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NUTRITIONAL STRATEGIES FOR ALLEVIATING SYMPTOMS OF POLYCYSTIC OVARIAN SYNDROME: A REVIEW OF CLINICAL EVIDENCE

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Abstract
This article offers a comprehensive synthesis of PubMed findings on Polycystic Ovary Syndrome (PCOS), delving into its intricate impact on lipid, carbohydrate, and hormonal metabolism. Exploring causative factors, disease progression, and dietary interventions, it also addresses associated health issues such as sleep disorders, mental health alterations, oxidative stress, and inflammation. PCOS is linked to severe complications like diabetes, organ fatty degeneration, infertility, cardiovascular diseases, dysbiosis, and cancer. The article underscores the modifiable nature of PCOS progression, emphasizing lifestyle adjustments, dietary choices, and nutrient selection. It explores both pharmaceutical and natural interventions, particularly herbal supplements, nutraceuticals strategies. The significance of individualized care is emphasized, acknowledging the interplay between lifestyle, genetics, and PCOS impact. In conclusion, this analysis contributes valuable insights into the complex interconnections of PCOS, metabolic pathways, and associated health outcomes, offering strategies for managing and alleviating this prevalent endocrine disorder through targeted dietary interventions and nutrient interventions with supplementation and functional food.

INTRODUCTION

Polycystic ovary syndrome (PCOS) stands out as the predominant female endocrinopathy, impacting a substantial 15% to 18% women in their reproductive years (Fauser *et al.*, 2012). Polycystic Ovary Syndrome (PCOS) is a prevalent endocrine disorder that impacts individuals with reproductive age, and its definition has indeed undergone changes over time. The Rotterdam criteria, established in 2003 during a meeting in Rotterdam, The Netherlands, broadened the definition of PCOS. The criteria expanded the diagnostic criteria beyond the typical manifestation of polycystic ovaries involves irregular menstrual cycles and hyperandrogenism, enabling the consideration of various phenotypes and manifestations (Szczuko *et al.*, 2017).

The Rotterdam criteria define PCOS based on the presence of at least two out of three features:

1. Oligoovulation or anovulation (irregular or absent menstrual cycles).
2. Clinical and/or biochemical signs of hyperandrogenism (excessive male hormone levels).
3. Polycystic ovaries on ultrasound examination.

Numerous studies have demonstrated the significance of elevated hormone concentrations, variations in gut microbiota makeup, and alterations in plasma metabolites in relation to the various phenotypes associated with Polycystic Ovary Syndrome (PCOS). Notably, the clinical phenomena of PCOS can evolve throughout an individual's lifespan, particularly in accountability to weight fluctuations, and may even coexist within the same patient. While individualized treatment remains the cornerstone of PCOS management, there is growing interest in categorizing phenotypes and adhering to therapeutic guidelines, which could prove to be clinically viable. It is crucial to implement precise recommendations well in advance of initiation of metabolic complications (Hong *et al.*, 2020). According to Universal evidence-based evaluation guidelines and treatment of PCOS, adopting a healthy diet is proposed for women experiencing PCOS throughout their lives. Specifically, for those who are overweight or obese, various balanced dietary approaches may be advised to manage energy intake and facilitate weight loss enhanced patient outcomes (Che *et al.*, 2021). The research is aimed at finding a diet that can help prevent and cure PCOS. Reducing impaired insulin sensitivity (IR) stands as a primary objective for Polycystic Ovary Syndrome treatment (PCOS) strategies. The initial approach to address IR, enhance ovulatory function, and reduce level of free testosterone in women with PCOS involves lifestyle changes, healthy eating coupled with routine physical activity, and achieving healthy weight attainment target of 5–10% (Moran *et al.*, 2009). Among anthropometric indicators, trunk fat, waist circumference (WC), and BMI emerge as the most reliable predictors of IR in PCOS.

Furthermore, dietary nutrient approaches have been proposed to provide additional benefits in terms of glucose and energy metabolism, as well as reproductive hormonal regulation. These include considerations such as carbohydrate distribution, meal frequency and timing, and ensuring adequate intake of n-3 fatty acids and vitamin D supplementation(Papavasiliou and Papakonstantinou, 2017). Exploring these dietary strategies can offer valuable support to women with PCOS.

