depth research on its etiology and innovative treatment strategies.

The etiology of PCOS is multifactorial and reflects the interplay between genetic susceptibility and environmental factors. Although early work focused largely on endocrine abnormalities, recent research has shifted toward a systems view, in which dysregulated metabolic–immune crosstalk is central. Genome-wide association studies have identified multiple susceptibility loci that are associated with sex hormone synthesis, insulin signaling pathway, and others; however, their inheritance patterns show non-Mendelian complexity, thus suggesting that environmental factors and epigenetic regulation play important regulatory roles in these processes [5]. The ~~**Error! Reference source not found.**~~genetic factors include polycystic ovarian morphology, hyperandrogenemia, insulin resistance, and insulin secretion defects, and the environmental factors include in utero androgen exposure and malnutrition during fetal life; moreover, obesity is considered the most important acquired risk factor [6]. Lipid metabolism disorders and chronic inflammation are important drivers of the pathophysiology of PCOS. Studies have demonstrated a close bidirectional regulatory relationship between abnormal lipid metabolism and inflammatory responses: saturated fatty acids trigger inflammatory responses through the activation of toll-like receptor 4 (TLR4) signaling [7], whereas TLR4 activation leads to the reprogramming of macrophage metabolism, including increased glycolysis and altered mitochondrial metabolism, which contribute to inflammatory responses [8]. This reciprocal promotion of metabolism and inflammation forms the basis of the PCOS metabolism–inflammation vicious cycle, which is particularly pronounced in PCOS subtypes associated with obesity, thus accelerating the onset and progression of the disease.

Current therapeutic practices have several limitations. Although the 2023 international evidence-based guideline designate "lifestyle intervention" as the first-line treatment for patients with PCOS, the guideline stops short of recommending any particular diet, thus leaving clinicians to rely chiefly on caloric restriction and conventional low-fat regimens, which yield only modest gains in metabolic and reproductive outcomes [9]. Although current pharmacological regimens have achieved some success in relieving symptoms, most of the existing drugs are directed at specific pathologies, and it is often difficult to consider

multiple intertwined metabolic and immune signaling pathways in the patient's body. This situation results in a treatment effect that is limited to partial symptomatic improvement rather than fundamentally regulating the overall course of the disease. At the same time, drug resistance, lack of tolerance, and multiple side effects during the long-term use of drugs [10][11] cause continuous health risks to patients and lead to challenges in treatment compliance.

Against this backdrop, PCOS is increasingly understood as a disorder rooted in complex metabolic and inflammatory interactions. However, current nutritional strategies often fail to disentangle the distinct effects of macronutrient composition, particularly conflating the ketogenic diet (KD) with the high-fat diet (HFD). This has left a critical gap in the mechanistic understanding necessary to optimize dietary interventions. Therefore, the present review proposes a novel hypothesis: the therapeutic efficacy of a KD in PCOS is not merely a function of high fat intake but is predominantly driven by the unique metabolic reprogramming effects arising from stringent carbohydrate restriction and sustained ketogenesis, which are fundamentally different from those elicited by isocaloric HFDs. Specifically, we synthesized and expanded the current knowledge on the lipid–inflammation axis in PCOS pathogenesis and, for the first time, provided a detailed mechanistic comparison between a KD and traditional HFDs. Furthermore, we constructed an integrative framework that elucidates how the KD circumvents the metabolic deterioration and inflammatory amplification typically induced by HFDs, thereby offering mechanistic clarity that is lacking in the literature. By consolidating previously disparate findings into a unified conceptual model, this review advances the theoretical basis for precise diet-based interventions in PCOS and underscores how dietary fat quality, carbohydrate restriction, and ketone-mediated signaling differentially modulate endocrine, metabolic, and immune pathways. Consequently, our work extends existing research by providing both mechanistic insights and practical guidance to inform more targeted nutritional strategies in the clinical management of PCOS.

2. Lipid Metabolic Dysregulation in PCOS

2.1 Abnormalities of fatty acid metabolism

The serum fatty acid profile of women with PCOS exhibits specific features, particularly elevated levels of specific fatty acids, such as myristic acid, palmitoleic acid, and oleic acid, which are closely correlated with parameters associated with insulin resistance [12]. Therefore, fatty acid metabolism disorders may be a central hallmark of metabolic abnormalities in PCOS. Women with PCOS had significantly increased concentrations of free fatty acids (FFAs) and decreased concentrations of anti-inflammatory fatty acids in the follicular fluid [13]; this lipid imbalance may induce localized oxidative stress and inflammatory responses in the ovary through the activation of the extracellular signal–regulated kinase 1/2 signaling pathway and the nucleotide-binding oligomerization domain–like receptor family pyrin domain containing 3 (NLRP3) inflammasome [14] as well as further disruptions in granulosa cell function by reactive oxygen species (ROS) and proinflammatory factors, thus inhibiting follicular maturation, promoting follicular membrane cell androgen synthesis, and forming a vicious cycle. In addition, mitochondrial dysfunction, which is evident in women with PCOS and individuals who are obese, leads to decreased fatty acid β-oxidation capacity [15][16]. This is significant because mitochondrial β-oxidation is the major pathway for fatty acid degradation and is essential for maintaining energy homeostasis in the body [17]. In women with PCOS, studies have documented mitochondrial impairments, such as reduced mitochondrial DNA content and increased oxidative damage, thus indicating compromised mitochondrial function. This type of dysfunction in turn diminishes fatty acid β-oxidation and contributes to the accumulation of fatty acid metabolites and energy imbalance [16]. These findings suggest that PCOS and obesity are associated with mitochondrial dysfunction, which can disrupt normal fatty acid metabolism and overall energy homeostasis. A decrease in mitochondrial β-oxidation capacity can lead to the insufficient oxidation of FFAs [18], thus resulting in the increased production of ROS and ectopic lipid deposition. The accumulation of ROS further impairs the activity of lipid metabolic enzymes, particularly carnitine palmitoyltransferase I (CPT1), which is a key enzyme in fatty acid oxidation [19][20]. The impairment of CPT1 activity may subsequently reduce the efficiency of the mitochondrial electron transport chain, thereby exacerbating metabolic risk [21].

