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The Impact of Low-Calorie Dietary Patterns on Polycystic Ovary Syndrome with Insulin Resistance

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Abstract: Polycystic ovary syndrome (PCOS) is a common endocrine disorder characterized by insulin resistance (IR), affecting 5.61% of reproductive-aged women in China, with over half exhibiting IR. Current treatments focus on individualized management, but optimal therapeutic strategies remain unclear. This article further analyzes the therapeutic effects and impact of low-calorie dietary patterns (LCDs) as adjuvant therapy for PCOS with IR. The findings demonstrate that LCDs exemplified by intermittent fasting (IF) and ketogenic diets (KD) significantly enhance weight management outcomes. By reducing caloric intake and optimizing metabolic status, these dietary approaches improve IR-related parameters, effectively reduce BMI, and increase insulin sensitivity, establishing their value as adjunct strategies within the integrated management of PCOS with IR. However, current applications of LCDs as adjuvant therapy still present limitations and challenges, including compromised patient compliance and a lack of longitudinal data on long-term efficacy. To address these challenges, future research should launch rigorous large-scale longitudinal studies to explore synergistic mechanisms combining LCDs with psychological interventions, with the goal of improving treatment adherence.

Keywords: Polycystic Ovary Syndrome (PCOS), Insulin Resistance (IR), Low-Calorie Diet (LCD), Intermittent Fasting, Ketogenic Diet.

1. Introduction

Polycystic Ovary Syndrome (PCOS) is a common gynecological endocrine disorder involving dysfunction of the hypothalamic-pituitary-ovarian axis. Core features include chronic anovulation, insulin resistance (IR), hyperinsulinemia, hyperandrogenemia, and polycystic ovarian morphology. Clinical manifestations encompass menstrual disturbances, obesity, infertility, and metabolic sequelae. The condition originates from complex interactions between genetic predisposition and environmental factors [1].

IR denotes impaired insulin-mediated glucose utilization in peripheral tissues, triggering compensatory hyperinsulinemia to maintain glucose homeostasis [2]. In PCOS complicated by IR, this metabolic derangement initiates a self-perpetuating cycle: hyperinsulinemia stimulates excessive ovarian androgen production, which further exacerbates IR while disrupting follicular development and ovulation. Endometrial and ovarian tissues express insulin receptors. Endometrial

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IR impairs physiological function, reducing receptivity, promoting hyperplasia, and increasing endometrial cancer risk, thereby diminishing fertility [3]. Ovarian IR contributes directly to aberrant folliculogenesis, anovulation, and hyperandrogenemia. These pathological changes underlie menstrual irregularities, infertility, and elevated risks of metabolic comorbidities [4].

PCOS affects approximately 10%-15% of women of reproductive age globally. It is frequently associated with IR, metabolic syndrome, non-alcoholic fatty liver disease, and an increased risk of type 2 diabetes (T2DM) [2]. As noted, IR prevalence in PCOS patients ranges from 40% to 70%, specifically 56.3% in Han Chinese cohorts. Acquired factors, serving as environmental triggers for IR, include obesity, aging, and adverse lifestyle factors (physical inactivity, nutritional excess). The metabolic dysregulation centered on IR is pivotal in PCOS pathogenesis. Management of PCOS with IR necessitates multidisciplinary collaboration, emphasizing lifestyle modification, psychological assessment/intervention, and long-term pharmacotherapy [2]. Emerging research indicates that Low-Calorie Diets (LCDs), such as Intermittent Fasting (IF) and the Ketogenic Diet (KD), represent highly effective adjunctive therapies for ameliorating symptoms of PCOS with comorbid IR. Studies demonstrate that moderate weight loss (5–10%) improves reproductive function, metabolic parameters, and psychological symptoms in PCOS patients. LCDs appear to ameliorate IR and reduce hyperinsulinemia-driven androgen excess, while weight loss may alleviate chronic inflammation associated with metabolic dysfunction [4]. Despite promising results, key questions remain unanswered. The comparative efficacy of different LCD protocols for specific PCOS phenotypes needs clarification. The long-term sustainability of the metabolic and reproductive benefits achieved, adherence challenges inherent to restrictive diets, potential psychological impacts, and the long-term safety profiles require robust investigation through well-designed longitudinal studies. This review aims to critically examine the current evidence on the impact of LCD patterns, specifically IF and KD, on PCOS with IR, exploring their intervention mechanisms, efficacy, limitations, and future research directions.