This review aims to delve into nutritional support and dietary interventions tailored for women with PCOS, striving to distill evidence-based conclusions applicable in clinical practice.

The Biophysical substrate of PCOS involves four main factors:

1. **Dysfunctions of Gonadotropin Hormonal Synthesis:** PCOS is linked with disruptions in the conflation of gonadotropin hormones. These hormones play a crucial role in regulating the menstrual phase and ovulation. Irregularities in their synthesis can provide to the characteristic hormonal imbalances observed in PCOS.
2. **Insulin Resistance:** The progression of insulin resistance is a key factor in PCOS. Individuals with PCOS often exhibit reduced responsiveness to insulin, leading to elevated levels of this hormone. Insulin resistance can further contribute to hormonal imbalances and the development of various symptoms associated with PCOS.
3. **Influence of Excessive Body Fat:** Excessive body fat exerts a significant influence on PCOS. Adipose tissue, especially abdominal fat, is metabolically active and can exacerbate insulin resistance. Additionally, adipose tissue plays a crucial role in the production of certain hormones that can affect the reproductive system, exacerbating the symptoms of PCOS.
4. **Metabolic Pathways Involved in PCOS:** The metabolic processes interconnected with PCOS include the excretion and performance of insulin. Dysregulation in insulin excretion and signaling pathways can impact glucose metabolism and contribute to the development of insulin resistance, a hallmark of PCOS. Understanding and targeting these metabolic network are crucial for managing and treating PCOS.

These four factors collectively contribute to the complex pathophysiology of PCOS, involving hormonal dysregulation, insulin resistance, and the interplay with adipose tissue. Addressing these aspects is crucial for formulating impactful strategies for the management and treatment of PCOS.(Hong *et al.*, 2020)

1. DIETARY INTERVENTIONS: -

Quantitative and qualitative adjustments to dietary patterns play a crucial role in effectively managing Polycystic Ovary Syndrome (PCOS) (Papavasiliou and Papakonstantinou, 2017). In-depth investigation indicates that both a conventional hypocaloric diet and a high-protein/low-glycemic-load hypocaloric diet have profitable outcomes on insulin sensitivity and hormonal imbalances, prompting a notable reduction in testosterone and an increase in the level estrogen (Scarfò *et al.*, 2022).

A slight reduction in carbohydrate (CHO) intake has been shown to enhance cell responsiveness, lowering basal-cell response, insulin level during fasting, blood sugar level during fasting, total testosterone, and various cholesterol measures. This reduction demonstrates a clear positive impact on insulin resistance (Scarfò *et al.*, 2022). Beyond metabolic improvements, dietary patterns featuring a lower glycemic index also positively influence ovulation, fertility, and cardiovascular health in women with PCOS (Kazemi *et al.*, 2021).

Furthermore, it is recommended to incorporate a high-fiber diet. Insufficient fiber intake can result in a higher glycemic load, exacerbating insulin resistance (Scarfò *et al.*, 2022). Embracing these dietary modifications not only improves the overall metabolic profile but also contributes to enhanced ovulatory function, fertility, and cardiovascular well-being in individuals with PCOS. The impact of a ketogenic diet on outcomes interconnected to Polycystic Ovary Syndrome (PCOS) has been explored in various studies. Typically characterized by a high-fat, moderate-protein, and very low carbohydrate intake (40–50 g/day), this specific dietary pattern has shown promise in improving anthropometric and biochemical parameters. These improvements include alterations in luteinizing hormone (LH), follicle-stimulating hormone (FSH), and sex hormone-binding globulin (SHBG), additionally, there is a decrease in the production of abnormal estrogen resulting from the modulation of androgen aromatization in adipose tissue. This leads to an overall enhancement in the LH/FSH ratio (Scarfò *et al.*, 2022).

Given that anovulation and infertility in PCOS are exacerbated by chronic inflammation affecting the ovaries and uterine cavity (Rudnicka *et al.*, 2021), the significance of a keto diet extends to its anti-rheumatic properties mediated by the ketone-hydroxybutyrate (BHB). Notably, in murine models, BHB has demonstrated the ability to impede the triggering of the NLRP3 inflammasome, which typically contributes to the production of interleukin-1 (IL-1) and interleukin-18 (IL-18) in human cells (Scarfò *et al.*, 2022).