2.2 Adipose tissue dysfunction

Adipose tissue dysfunction plays an important role in the pathophysiology of PCOS, including abnormally enhanced lipolysis and disturbances in adipokine secretion, which ultimately lead to metabolic abnormalities. This dysfunction is not only related to excessive obesity but also involves multifactorial mechanisms, such as epigenetic changes and mitochondrial stress [22].

Adipose tissue dysfunction drives disease progression in patients with PCOS from the early stages of the disease [23] and manifests as a dual dysfunction of function and distribution. Abnormalities in subcutaneous adipose function have been found to be an important driver of insulin resistance in PCOS, and subcutaneous adipocyte volume is negatively correlated with insulin sensitivity, i.e., a larger subcutaneous adipocyte volume is correlated with worse insulin sensitivity [22]. Despite the absence of significant abnormalities in insulin receptor binding and its signaling pathway, the expression level of glucose transporter protein type 4 (GLUT4) in adipocytes is significantly reduced, thus resulting in the blockage of insulin-mediated glucose transport and a decrease in adipose tissue responsiveness to insulin, which directly exacerbates systemic insulin resistance [22]. As a result of weakened insulin action, the inhibitory ability of adipose tissue on lipolysis is reduced, and patients with PCOS tend to exhibit enhanced lipolytic activity [24] and a sustained release of excess FFAs into the circulation. These FFAs are ectopically deposited in non-adipose tissues, such as the liver and skeletal muscle, triggering lipotoxicity, further exacerbating insulin resistance, and inducing oxidative stress. In addition, these excess FFAs trigger mitochondrial β-oxidation overload, thus generating a large amount of ROS [25]. Simultaneously, FFAs induce an aberrant calcium release from the endoplasmic reticulum, further exacerbating ROS [26], which are important markers of cellular oxidative stress and are key triggering factors for NLRP3 inflammatory vesicle activation [27][28]. This promotes the caspase-1-mediated maturation and release of interleukin-1 beta (IL-1β) and interleukin-18 (IL-18), thus forming an inflammatory cascade [29].

2.3. Imbalance of adipokine secretion

Adipose tissue not only functions as an energy storage site but also as an important endocrine organ, and the secretion of various adipokines plays a central role in maintaining metabolic homeostasis. Recent

studies have increasingly highlighted that an imbalance in adipokine secretion, particularly reduced adiponectin levels, is a key driver of lipid metabolic dysregulation in PCOS.

Adiponectin, which is a high-molecular-weight protein secreted by the adipose tissue, has significant anti-inflammatory and insulin-sensitizing effects [30]. Clinical evidence shows that women with PCOS exhibit significantly lower circulating adiponectin concentrations than healthy controls irrespective of body mass index (BMI), and this deficiency closely correlates with elevated insulin resistance indices and atherogenic lipid profiles, including increased triglycerides and small, dense low-density lipoprotein (LDL) particles [31][32][33]. Moreover, adiponectin levels are inversely associated with markers of hepatic gluconeogenesis and directly associated with fatty acid β-oxidation capacity, thus underscoring its role in maintaining lipid homeostasis [34][22]. Experimental models further substantiate these observations: in a PCOS mouse model: the restoration of adiponectin levels effectively prevented the onset of insulin resistance and dyslipidemia, whereas adiponectin deficiency exacerbated these metabolic disturbances [35]. Similarly, interventions that elevate adiponectin levels in animal models of PCOS, such as low-dose spironolactone, have been shown to ameliorate lipid accumulation and systemic inflammation by enhancing adiponectin-mediated metabolic pathways [36]. Collectively, these findings suggest that adiponectin insufficiency is not merely a biomarker but also a pathogenic factor linking visceral adiposity to impaired fatty acid metabolism and insulin signaling in PCOS. This sets the stage for understanding how disruptions in other adipokines, such as leptin, further complicate the metabolic landscape of this syndrome.

Another key adipokine is leptin, which is primarily synthesized by adipose tissue and regulates appetite and energy expenditure by binding to hypothalamic receptors to maintain energy homeostasis. Leptin is also involved in multisystem metabolic integration by regulating the neuroendocrine activity of the thyroid, reproductive, and growth hormone axes [37]. However, patients with PCOS often exhibit leptin resistance [38], i.e., reduced hypothalamic sensitivity to leptin signaling, thus leading to failure of feeding inhibition and reduced energy expenditure, which promotes lipid accumulation. More importantly, leptin resistance inhibits the negative feedback regulation of the suppressor of cytokine signaling 2 in the leptin

signaling pathway and interferes with the Janus kinase 2–signal transducer and activator of transcription 3 signaling pathway, which in turn affects lipolytic enzyme activity, inhibits fat oxidation, and promotes triglyceride (TG) deposition [39][40]. Collectively, these mechanisms exacerbate lipid metabolism disorders in patients with PCOS.

3. Chronic Inflammation

3.1 Insulin resistance

In the adipose tissue of patients with PCOS, macrophages are abnormally activated and secrete increased levels of proinflammatory cytokines, thus leading to chronic low-grade inflammation and insulin resistance, which occur even in the absence of obesity [41]. Under physiological conditions, macrophages in the adipose tissue predominantly exhibit an anti-inflammatory (M2) phenotype, which helps maintain metabolic homeostasis. However, in patients with PCOS, particularly those who are overweight or obese, the ratio of proinflammatory (M1) to M2 macrophages is disrupted, with a shift toward the M1 profile [42]. Notably, clinical studies comparing normal-weight women with PCOS to BMI-matched healthy controls have found significantly higher expression of the proinflammatory macrophage marker cluster of differentiation 11c in the subcutaneous adipose tissue of women with PCOS [43]. Other macrophage markers, such as cluster of differentiation 14 and cluster of differentiation 163, also show a trend of elevated expression in patients with PCOS, particularly in individuals who are overweight or obese [44]. These findings indicate that metabolic disturbances inherent to PCOS, irrespective of obesity, can drive macrophages in the adipose tissue toward a proinflammatory phenotype.

M1 macrophages create a network that interferes with insulin signaling by persistently elevating large amounts of proinflammatory mediators, such as tumor necrosis factor alpha (TNF-α), IL-1β, and interleukin-6 (IL-6). In vitro experiments have shown that TNF-α and IL-1β directly act on insulin signaling molecules, thus increasing the inhibitory phosphorylation of insulin receptor substrate 1 (IRS-1) and reducing IRS-1 protein levels. When IRS-1 function is impaired, the insulin-stimulated translocation of glucose transporters, such as GLUT4, decreases, thus reducing the capacity of the cell to uptake glucose [45][46].