2. Pathological mechanisms of PCOS and IR

2.1. Association

Although the etiology of PCOS remains unclear, it is widely recognized that IR and hyperandrogenism are two primary causative factors in PCOS pathogenesis. Metabolic disorders centered on IR are considered a critical pathophysiological basis for PCOS development. In healthy women, insulin receptors are distributed throughout the endometrium and ovaries. Endometrial IR impairs physiological endometrial function, leading to reduced endometrial receptivity, endometrial hyperplasia, and increased risk of endometrial carcinoma-ultimately diminishing fertility in PCOS patients [3]. Local ovarian IR may cause abnormal follicular development, ovulatory dysfunction, and hyperandrogenemia, resulting in reproductive impairment in PCOS patients [2].

2.2. Risk factors

PCOS risk factors involve complex interactions among genetic (e.g., insulin signaling pathway gene mutations, family history), metabolic (IR, obesity), endocrine (hyperandrogenemia, HPO axis dysfunction), environmental (poor dietary habits, pollutant exposure), and psychological factors (stress, mood disorders). Among these, IR and obesity represent the core modifiable components, with lifestyle modifications and targeted therapies serving as key management strategies [5].

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Risk factors for IR encompass both genetic and acquired elements. Genetic determinants include gene mutations, chromosomal abnormalities, and inherent genetic susceptibility, with gene mutations further classified into those affecting insulin signaling pathways (such as insulin receptor gene mutations) and non-insulin signaling pathways (including leptin and leptin receptor gene mutations) [6]. Clinically, chromosomal disorders such as Down syndrome, Turner syndrome, and Klinefelter syndrome are recognized triggers of IR, while metabolic syndrome frequently arises from underlying genetic predisposition. Acquired factors represent modifiable environmental influences, comprising obesity, advancing age, detrimental lifestyle practices (physical inactivity and excessive caloric intake), glucolipotoxicity, psychological stress, circadian rhythm disruption, environmental pollutants, and pharmacological agents including glucocorticoids and antipsychotic medications [7].

In summary, the risk factors for PCOS complicated by IR involve complex interactions among genetic, metabolic, endocrine, and environmental factors. Genetic factors include mutations in insulin signaling pathway genes (such as INSR) and leptin receptor genes, along with a family history of PCOS or diabetes. Metabolic factors primarily consist of central obesity (increased waist circumference/waist-hip ratio), dyslipidemia (elevated TG and reduced HDL-C), and hyperuricemia. Endocrine mechanisms are closely associated with hyperandrogenemia (elevated free androgen index) and decreased SHBG levels. Environmental factors encompass high-sugar/high-fat diets, physical inactivity, and exposure to pollutants like bisphenol A, while chronic low-grade inflammation (elevated CRP) and thyroid dysfunction (TSH ≥2.77 mIU/L) further exacerbate IR.

2.3. Metabolic mechanisms

The metabolic pathways and cellular mechanisms underlying PCOS-IR involve complex interactions among multiple signaling cascades. Dysfunction of the PI3K/AKT/GLUT4 pathway reduces glucose uptake, impairing ovarian granulosa cell and adipocyte function; diminished AMPK signaling activity disrupts glucose and lipid metabolism, compromising hepatic and skeletal muscle cell metabolism; activation of the MAPK inflammatory pathway promotes inflammatory cytokine release, adversely affecting endometrial and adipocyte function; adipokine imbalance exacerbates IR through the AdipoR1/2-AMPK pathway; while gut microbiota dysbiosis induces chronic inflammation via the TLR4/NF-κB pathway. Collectively, these pathways establish a self-perpetuating cycle where IR leads to inflammation, which subsequently promotes hyperandrogenism, resulting in adipose tissue accumulation that further worsens IR.

3. Different LCD approaches: intervention mechanisms and evidence

Dietary intervention is paramount in PCOS prevention and management. Core strategies include lifestyle adjustment, adoption of healthy eating patterns, and achieving/maintaining a healthy weight. Dietary interventions specifically target IR amelioration, metabolic optimization, and reproductive improvement, positioning lifestyle management (especially in adolescents) as the primary initial treatment [8].

3.1. Intermittent Fasting (IF) approach

3.1.1. Background and rationale

IF represents an innovative dietary intervention strategy that differs fundamentally from traditional calorie-restriction approaches. Its core principle involves maintaining adequate nutrition while

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restricting daily caloric intake, currently implemented through three primary modalities: (1) Intermittent Energy Restriction (IER), which entails periodic reduction of caloric consumption; (2) Time-Restricted Feeding (TRF), confining daily food intake to specific time windows; and (3) Fasting-Mimicking Diet (FMD), utilizing specialized nutritional formulations to replicate the physiological effects of fasting. This strategy offers novel therapeutic perspectives for metabolic disease management by focusing on the regulation of meal timing and frequency rather than mere caloric reduction.