In the context of Polycystic Ovary Syndrome (PCOS), the administration of natural compounds through oral supplementation has demonstrated remarkable efficacy in mitigating inflammation. Studies have revealed that a supplementation of magnesium, zinc, calcium, and vitamin D exerts a beneficial impact on PCOS-afflicted women by reducing oxidative stress and inflammation, thereby enhancing antioxidant capacity(Scarfò *et al.*, 2022). This positive effect is evidenced by a notable decrease in plasma malondialdehyde (MDA), a recognized marker of lipid peroxidation(Mas-Bargues *et al.*, 2021)(Mas-Bargues *et al.*, 2021), leading to an improved metabolic profile(Scarfò *et al.*, 2022). Certainly, I can help you modify and refine the text. Here's an edited version:

Additionally, vitamin D possesses anti-inflammatory and antioxidant properties, resulting in reduced levels of hs-CRP and MDA(Scarfò *et al.*, 2022) Due to their well-established anti-inflammatory characteristics(Cincione *et al.*, 2021) the association between omega-3 polyunsaturated fatty acids (n3 PUFAs) supplementation and PCOS has been explored. Evidence suggests that n3 PUFAs have a positive impact on inflammation, oxidative stress, and hormonal parameters, leading to a decrease in hs-CRP, MDA, total testosterone, and an increase in antioxidant capacity. However, these effects appear to be more pronounced in women over 40 years old with cardiovascular and metabolic abnormalities(Unfer, 2021).

Specifically, n3 PUFAs, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), play a role in reducing inflammation by decreasing TNF-, IL-6, and IL-1 and interfering with the activity

of nuclear factor kappa B (NF-B), thereby reducing the activation of several proinflammatory genes (Salek *et al.*, 2019). Moreover, n3 PUFAs promote the oxidation of mitochondrial fatty acids, reducing lipid deposits and the generation of free radicals(Salek *et al.*, 2019).
The ovarian microenvironment is also influenced by oral supplementation with L-carnitine. In a murine model, acetyl and propionyl L-carnitine have been shown to enhance ovarian functions by ameliorating ovarian oxidative stress, preventing the upregulation of SIRT1, SIRT3, and SOD2. Additionally, this study demonstrated that L-carnitine acts against glycative molecular pathways (Di Emidio *et al.*, 2020). In women with PCOS, L-carnitine can improve the metabolic profile, leading to better levels of insulin, adiponectin, testosterone, LH, and FSH(Scarfò *et al.*, 2022).
Furthermore, nonpharmacological intervention with flavonoids should be considered for women with PCOS due to their significant anti-inflammatory and antioxidant activities. In murine models, flavonoids extracted from Nervilia Fordii positively balance FSH, LH, testosterone, and insulin levels, preventing JAK2/STAT3 pathway activation and upregulating IL-6 expression(Zhou *et al.*, 2019).

2. SUPLEMENTATION: -

In the context of polycystic ovary syndrome (PCOS) in women, the oral supplementation of natural molecules has demonstrated notable efficacy in reducing inflammation. Specifically, a magnesium zinc–calcium–vitamin D co - supplementation has been found to decrease oxidative stress and inflammation in women with PCOS, leading to an increase in antioxidant capacity(Scarfò *et al.*, 2022) This positive impact is reflected in the reduction of plasma malondialdehyde (MDA), a marker of lipid peroxidation(Mas-Bargues *et al.*, 2021), and consequently, an improvement in the metabolic profile(Papavasiliou and Papakonstantinou, 2017).

Additionally, the anti-inflammatory and antioxidant properties of vitamin D contribute to reduced levels of hs-CRP and MDA (Yang *et al.*, 2022). The investigation into omega-3 polyunsaturated fatty acids (n3 PUFAs) supplementation and its relationship with PCOS has revealed promising outcomes. Evidence suggests that n3 PUFAs positively influence inflammation, oxidative stress, and hormonal parameters, leading to a decrease in hs-CRP, MDA, total testosterone, and an increase in antioxidant capacity(Scarfò *et al.*, 2022). Notably, these effects appear to be more pronounced in women over 40 years old with cardiovascular and metabolic abnormalities(Nafld *et al.*, no date) . Specifically, n3 PUFAs such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) act on inflammation by reducing TNF-, IL-6, and IL-1 and interfering with the activity of nuclear factor kappa B (NF-B), thereby reducing the activation of several proinflammatory genes (Mas-Bargues *et al.*, 2021). Moreover, n3 PUFAs promote the oxidation of mitochondrial fatty acids, leading to a reduction in lipid deposits and the generation of free radicals(Salek *et al.*, 2019).