IL-6 indirectly inhibits the insulin signaling pathway by upregulating the expression of suppressor of cytokine signaling 3 (SOCS3) in adipocytes, thus promoting the degradation of IRS-1 and insulin receptor substrate 2 and ultimately leading to insulin resistance [47][48].

The NLRP3 inflammasome is composed of NLRP3, the adaptor molecule apoptosis–associated speck-like protein containing a caspase activation and recruitment domain (ASC), and the effector protein pro-caspase-1. Upon activation, the NLRP3 inflammasome cleaves procaspase-1 to generate active caspase-1 and releases mature proinflammatory cytokines IL-1β and IL-18, thereby disrupting insulin signaling and glucose homeostasis. Studies have reported that NLRP3 gene knockout mice fed a HFD exhibited significantly better glucose tolerance and insulin sensitivity than wild-type mice; therefore, the absence of the inflammasome mitigates diet-induced metabolic inflammation and insulin resistance [49]. Evidence from humans also supports this finding: in patients with type 2 diabetes, the use of interleukin-1 receptor antagonists improves glycemic control, thus suggesting that inhibition of the IL-1β pathway helps alleviate insulin resistance [50].

Recent studies have shown that both obesity and PCOS are associated with elevated NLRP3 inflammasome activity. A systematic review analyzing nine studies (three in human populations and six in PCOS animal models) concluded that, except for a few reports, the expression of NLRP3 and its related components (ASC, caspase-1, IL-1β) is generally upregulated in women with PCOS and in animal models. Correspondingly, significantly higher gene expression levels of NLRP3, ASC, and IL-1β have been detected in the adipose tissues of obese individuals than in those of non-obese controls. These findings indicate that increased NLRP3 inflammasome activity is present in individuals who are obese and patients with PCOS [51].

Even in the absence of obesity, patients with PCOS can exhibit proinflammatory macrophage polarization and elevated NLRP3 inflammasome activity in the adipose tissue, thus forming a network centered on various inflammatory mediators that collectively disrupt insulin signaling pathways and ultimately leading to insulin resistance and exacerbating metabolic imbalance.

3.2. Hyperandrogenemia

In PCOS, IL-1β and TNF-α levels are significantly elevated, and evidence from in vitro studies using rodent models shows that these proinflammatory cytokines can stimulate androgen synthesis in ovarian cells, thus potentially contributing to hyperandrogenemia [52]. In vitro studies in rat ovarian theca–interstitial cells have shown that exposure to inflammatory stimuli can significantly increase androgen production and induce widespread changes in gene expression, thereby providing a mechanistic basis for the androgen excess observed in PCOS [53]. The NLRP3 inflammasome is an important upstream regulator of this process. Animal studies have shown that the inhibition of the NLRP3 inflammasome in mice significantly reduces androgen levels [54], thus suggesting that the activation of the inflammasome is closely related to androgen hypersecretion. In a further PCOS model, it was found that the activation of NLRP3 inflammasome led to elevated levels of IL-1β, which indirectly upregulated androgen synthesis in follicular membrane cells by impairing ovarian granulosa cell function [55].

In addition, the inflammatory response inhibits the hepatic synthesis of sex hormone–binding globulin, thereby increasing free testosterone (FT) levels in circulation. Notably, the cited study demonstrating this relationship was conducted in a cohort of men with atherosclerosis [56], which, while mechanistically informative, highlights the need for more direct evidence in women with PCOS. FT, which is the most biologically active androgen component, increases not only the total amount of potent androgens but also reinforces the direct action on the receptor, thus further amplifying the clinical effects of hyperandrogenemia.

3.3. Ovarian dysfunction

Interactions between inflammatory cytokines in PCOS ovaries suggest that inflammatory markers play an important role in regulating ovarian function [57]. As ovulation approaches, a sharp increase in progesterone levels within the follicular fluid promotes the dissociation of cortisol from cortisol-binding proteins, thereby enabling cortisol to acquire biological activity. This process ensures the timely and effective resolution of inflammation, which is critical for normal follicular rupture and oocyte release in humans, as demonstrated in a study on intrafollicular cortisol dynamics [58]. Therefore, ovulation is essen-

tially a localized, controlled, inflammatory-like event involving the infiltration of leukocytes and the expression of inflammatory factors that promote follicular development and ovulation by modulating the inflammatory response and tissue remodeling [59]. Subsequently, glucocorticoids shut down the inflammatory chain in a timely manner to ensure that ovulation is complete and that inflammation does not spread excessively.

When the termination of inflammation fails, local inflammation is maintained at a chronically low level, which can lead to follicular stagnation and impaired oocyte maturation. This situation is particularly evident in PCOS and premature ovarian failure [60]. The persistent elevation of follicular fluid IL-6, TNF-α, and oxidative stress markers is negatively correlated with a decrease in the quantity and quality of oocytes [61]. Low-dose endotoxin experiments in cattle further confirmed that mild persistent inflammation can downregulate circulating and follicular estradiol levels, thereby impairing oocyte maturation [62]. At the molecular level, telomerase reverse transcriptase induces granulosa cell apoptosis and inhibits follicular maturation in rats with PCOS possibly by modulating the NF-κB signaling pathway and amplifying IL-6- and TNF-α-mediated chronic inflammatory responses [63]. In summary, the role of inflammation in ovarian function is twofold: controlled inflammation is an indispensable physiological component of ovulation, whereas uncontrolled or persistent inflammation promotes follicular dysplasia, decreased oocyte quality, and even ovulation failure, which constitute an important pathological cornerstone of PCOS.

3.4. Cardiovascular disease risk

Chronic low-grade inflammation in patients with PCOS is an important risk factor for cardiovascular complications, including hypertension, atherosclerosis, and other cardiovascular diseases. The following pathological mechanisms are intertwined and work together to promote an elevated cardiovascular risk [64]. Oxidative stress and inflammatory responses in patients with PCOS can cause damage to the vascular endothelium, which manifests as differences in endothelium-dependent and non-dependent vascular responses; these are correlated with high-sensitivity C-reactive protein concentrations and insulin resistance [65]. The compromised endothelial barrier promotes monocyte adhesion and infiltration of the

vessel wall, followed by their transformation into foam cells, which is a critical early step in atherosclerotic plaque formation [64].