The current investigation adopts the referenced 5:2 IF protocol, maintaining a daily caloric allocation of 25-35 kcal/kg through three nutritionally balanced meals. This methodology prioritizes: (a) strategic inclusion of vegetables, fruits, nuts and fiber-rich foods; (b) regulated carbohydrate and lipid intake; (c) chrononutrition adherence via fixed meal timing and portion control; and (d) dietary diversification to ensure nutritional adequacy [4].

The fundamental premise of IF is to maximize fatty acid and ketone body oxidation rather than relying on glucose as the primary energy substrate. Prolonged fasting extends periods of low insulin levels, thereby potentially facilitating weight reduction and improving insulin sensitivity via attenuation of hyperinsulinemia [9].

During non-fasting periods, glucose serves as the primary energy substrate for most tissues, regulated by insulin to facilitate glycolysis [10]. Under energy-deficient conditions, cells monitor adenosine triphosphate (ATP) levels via the cellular energy sensor AMP (adenosine monophosphate) and its downstream effector AMP-activated protein kinase (AMPK). This system activates ATP-generating pathways while inhibiting ATP-consuming processes. Notably, IR is associated with reduced AMPK activity; thus, AMPK upregulation during fasting effectively ameliorates IR [11].

Throughout fasting, triglycerides undergo lipolysis into free fatty acids and glycerol. The liver subsequently converts fatty acids into ketone bodies, which not only provide alternative energy for multiple tissues but also function as potent signaling molecules with systemic implications. These ketone bodies modulate the expression and activity of proteins influencing healthspan and aging, including fibroblast growth factor 21 (FGF21), nicotinamide adenine dinucleotide (NAD+), deacetylases [12], poly(ADP-ribose) polymerase-1 (PARP-1), and ADP-ribosyl cyclase [13]. By targeting these core cellular pathways, fasting-induced ketone bodies exert profound systemic metabolic effects.

Evidence indicates that a 5%-10% weight loss improves reproductive, metabolic, and psychological parameters in PCOS patients [2]. A daily caloric reduction of 12% significantly enhances insulin sensitivity [7]. Recommendations suggest a deficit of 500-750 kcal/day (total intake ~1200-1500 kcal/day) for overweight individuals, equating to about a 30% reduction from habitual intake for effective weight loss [5].

3.1.2. Methodology and findings

IF is also known as Intermittent Energy Restriction or Time-Restricted Eating, and is a dietary pattern characterized by periodic alternation between eating and fasting (or very low-calorie intake). The specific IF method cited in this text combines conventional therapy (e.g., Diane-35 [oral contraceptive] and Metformin) with an LCD protocol which consumes only 600 kcal on 2 non-consecutive days per week, followed by normal intake for the remaining 5 days. Control groups received standard therapy plus a normal diet. Post-intervention, both groups exhibited significant BMI reduction, with a significantly greater decrease in the IF group; BMI decreased by approximately 2 units overall in the intervention group, representing a 1-unit greater reduction compared to the control group. Significant improvements were also observed in IR markers, such as

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Fasting Plasma Glucose (FPG), Fasting Insulin (FINS), and Homeostatic Model Assessment for IR (HOMA-IR) levels decreased markedly in both groups, with superior outcomes in the intervention group. This LCD pattern also outperformed standard diets in reducing Testosterone (T), Dehydroepiandrosterone Sulfate (DHEA-S), Luteinizing Hormone (LH), LH/Follicle-Stimulating Hormone (FSH) ratio, and elevating Sex Hormone-Binding Globulin (SHBG) [4].

Specifically, despite comparable baseline BMI between groups, the intervention group achieved significantly greater reductions in BMI and IR markers (FPG, FINS, HOMA-IR) alongside improved androgen profiles—notably decreased testosterone, DHEA-S, LH, and LH/FSH ratio with elevated SHBG [5,7].

3.2. Ketogenic Diet (KD)

The KD refers to any nutritional intervention aimed at inducing ketosis. Currently adopted variants include the Atkins Diet, High-Fat Ketogenic Diet, Very Low-Calorie Ketogenic Diet (VLCKD), and VLCKD. Although these dietary patterns differ in their specific macronutrient composition, their mechanisms of action are similar [14]. The KD is characterized by high fat, adequate protein, and very low carbohydrate intake (<30-50g/day), aiming to modulate carbohydrate metabolism and IR. It induces ketosis, shifting primary energy substrate utilization to ketone bodies (acetone, acetoacetate, β-hydroxybutyrate) [15]. KD demonstrates benefits in metabolic disorders, including T2DM, cardiovascular disease, and PCOS [16].

As early as 2005, a US prospective study involving 11 women diagnosed with obese PCOS undergoing 6 months of KD therapy showed significant improvements: mean fasting serum insulin levels decreased from 23.5 μU/ml to 8.2 μU/ml, the LH/FSH ratio decreased from 2.23 to 1.21, and free testosterone levels decreased from 2.19 ng/dl to 1.70 ng/dl. Additionally, subjects experienced an average weight loss of 12.1% and a BMI reduction of 4.0 kg/m² [17].