The ovarian microenvironment is also positively influenced by oral supplementation with L-carnitine. In a murine model, acetyl and propionyl L-carnitine have been shown to enhance ovarian functions by ameliorating ovarian oxidative stress status, preventing the upregulation of SIRT1, SIRT3, and SOD2. Additionally, L-carnitine acts against glycative molecular pathways (Di Emidio *et al.*, 2020). In women with PCOS, L-carnitine has been demonstrated to improve the metabolic profile, resulting in better insulin, adiponectin, testosterone, LH, and FSH levels (Scarfò *et al.*, 2022).

Furthermore, a nonpharmacological intervention involving flavonoids are a noteworthy consideration for women with PCOS due to their extensive anti-inflammatory and antioxidant activities. In murine models, flavonoids derived from Nervilia fordii have been found to positively balance FSH, LH, testosterone, and insulin levels. This intervention prevents JAK2/STAT3 pathway activation and upregulates IL-6 expression(Zhou *et al.*, 2019).
The research findings underscore a prevalent inadequacy in the nutritional intake of women with PCOS, revealing deficiencies in essential nutrients such as fiber, omega-3, calcium, magnesium, zinc, and several vitamins, including folic acid (vitamin B9), ascorbic acid (vitamin C), cobalamin (vitamin

B12), and calciferol (vitamin D) (Szczuko *et al.*, 2021). Conversely, an overabundance of nutrients, specifically sucrase, sodium, overall lipid content, saturated fat compounds, and cholesterol levels were observed (Szczuko *et al.*, 2021).

Efforts were made to explore whether addressing these deficiencies through a calorie-controlled plan with an emphasis on low-glycemic foods (GI) could yield positive outcomes, particularly in relation to water-soluble vitamins(Tobergte and Curtis, 2013). Results indicated a favorable impact on most B vitamins, with increased dietary supply correlating with elevated plasma levels in women with PCOS. Notably, this implication was not as pronounced for vitamin B3, and the levels of B2 and vitamin B1 (thiamine) did not exhibit the same degree of improvement as their counterparts(Szczuko, Szydłowska and Nawrocka-Rutkowska, 2021).

Highlighting the significance of vitamin B3, research suggests a potential link between its insufficient supply and progression of inflammation, associated diseases(Szczuko *et al.*, 2021) and an elevated risk of cardiopathic conditions (Szczuko *et al.*, 2021) Emphasizing the cardiovascular benefits, thiamine supplementation is recommended due to its activation of transketolase, which contributes to inhibiting mechanisms that can damage blood vessels, thereby reducing the risk of cardiovascular diseases(Tobergte and Curtis, 2013).

In the context of PCOS, consideration should also be given to coenzyme Q10 supplementation, as an 8-week regimen demonstrated improvement in Inflammatory and Endothelial Dysfunction Markers Observed in Overweight and Obese Patients with Polycystic Ovary Syndrome (PCOS) (Szczuko *et al.*, 2021)

Moreover, the literature emphasizes the pivotal role of Calciferol (vitamin D) in PCOS, citing its influence on insulin production and release, receptor expression, and response to blood sugar transport(Mavropoulos *et al.*, 2005). Vitamin D indirectly normalizing extracellular calcium and parathyroid hormone concentration regulates carbohydrate metabolism, as well as impacting the expression of genes in metabolic pathways that affect systemic inflammation. This inhibition of pro-inflammatory cytokine synthesis may contribute to alleviating insulin resistance (IR)(He *et al.*, 2015). Notably, women with polycystic ovary syndrome (PCOS) undergoing a weekly supplementation of 20,000 IU of cholecalciferol. exhibited improved carbohydrate metabolism, evidenced by reductions in fasting glucose, triglycerides, and estradiol. Although androgen levels remained unchanged, enhancements in menstrual frequency were observed and documented (Szczuko *et al.*, 2021)

Additionally, n a separate research study, the concurrent administration of magnesium, zinc, calcium, and vitamin D demonstrated a noteworthy decrease in both hirsutism and total testosterone levels when compared to a placebo.