Lipid metabolism disorders in patients further exacerbate cardiovascular risk. Patients with PCOS have increased numbers of small, dense LDL (sdLDL) particles, which are more susceptible to oxidization and have a greater ability to penetrate the vascular endothelium, thus significantly increasing the risk of atherosclerosis. By contrast, high-density lipoprotein (HDL) particles in patients with PCOS are usually smaller, thus resulting in "dysfunctional HDL," which is characterized by reduced antioxidant and cholesterol reverse transport capacity and weakens vascular protection [66][67][68]. In addition, even a modest increase in androgen levels in women can lead to elevated blood pressure, which is a key driver of cardiovascular disease risk. This effect is thought to be mediated, at least in part, by the upregulation of proinflammatory cytokines and T lymphocyte subsets, thus underscoring the importance of studying systemic inflammation in women with PCOS [69].

According to the mechanisms described above, chronic low-grade inflammation is closely linked to lipid metabolic dysregulation and PCOS pathogenesis, forming an "inflammatory hub" that drives disease progression. This also highlights the limitations of conventional therapies that primarily focus on glycemic control or antiandrogen strategies, which are insufficient to comprehensively reverse PCOS. Within this pathological framework, traditional treatment approaches that target only hyperglycemia or hyperandrogenism yield limited benefits in isolated aspects and fail to disrupt the vicious cycle of inflammation, metabolism, and endocrine dysfunction. The KD offer a novel therapeutic strategy for breaking this pathological hub.

4. KD: Mechanisms and Therapeutic Potential

Dietary intervention has demonstrated significant potential as a modifiable lifestyle factor for the comprehensive management of PCOS. Studies have clearly indicated that an appropriate dietary pattern is an effective, acceptable, and safe intervention for alleviating insulin resistance in patients with PCOS [70]. Among the numerous dietary strategies, high-fat nutritional regimens, such as the KD, have gained attention because of their advantages in weight loss and the optimization of metabolic parameters [71]. The KD

is a dietary strategy characterized by a high-fat, moderate protein, and low-carbohydrate intake where the proportion of fat for energy is usually ⩾70% and daily carbohydrate intake is generally controlled at <50 g [72][73].

Tight carbohydrate restriction lowers blood glucose levels and inhibits insulin secretion. The decrease in insulin concentration has an inhibitory effect on hormone-sensitive lipase (HSL), which induces a massive hydrolysis of TG in adipose tissue to FFAs and glycerol [74]. FFAs are then transported via the bloodstream to the liver and peripheral tissues and enter mitochondria for oxidative energy production under the mediation of CPT1. In the liver, fatty acids enter mitochondria for β-oxidation under the action of CPT1. The KD can upregulate CPT1 and its encoding gene, thereby significantly enhancing the flux of fatty acids into mitochondrial β-oxidation. During this process, a large amount of acetyl coenzyme A (acetyl-CoA) is produced. Owing to glycogen depletion, the supply of oxaloacetate becomes insufficient, thus limiting the utilization of acetyl-CoA in the tricarboxylic acid (TCA) cycle. Consequently, excess acetyl-CoA is condensed through the ketogenesis pathway to form acetoacetate, which can subsequently be reduced to β-hydroxybutyrate (β-HB) or undergo decarboxylation to produce acetone. These three compounds collectively constitute ketone bodies [75][76].

Ketone bodies not only serve as efficient alternative energy substrates for extrahepatic tissues, particularly the brain, skeletal muscle, and myocardium, but also function as signaling molecules involved in multiple physiological processes, including energy homeostasis, inflammation regulation, and oxidative stress response. Therefore, ketone bodies confer metabolic and endocrine benefits to patients with PCOS.

4.1 Metabolic reprogramming

4.1.1. Regulation of lipid metabolism

In terms of lipid synthesis and utilization, the KD rapidly downregulates insulin through very-low-carbohydrate intake, deregulates the insulin inhibition of HSL, and downregulates the activity of sterol regulatory element–binding protein-1c and carbohydrate-responsive element-binding protein, thus decreasing the supply of substrates for lipid synthesis; the body is then forced to rely on ketone bodies as the

primary energy source [77][78]. The increased production of ketone bodies as an efficient alternative energy source further promotes lipolysis and utilization [79][80]. On the other hand, KD significantly upregulated the expression of peroxisome proliferator–activated receptor αlpha (PPAR-α) in the liver and skeletal muscle. PPAR-α transcriptionally activates key enzymes such as carnitine palmitoyltransferase-1A/P and peroxidase-1, promotes the acetyl-CoA to cross the restriction of the outer mitochondrial membrane, and enhances β-oxidative flux [81]. After fatty acids enter the mitochondria in large quantities, the increase in the oxidized/reduced nicotinamide adenine dinucleotide ratio further activates acetylase sirtuin-1 (SIRT1), which is a metabolic sensor that regulates lipid homeostasis. SIRT1-mediated deacetylation enhances the activity of peroxisome proliferator–activated receptor gamma coactivator 1 alpha and promotes mitochondrial biogenesis and fatty acid oxidative capacity [82][83]. Thus, SIRT1 systematically enhances the body's ability to oxidize and utilize lipids.

The KD also drives the functional remodeling of adipose tissue. KD increased the secretion of fibroblast growth factor 21 (FGF21), which activates the browning of white adipose tissue (WAT) and significantly enhances the expression of uncoupling protein 1 (UCP1), which is a mitochondrial inner membrane–specific protein. UCP1 uncouples the electron transport chain during ATP synthesis and converts chemical energy into heat, thereby enhancing both fat oxidation and thermogenic efficiency. Notably, the FGF21–UCP1 axis activated by the KD exhibits tissue-specific effects: it promotes the initiation of browning-related gene programs in WAT while further enhancing mitochondrial biogenesis in brown adipose tissue. This dual regulatory mechanism not only increases energy expenditure and lipid turnover but also remodels metabolic homeostasis by improving lipid turnover [77][84].