KD also reduces androgen production and subsequent dysregulated estrogen synthesis, improving the LH/FSH ratio. Variants include the VLCKD, restricting intake to 700-800 kcal/day [15]. Studies in PCOS patients indicate KD improves anthropometric (weight, BMI) and biochemical parameters: LH, FSH, SHBG, insulin sensitivity, and HOMA index [18]. PCOS patients following VLCKD (800 kcal/day) for 12 weeks exhibited a decrease in HOMA-IR from 4.2 to 2.1, indicating insulin sensitivity approaching normal levels.

3.3. Research status of LCDs combination therapy

The pathological core of PCOS with IR manifests as dysfunction in insulin signaling pathways (e.g., PI3K/AKT/GLUT4) and a self-perpetuating metabolic-endocrine cycle. Obesity (BMI ≥25 kg/m²), affecting 50%-80% of patients, represents a key modifiable factor. Targeting this pathological basis, LCDs enhance pharmacological efficacy through distinct mechanisms: IER employs cyclic caloric control (e.g., 600 kcal/day fasting in the 5:2 protocol) to activate AMPK pathways, promoting fatty acid oxidation and suppressing inflammation. When combined with metformin, IER reduces HOMA-IR by 40%-60% and increases pregnancy rates to 51.6%. KD achieves metabolic shift via very low carbohydrate intake (<30 g/day), inducing ketone bodies (e.g., β-hydroxybutyrate) to replace glucose as fuel while directly inhibiting androgen synthesis. After 12-week interventions, HOMA-IR decreases from 4.2 to 2.1 with a 22.4% reduction in testosterone. Conversely, the Mediterranean Diet focuses on modulating the gut microbiota-short-chain fatty acid axis through monounsaturated fats and phytochemicals, significantly improving dyslipidemia and chronic inflammation. Clinical implementation requires stratified approaches: Patients with BMI ≥30 should

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adopt VLCKD combined with GLP-1 receptor agonists to achieve >10% weight loss; those with BMI 25-30 benefit from IER plus metformin for insulin sensitivity optimization; while non-obese patients are suited for Mediterranean Diet to regulate metabolic microenvironments. Current limitations include insufficient long-term evidence and undeveloped precision nutrition strategies, necessitating future exploration of novel directions like SGLT2 inhibitor combinations and microbiota transplantation [2].

4. Discussion: challenges and future directions

4.1. Limitations and implementation challenges

Despite demonstrated efficacy, practical application of LCD patterns faces challenges. Intermittent fasting may induce hunger and psychological stress, impacting adherence. The stringent carbohydrate restriction in KD poses risks of nutritional imbalance and long-term sustainability difficulties. Crucially, robust longitudinal data on the long-term efficacy and safety profiles of these dietary regimens remain limited.

4.2. Future research imperatives

Future research priorities should form an integrated framework: initiating with rigorous large-scale longitudinal studies to assess the long-term efficacy and safety of LCDs; subsequently developing and validating individualized dietary protocols tailored to patients' physiological profiles, dietary preferences, and lifestyles; further exploring synergistic mechanisms integrating LCD with exercise prescriptions and psychological interventions; and ultimately formulating comprehensive strategies to mitigate hunger, prevent nutritional deficiencies, and enhance long-term compliance.

5. Conclusion

This article first introduces the concepts of PCOS and IR and their interrelationship, presenting epidemiological data to illustrate the significant prevalence of this condition. It subsequently analyzes the therapeutic advantages of LCDs, particularly IF and KD, as adjuvant therapies for PCOS with comorbid insulin resistance. Current evidence indicates that IF supports weight management by reducing BMI while enhancing insulin sensitivity, whereas KD improves IR-related metabolic parameters. These outcomes confirm the value of LCDs as adjunctive strategies within comprehensive PCOS-IR management, highlighting their substantial potential to augment conventional therapies and play a pivotal role in holistic treatment. This review establishes a foundation for future research directions and identifies promising approaches to optimize evidence-based, personalized nutritional interventions for PCOS-IR patients.

Nevertheless, current research on LCD-based adjuvant strategies faces persistent challenges. Low-calorie dietary regimens may induce psychological distress and carry risks of nutritional imbalances, leading to suboptimal treatment adherence. Furthermore, longitudinal data regarding the long-term efficacy of these interventions remains limited. Future studies should prioritize rigorous large-scale longitudinal investigations to generate robust efficacy evidence. Concurrently, developing integrated protocols that combine dietary interventions with psychological support could enhance adherence. Optimizing dietary frameworks and incorporating them within multimodal treatment approaches shows considerable promise for advancing clinical management of PCOS-IR.

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