However, this supplementation did not affect sex hormone-binding globulin (SHBG) levels or the Androgenic Activity Index (Szczuko *et al.*, 2021)

In traditional medicine, isoquinoline alkaloids are natural substances that have been historically employed to regulate androgen synthesis, as well as fat and carb metabolism. Berberine, akin to metformin, exhibits favorable metabolic effects in type II diabetes by activating Adenosine Monophosphate-activated Protein Kinase (AMPK). Berberine demonstrates notable hypoglycemic and hypolipidemic effects, lower body weight, and acts as an effective insulin sensitizer(Bertuccioli *et al.*, 2020). It also mitigates steroid hormone synthesis and ovarian aromatase expression through its impact on the hypothalamic–pituitary–ovarian axis, leading to improved ovulation rates, menstrual regulation, and increased live birth rates and pregnancy. Studies suggest that the prolonged use of berberine has been linked to temporary and minor side effects such as constipation and nausea underscoring its potential safety and promise in treating PCOS patient(Szczuko *et al.*, 2021).

Chromium, a fundamental element in carbohydrate and lipid metabolism, has become a widely consumed dietary supplement in the USA(Lucidi *et al.*, 2005). Research and available literature propose that supplementing with zinc and selenium may be beneficial in addressing deficiencies in some PCOS patients. Zinc, vital for structural functions and intracellular signaling, influences lipid and glucose metabolism as well as fertility(Maxel *et al.*, 2017). In the context of obesity, a deficiency in zinc intake is associated with heightened levels of hyperinsulinemia and increased inflammation and worsened lipid profiles. Zinc ions also exhibit insulin-mimetic properties in adipocytes,

facilitating lipogenesis and glucose transport is achieved by promoting the translocation of glucose transporter 4 (GLUT4) to the plasma membrane, thereby stimulating the cellular processes responsible for increased lipid synthesis and efficient glucose uptake (Nasiadek, Stragierowicz and Kilanowicz, 2020). A deficiency in zinc could potentially exert a notable influence on Polycystic Ovary Syndrome (PCOS) pathogenesis and serve as a potential prognostic marker. Studies indicate that PCOS patients have significantly lower serum zinc levels than healthy controls. Furthermore, individuals with polycystic ovary syndrome (PCOS) exhibiting impaired glucose tolerance have been observed to possess lower serum zinc levels in comparison to those with normal glucose tolerance.
Selenium, associated with lower C-Reactive Protein (CRP) levels, possesses antioxidant and anti-inflammatory properties. Lastly, supplementation with omega-3 fatty acids is crucial, as they are often deficient in food of women with PCOS. Supplementing with polyunsaturated fatty acids (PUFAs) can boost reproductive performance in PCOS by enhancing the expression of key enzymes like CYP51, CYP19, StAR, and 3-HSD, crucial for hormone secretion and ovarian functions.(Szczuko *et al.*, 2021)

In summary, dietary supplementation is an individualized subject that necessitates consultation with the patient. Active participation and compliance are desirable for achieving overall improvements in metabolic equilibrium. A healthy lifestyle and balanced diet should be prioritized as the primary elements of PCOS therapy.