4.1.2 Appetite suppressant

The unique advantages of the KD in weight management stem in part from its profound effect on the appetite regulatory system. During conventional weight loss, ghrelin levels tend to increase to compensate for weight loss, which induces hunger and predisposes individuals to regain weight. By contrast, KD significantly inhibits the synthesis and secretion of gastric-derived ghrelin [85][86][87], thus breaking this vicious cycle. The mechanism underlying this effect remains unclear; however, one of the primary factors

may be the direct action of ketone bodies. A study investigating exogenous ketones confirmed this notion, thus demonstrating that higher levels of β-HB ester are associated with a smaller increase in ghrelin, reduced hunger sensation, and a greater increase in satiety peptides [86]. Satiety peptides, such as glucagon-like peptide-1 (GLP-1) and its receptor agonists, directly enhance satiety signaling by activating pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus, thereby suppressing appetite and reducing food intake [88][89]. Some studies have further suggested that this may indirectly affect neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons, thus consolidating the appetite-suppressing effects; however, direct assessments of AgRP neuronal activity under KD conditions are lacking [90]. Notably, a study conducted in athletes adhering to the KD revealed that the subjective perceptions of appetite did not align with hormonal markers, such as GLP-1 [91], thus underscoring the need for the cautious interpretation of these neuroendocrine relationships. In addition, β-HB, which is the principal circulating ketone body, also acts as an endogenous inhibitor of class IV histone deacetylase, which regulates the epigenetic expression of satiety-related genes in peripheral tissues and prolongs the appetite suppression effect [92][93].

However, in an animal model, after β-HB reached ⩾3 mM in the brain by carotid artery injection, hypothalamic adenosine monophosphate–activated protein kinase (AMPK) phosphorylation increased rapidly and was accompanied by an increase in the expression of NPY and AgRP messenger RNA (mRNA); furthermore, the amount of food consumed also increased transiently, thus suggesting that a high concentration of ketone bodies can act as an energy-deficient signal to activate the starvation loop. AMPK is the metabolic switch of hunger-satiety integration, and its activation tends to inhibit POMC and upregulate NPY/AgRP, thereby promoting appetite. AMPK is a metabolic switch for hunger-satiety integration, and its activation tends to inhibit POMC, upregulate NPY/AgRP, and promote appetite [94].

This epigenetically contradictory mechanism indicates that moderate peripheral ketosis and high central ketosis produce appetitive effects in opposite directions. Nutritional ketosis maintains satiety primarily through the peripheral–vagal–hypothalamic axis, whereas β-HB ⩾ 3 mM is only sufficient to significantly activate the AMPK–NPY/AgRP pathway for appetitive signaling [94][95].

Table 1. Comparison of peripheral-central effects at both ketosis levels.

Influencing Factors	Peripheral Effect	Central Effects	Outcomes
Nutritional ketosis[1]	⬇ghrelin, ⬆GLP-1, HDAC inhibition Maintain satiety	Activate POMC Indirectly inhibit NPY/AgRP neurons Inhibit POMC	Appetite suppression, weight loss
Hyper ketosis[2]	Same as above table	Activate AMPK–NPY/AgRP pathway	Stimulate appetite

[1] β-HB 0.5-3.0 mmol/L; [2] β-HB ≥3.0 mmol/L

Abbreviations: GLP-1, glucagon-like peptide-1; HDAC, histone deacetylase; POMC, pro-opiomelanocortin; NPY, neuropeptide Y; AgRP, agouti-related peptide; AMPK, adenosine monophosphate–activated protein kinase

The KD usually maintains patients in the moderate ketosis range, thus resulting in overall stable appetite suppression and weight loss. Experimental or pathologic intracerebral hyper ketosis reveals potential

"appetitive back-up pathways," a model that suggests monitoring blood ketone levels and avoiding prolonged hyper ketosis during the clinical use of the KD. If hyperketosis is chronic or recurrent, the weight-loss benefits of the KD may be diminished.

4.1.3 Insulin resistance

As previously described, KD rapidly restores the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway by lowering fasting insulin and deregulating IRS-1 inhibition, thus resulting in a rapid rebound in skeletal muscle and hepatic response to insulin [77][96]. A KD-induced rapid reduction in body weight and visceral fat directly ameliorates insulin resistance in patients with PCOS. The adipocyte secretion profile is also remodeled: adipose tissue secretes lower levels of proinflammatory factors and increases adiponectin secretion, which together alleviate lipotoxicity, inflammatory stress, and inhibition of insulin signaling [97][98]. This shift has been independently associated with increased insulin sensitivity in a recent meta-analysis [99]. On the basis of this phenomenon, KD reshapes the gut microbiota structure, particularly altering the Firmicutes/Bacteroidetes ratio and regulating secondary bile acid metabolism and short-chain fatty acid (SCFA) production, as demonstrated in rat models of PCOS [100]~~[98]~~. Clinical evidence, including meta-analyses, supports the role of SCFAs in enhancing insulin sensitivity [101]~~[99]~~. Additionally, clinical studies have indicated that the KD may downregulate the activity of insulin-like growth factor-1 receptors in the ovaries, thus inhibiting the expression of cytochrome P450 family 17 subfamily A member 1, which is a key enzyme in androgen synthesis, and disrupting the vicious cycle of hyperandrogenism and insulin resistance in women with PCOS [102]~~[100]~~.

4.2. Potential anti-inflammatory effects of KD in PCOS

4.2.1. Direct anti-inflammatory of ketone bodies

β-HB is a ketone body that acts as a KD metabolite; it not only provides an alternative substrate in times of energy deficiency but also exhibits significant immunomodulatory activity. The central mechanism involves the inhibition of NLRP3 inflammatory vesicles. β-HB inhibits the activation of NLRP3 inflammatory vesicles by blocking intracellular K^+ efflux and limiting ASC oligomerization and spot formation. This inhibitory effect is not dependent on the chiral or starvation-regulated mechanisms of β-HB,

414 such as AMPK, ROS, autophagy, or glycolytic inhibition. Furthermore, β-HB acts independently of oxida-
415 tive processes and other metabolic regulators of the TCA cycle [103]. In animal models of gout, acute
416 pancreatitis, and Alzheimer's disease, β-HB was able to reduce the production of IL-1β and IL-18 and
417 downregulate the above mentioned inflammatory mediators, thus confirming its NLRP3 inhibitory effect
418 across the disease spectrum and providing a direct molecular basis for the anti-inflammatory potential of
419 KD [104][105][106].

420 4.2.2. Reshaping of the gut microbiota

421 Emerging clinical evidence suggests that ketogenic interventions strongly enriched the mucus-degrad-
422 ing bacterium *Akkermansia muciniphila*, with a 3- to 10-fold increase in relative abundance over days to
423 weeks in mice and humans following classical or very-low-calorie KD regimens [107][108][109]. This
424 flora displacement is strongly associated with the structural enhancement of intestinal barrier function,
425 with *Akkermansia* inducing cup cells to secrete more mucus and upregulate the transcript levels of the
426 tight junction proteins occludin, claudin-5, and zonula occludens-1, thus reducing barrier aperture and de-
427 creasing permeability [110][111]. In an eight-week ultra-low-calorie KD clinical trial, patients experi-
428 enced a significant reduction in barrier permeability markers and a simultaneous 15%–30% reduction in
429 urine/blood lipopolysaccharide (LPS) levels, thus suggesting the inhibition of endotoxin translocation
430 [112]. The reduction of endotoxin load interrupts the classic inflammatory chain mediated by LPS–TLR4,
431 and evidence suggests that the KD regimen additionally downregulates circulating IL-6 and TNF-α by ap-
432 proximately 10%–25% [113][114].

433 In addition to elucidating how the KD remodels the gut microbiota, it is instructive to compare these
434 alterations with those induced by the Mediterranean diet (MD), which is characterized by a high consump-
435 tion of whole grains, fruits, vegetables, legumes, nuts, and olive oil and is frequently recommended for
436 metabolic and inflammatory disorders [115][116]. Although the KD markedly enriches certain mucin-de-
437 grading and ketone-associated taxa, the MD preferentially enhances the abundance of SCFA-producing
438 bacteria such as *Faecalibacterium prausnitzii* and *Roseburia* spp owing to its high content of dietary fiber,
439 polyphenols, and monounsaturated fats [117][118]. These microbes contribute significantly to butyrate

production; support intestinal epithelial integrity; and exert anti-inflammatory effects through different mechanisms, including histone deacetylase inhibition [119][120].

Therefore, the distinct microbial signatures and metabolic outputs elicited by the KD and MD highlight the importance of tailoring dietary interventions for gut microbiota–mediated immunometabolic objectives in the management of PCOS. Table 2 summarizes the primary differences between the KD and MD in terms of gut microbiota modulation, metabolic–immune outcomes, and potential risks. The data show that individualized nutritional strategies are needed in the management of patients with PCOS.

Table 2. Comparative impacts of the KD and MD on gut microbiota composition

Parameters	KD	MD
Main microbial shifts	↑ [1] *Akkermansia muciniphila*	↑ SCFA-producing bacteria
Intestinal barrier integrity	↑ Tight junction proteins via *Akkermansia*; ↓ [2] permeability	↑ Barrier function via histone deacetylase inhibition
Inflammatory markers	↓ IL-6, TNF-α via β-HB and reduced endotoxemia	↓ CRP, IL-6, TNF- α via polyphenols and SCFAs [121][122]
Clinical implications in PCOS	Rapid reduction of systemic inflammation and insulin resistance; modulates gut–ovary axis [100][123]	Long-term metabolic health via gradual anti-inflammatory effects [124][125][126]

Potential risks or limitations	Possible dyslipidemia, micronutrient deficiencies, and renal strain; unclear long-term gut ecosystem effects [127]	Caution in high-energy variants with excessive refined carbohydrates [128]

[1] Increased

[2]Decreased

Abbreviations: KD, ketogenic diet; MD, Mediterranean diet; SCFA, short-chain fatty acid; IL-6, interleukin-6; TNF-α, tumor necrosis factor alpha; β-HB, β-hydroxybutyrate; CRP, C-reactive protein; PCOS, polycystic ovary syndrome

4.2.3. Inhibition of inflammatory pathways

KD exerts anti-inflammatory and antioxidant effects through multiple target mechanisms, and its pathways of action are characterized by molecular-level regulation. In terms of anti-inflammatory effects, the KD significantly reduces the biosynthesis of proinflammatory cytokines via multiple pathways [129][130][131]. KD specifically regulates key inflammatory markers such as TNF and IL-6, but its inhibitory effect on other inflammatory mediators has not yet reached statistical significance [114]. Further evidence is required to confirm these findings.

In terms of oxidative stress, KD reduces the proton gradient of the electron transport chain by upregulating the expression and activity of mitochondrial uncoupling proteins, thereby reducing the aberrant accumulation of ROS and improving the efficiency of oxidative phosphorylation by optimizing the function of the mitochondrial respiratory chain complex [132]. By contrast, ROS levels and reactive nitrogen species production are effectively reduced by stimulating the endogenous antioxidant system and optimizing the efficiency of the mitochondrial electron transport chain [129][133]. This not only enhances the efficiency of energy metabolism but also indirectly enhances the overall anti-inflammatory capacity of the

organism by improving mitochondrial function and reducing oxidative stress to reduce ROS production [134].

4.3. Challenges and potential risks

Although the KD offers multifaceted metabolic and endocrine benefits, it is crucial to recognize and weigh its potential risks and limitations, particularly concerning long-term cardiovascular, renal, and nutritional health. The KD has shown multiple benefits in women with PCOS, such as lowering androgen levels by reducing fat mass [135] while promoting weight loss and improving insulin resistance to increase insulin sensitivity. However, many studies have not clearly distinguished between the direct effects of the KD on insulin sensitivity and its indirect effects on weight loss [77][107]. Short-term applications may trigger paradoxical metabolic responses. For example, one study found that short-term KD may lead to more severe hepatic insulin resistance rather than improvement [136]. In terms of metabolic risk, KD may lead to ketoacidosis and dyslipidemia (particularly elevated LDL and total cholesterol levels) in the short term [137], and patients with familial hypercholesterolemia may have a significantly increased risk of atherosclerotic cardiovascular disease [138]. In addition, the potential association between high saturated fat intake and increased cardiovascular mortality warrants caution [139]. The extremely restrictive nature of the KD may lead to nutritional deficiencies, including vitamin and mineral deficiencies. Therefore, micronutrient supplementation is recommended prior to initiating the KD [140].