3. Nutraceutical strategy:-

A well-balanced diet plays a pivotal role in regulating insulin levels for individuals with Polycystic Ovary Syndrome (PCOS). Complementary to this dietary approach, herbal infusions can play a supportive role in PCOS therapy. Some beneficial herbs include cinnamon (Cinnamomum verum), Aloe vera, green tea (Camellia sinensis), chamomile (Matricaria chamomilla), and white mulberry (Morus alba)(Szczuko *et al.*, 2021). These herbs have properties that can regulate lipid profile and carbohydrate metabolism, adapting them to cater to all manifestations of PCOS.
Certain herbs also impact the lipid profile, blood glucose level, and insulin resistance (IR). Among these, green tea and marjoram (Majorana hortensis) have demonstrated advancements in endocrine function, ovarian weight, insulin sensitivity, antioxidants, and anti-inflammatory parameters. Herbal remedies is recommended, particularly for PCOS patients exhibiting increased androgen levels. Green mint (Mentha Spicata L.) has antiandrogenic effects, revitalizing follicular development in Ovarian Tissue. Licorice smooth is utilized for its anti-androgen and estrogen-like activity, effectively reducing excess testosterone. However, caution is advised, as licorice may induce the condition of hypertension, hypokalemia, and metabolic alkalosis, Particularly for individuals experiencing heightened cortisol levels(Szczuko *et al.*, 2021).

Herbs like Camellia sinensis, Serenoa repens, Rosmarinus officinalis, and Glycyrrhiza glabra possess the ability to decrease androgen levels and hinder androgenetic alopecia by opposing the 5-alpha-reductase enzyme(Kakadia *et al.*, 2019) . Vitex agnus-castus oversees the menstrual cycle and boasts an extensive traditional usage(Kakadia *et al.*, 2019). Flaxseed lignans are thoroughly researched dietary phytoestrogens that may alter sex hormone levels. (Szczuko *et al.*, 2021).

Turmeric, specifically curcumin, is biologically active and alleviates Oxidative Stress-Associated Complications in Individuals with Polycystic Ovary Syndrome (PCOS)(Yuandani *et al.*, 2021). Nettle (Urtica dioica) is a versatile herb with antioxidative, anti-inflammatory, antimutagenic, and antitumor properties(Yuandani *et al.*, 2021). Flavonoids in nettle have antioxidant activities that can modify specific enzymes, inactivating agents like hydroxide radicals and nitrite peroxide(Sarma Kataki, 2012)(Ferro *et al.*, 2020).

For PCOS with Metabolic Syndrome and NAFLD, herbs with hepatoprotective activities should be considered. Silymarin in milk thistle (Silybum marianum) and sesquiterpenes in artichoke extract are examples (MacDonald-Ramos *et al.*, 2021)(Nafld *et al.*, no date).Taraxacum officinale and its component taraxasterol may silence the SIRT1 gene, preventing disruption of hepatic cells. Black cumin (Nigella sativa) also possesses similar properties and can include the following in the diet of individuals with obesity and Polycystic Ovary Syndrome (PCOS)(Szczuko *et al.*, 2021).

In summary, herbs provide diverse possibilities for interventions at various stages of PCOS, supporting its treatment.

Conclusion

In conclusion, strategies for PCOS involves a multifaceted approach, with dietary interventions, supplementation, and nutraceutical strategies playing pivotal roles. The research highlights the impact of various dietary patterns, such as hypocaloric and high-protein/low-glycemic-load diets, in improving insulin sensitivity and hormonal imbalances. Additionally, a keto diet has exhibited positive results in enhancing anthropometric and biochemical parameters, along with anti-inflammatory effects mediated by ketone-hydroxybutyrate.

Supplementation with natural compounds, including magnesium, zinc, calcium, vitamin D, omega-3 polyunsaturated fatty acids, L-carnitine, and flavonoids, has demonstrated efficacy in mitigating inflammation, reducing oxidative stress, and improving metabolic profiles in women with PCOS. These interventions address deficiencies in essential nutrients and contribute to enhanced ovarian function, hormonal balance, and overall well-being.

Furthermore, nutraceutical strategies involving herbal infusions showcase the potential of herbs like Aloe vera, cinnamon, green tea, chamomile, and white mulberry in regulating lipid and carbohydrate metabolism. Specific herbs, such as licorice and Vitex agnus-castus, show promise in managing androgen levels, while turmeric and nettle exhibit antioxidant and anti-inflammatory properties.

The comprehensive review emphasizes the importance of a balanced diet, lifestyle modifications, and individualized approaches to supplementation and herbal interventions. It underscores the need for active patient participation and compliance to achieve holistic improvements in metabolic equilibrium. Ultimately, these dietary and nutraceutical strategies provide diverse and promising avenues for the comprehensive management of PCOS at various stages, supporting its treatment and improving the quality of life for affected individuals.

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