In terms of organ-specific effects, the KD may exacerbate the risk of metabolic acidosis and kidney stones in patients with chronic kidney disease [141], The long-term effects of a high-protein HFD on individuals with impaired hepatic and renal functions have not yet been clarified. The dynamic balance of the gut microbiome may be dysregulated by drastic changes in dietary structure, which in turn affect metabolic regulation, immune function, and nutrient uptake [142]. Short-term adverse effects such as hypoglycemia, fatigue, weight fluctuations, and digestive symptoms have also been observed in clinical practice [143].

Although cyclical ketogenic regimens may improve adherence, long-term sustainability remains challenging. There is also a lack of high-quality evidence to support their long-term safety, particularly with

regard to long-term effects on the cardiovascular, renal, and metabolic systems, which still need to be validated in large-scale, long-term studies. In conclusion, the use of the KD for the management of PCOS should be weighed against its metabolic benefits and potential risks. In clinical practice, individualized assessments should be strengthened and supplemented with nutritional monitoring and supplementation when necessary. More studies are needed to clarify the long-term effects and safety boundaries of the KD.

5. Comparative Analysis: HFD vs. KD

Although the multiple benefits of the KD in improving metabolic dysfunction and inflammatory status in PCOS have been systematically described previously, the concept of "high fat" does not, by itself, necessarily lead to metabolic benefits. The quality of fat, the concomitant carbohydrate load, and the total calories are key variables in determining dietary effects. In clinical practice, many patients with PCOS do not follow a strict low-carbohydrate pattern and consume traditional HFDs, which are based on saturated fats and refined carbohydrates. Instead of stimulating the physiological state of ketosis via the KD, this dietary structure may further worsen the metabolic and reproductive outcomes of PCOS by inducing obesity, insulin resistance, and chronic inflammation. Therefore, after an in-depth analysis of the benefits of the KD, a systematic assessment of the negative effects of conventional HFDs is necessary to highlight the importance of rational lipid sources and carbohydrate restrictions in nutritional interventions for PCOS. In the following, we will focus on the adverse effects of HFDs in terms of lipid regulation, inflammatory response, and insulin sensitivity. Furthermore, the KD will be used as a control to elucidate the differences between the KD and HFD in terms of mechanisms and outcomes and to provide a scientific basis for the development of more precise dietary strategies.

Compared with the KD, uncontrolled HFDs tended to negatively affect lipids and often result in elevated TGs, decreased HDL cholesterol, and increased LDL levels, particularly in small, dense LDL particles [144][145][146]. The mechanism for this is that such diets predispose to insulin resistance and hyperinsulinemia. High insulin levels stimulate the liver to synthesize more TGs and secrete very LDL particles, thus leading to elevated blood TG levels [147][148], which, in combination with high fat, inhibit HDL production and promote the formation of small, dense LDL [149]. High saturated fat intake has also been

shown to indirectly affect lipoprotein metabolism by worsening insulin sensitivity and promoting inflammation.

High-calorie HFDs often lead to obesity and increased visceral fat, which prompts the LPS produced by the metabolism of intestinal flora to penetrate the intestinal wall and enter the bloodstream, triggering metabolic endotoxemia [150]. LPS activates the TLR4/myeloid differentiation factor 2 (MD-2) complex, thus leading to the release of proinflammatory cytokines and mediators, such as IL-1β, TNF-α, and IL-6 [151], This activation also involves other signaling pathways, such as PI3K/Akt and the nicotinamide adenine dinucleotide phosphate oxidase–mediated response, which further contributes to inflammatory responses [152][153]. In patients with PCOS, high saturated fat intake further induces the expression of the proinflammatory signaling molecule SOCS3, which inhibits insulin signaling and promotes the release of inflammatory factors [154]. HFDs lead to adipocyte expansion, which is closely associated with insulin resistance. Even in the absence of significant inflammation, adipocyte expansion leads to impaired insulin signaling [155][156] as well as increased macrophage infiltration and proinflammatory factor secretion, which negatively affects the local environment of the ovary and interferes with follicular development.

A diet high in saturated fat leads to the accumulation of diacylglycerol and ceramides in the muscle and liver. These lipid metabolites impede insulin signaling by inducing the upregulation of SOCS3 via proinflammatory mediators, which interferes with the phosphorylation of IRS-1, a key protein in the insulin signaling pathway [157]. Simultaneously, HFD-induced hyperinsulinemia forms a vicious cycle, and excess insulin further reduces receptor sensitivity. Animal studies have shown that mice fed with a HFD exhibit higher fasting glucose and insulin levels, lower glucose tolerance, and higher homeostatic model assessments of insulin resistance values [158]. In an animal model of PCOS, the addition of high-fat chow significantly exacerbated glucose metabolism disorders, with significant insulin resistance and hyperglycemia occurring compared with the normal chow group [159].

Therefore, in contrast to the adverse consequences caused by HFDs, the KD helps correct lipid and glucose metabolism abnormalities and alleviates inflammation.

Table 3. Comparative mechanisms of the effects of KD and HFDs on metabolism, inflammation, and reproductive health.

Parameters	KD	HFDs	Potential underlying mechanisms
Body weight	↓ [1]	↑ [2]	KD reduces caloric intake, enhances satiety, and promotes lipolysis; HFDs induces obesity through caloric overloading.
HDL	↑	↓	KD enhances HDL production via mobilizing fatty acid oxidation, while HFDs suppresses HDL function.
sdLDL	↓	↑	KD elevates LDL particle size by lowering insulin and triglycerides; HFDs promotes sdLDL formation due to insulin resistance.
Systemic inflammation markers	↓	↑	KD derived ketone body β-HB inhibits NLRP3 inflammasome and NF-κB signaling; HFDs induced LPS activates NF-κB via TLR4 pathway.
Proinflammatory cytokines	↓	↑	KD upregulates adiponectin and β-HB suppresses inflammasome activation; HFDs upregulates proinflammatory gene expression.

Insulin function	↓	↑	KD improves insulin sensitivity through reduced insulin levels and AMPK activation; HFDs impairs insulin action by disrupting IRS-1 function.
Glucose homeostasis	↑	↓	KD decreases hepatic glucose output and enhances muscle glucose uptake; HFDs causes glucose metabolic dysregulation with significant glycemic fluctuations.
Androgen levels	↓	↑	KD reduces ovarian androgen synthesis and elevates SHBG to bind FT; HFDs exerts the opposite effect.
Ovulation	↑	↓	KD restores hypothalamic ovulation-promoting signals by improving metabolic homeostasis; HFDs leads to ovarian cystic changes and impaired ovulation.
Follicular microenvironment	↓	↑	KD suppresses ovarian cGAS-STING/NF-κB pathways to reduce granulosa cell apoptosis; HFDs exacerbates ovarian oxidative stress and inflammation, accelerating follicular atresia.

[1] Increased or worsening

[2] Decreased or improvement

Abbreviations: KD, ketogenic diet; HFD, high-fat diet; HDL, high-density lipoprotein; LDL, low-density lipoprotein; sdLDL, small, dense LDL; β-HB, β-hydroxybutyrate; NLRP3, nucleotide-binding oligomerization domain–like receptor family pyrin domain containing 3; LPS, lipopolysaccharide; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IRS-1, insulin receptor substrate 1; SHBG, sex hormone–binding globulin; FT, free testosterone; cGAS–STING, cyclic guanosine monophosphate–adenosine monophosphate synthase–stimulator of interferon genes

6. Strengths and Limitations

This review provides a rigorous and mechanistically integrated examination of the coalescence of dysregulated lipid metabolism and chronic low-grade inflammation to drive the pathophysiology of PCOS. By systematically dissecting molecular, cellular, and systemic pathways and by distinguishing the distinct metabolic and immunological effects of the KD from conventional HFDs, this study advances a more precise conceptual framework for dietary modulation in PCOS. Notably, this review synthesizes evidence from preclinical mechanistic studies, clinical metabolic data, and interventional trials to construct a cohesive pathogenic model that links fatty acid turnover, adipokine imbalance, macrophage polarization, and inflammasome activation to the endocrine and reproductive disturbance characteristics of PCOS. This integrative perspective lays a solid foundation for the rational design of precision nutrition strategies and has the potential to inform individualized dietary counseling and broader clinical practice guidelines.

This study has a few limitations. Although this review draws on an extensive body of literature, the inherent complexity and heterogeneity of PCOS indicates that some mechanistic pathways, particularly those involving the long-term modulation of specific immune cell subsets and lipid subclasses by ketone bodies, remain incompletely characterized. In addition, the current evidence base for ketogenic interventions in PCOS is constrained by the limited number of large-scale, long-term, randomized controlled trials, thus restricting the development of firm conclusions on sustainability and long-term safety, particularly regarding cardiovascular and renal outcomes. It also remains challenging to separate the direct effects of nutritional ketosis from secondary improvements attributable to weight loss or caloric restriction, which is an important distinction in elucidating causal mechanisms. Patient heterogeneity, including variations in obesity status, baseline insulin sensitivity, genetic factors, and gut microbiota composition, may further

influence the responsiveness to ketogenic interventions, thereby limiting the generalizability of the current findings. These considerations highlight the need for future research to validate and refine the proposed mechanistic framework, ideally through biomarker-driven approaches that enable tailored dietary prescriptions aligned to individual metabolic and immunological profiles.

7. Discussion

This review provides a mechanistic and comparative exploration of how ketogenic diets and HFDs distinctly influence the metabolic–inflammatory networks that drive the pathogenesis of PCOS. This underscores the fact that insulin resistance, ectopic lipid deposition, and chronic low-grade inflammation act synergistically to perpetuate a vicious cycle that worsens endocrine and metabolic disturbances in PCOS. The KD has emerged as a promising strategy for disrupting this pathological loop by simultaneously addressing metabolic reprogramming and immune modulation.

Specifically, patients with PCOS commonly exhibit insulin resistance, ectopic fat deposition, and elevated levels of inflammatory mediators, which interact with each other to form a vicious circle and exacerbate metabolic disorders. The KD can effectively reduce glucose and insulin fluctuations by shifting the main energy utilization from glucose to fatty acid β-oxidation and ketone production. Thus, the KD helps break the vicious circle between hyperinsulinemia and hyperandrogenemia at the metabolic level. Meanwhile, the ketone bodies produced by the KD not only serve as alternative energy sources but also as signaling molecules that can inhibit proinflammatory pathways, reduce the release of proinflammatory cytokines, and promote the expression of anti-inflammatory mediators, thus alleviating the systemic low-grade inflammatory state at the immunological level. The above mechanistic integration model illustrates how the KD can intervene in the PCOS disease process in both metabolic and inflammatory dimensions, thus achieving improvements in endocrine homeostasis and the local ovarian microenvironment.

From a clinical perspective, these mechanistic insights suggest that the KD could serve as an adjunctive first-line intervention, alongside lifestyle modifications and pharmacotherapy, to address the intertwined metabolic and reproductive dysfunctions of PCOS more comprehensively. This could translate into

improved insulin sensitivity, attenuation of hyperandrogenemia, enhanced ovulatory function, and potentially higher pregnancy rates, thereby directly affecting patient care. Understanding these pathways empowers healthcare providers to move beyond traditional calorie-centric approaches toward more mechanistically informed nutritional interventions that are tailored to disrupt the unique metabolic–inflammatory signatures present in individual patients with PCOS.

8. Conclusions

Several critical areas require further explorations to fully translate these insights into clinical practice. Robust, long-term randomized controlled trials are needed to confirm the sustainability and safety of the KD across different PCOS phenotypes and to disentangle the specific contributions of ketosis from weight loss. Furthermore, mechanistic studies employing multiomics platforms, including metabolomics, transcriptomics, and microbiome profiling, could identify predictive biomarkers of dietary responsiveness, thus paving the way for personalized dietary prescriptions. Given the heterogeneity of PCOS in metabolic burden and gut microbiota composition, future research should investigate how these factors modulate individual responses to the KD to inform precise nutrition frameworks that optimize therapeutic efficacy while minimizing risks.

9. Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: Data sharing is not applicable to this article because no datasets were generated or analyzed in the current study.

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10. List of Abbreviations

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12. Figure Legends

Figure 1. Graphical Abstract