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Effect of Dietary Patterns and Nutrients on Symptoms of Polycystic Ovary Syndrome

Research Article

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Abstract

Polycystic Ovary Syndrome (PCOS) is now a commonly occurring endocrine-metabolic condition. Symptoms of PCOS include hyperandrogenism, hirsutism, and menstrual irregularities. Dietary intake is a modifiable risk factor and can be modified to prevent or manage PCOS. In this review, we aimed to summarize the current evidence for various dietary patterns and nutrients that have been studied in association with PCOS or the symptoms of PCOS. In addition, we have also summarized the existing evidence on probiotics in relation to PCOS. The dietary patters of interest are low-carbohydrate diet, Mediterranean diet and intermittent fasting. The nutrients of interest are inositol, selenium, vitamin D and omega-3 fatty acids. Extensive literature review was conducted through PubMed/MEDLINE, Scopus, and Web of Science. Our review identified that dietary patterns including low-carbohydrate diets, the Mediterranean diet, and intermittent fasting, nutrients like inositol, vitamin D, probiotics, omega-3 fatty acids, and selenium, and probiotics seem to offer benefits for PCOS symptoms such as hormone level improvement, better glycemic control, enhanced insulin sensitivity, improved lipid levels, and reduced inflammation. Therefore, it has been shown that in addition to pharmacotherapy, dietary modifications and supplements can be effective adjunct therapy for PCOS..

Keywords: Polycystic Ovary Syndrome (Pcos); Endocrine Disorders; Dietary Patterns; Nutrients

Introduction

Polycystic ovary syndrome (PCOS) is a complex but common endocrine-metabolic condition that affects 6 to 20% of women of reproductive age, depending on the criteria used for diagnosis [1] .It is an oligogenic disorder in which a variety of genomic and environmental variables interplay to determine the diverse clinical, and biochemical phenotype of the disorder [2] .The pathogenesis of this condition is not completely known but is considered multifactorial, which includes genetic, transgenerational, and environmental components, comprising diet and other lifestyle issues. These factors drive the abnormalities involved in the pathophysiology of PCOS, primarily defects in the hypothalamic–pituitary-axis, ovarian function, and insulin secretion/action which in turn affects steroidogenesis, ovarian follicle development, and metabolism [3,4]. PCOS cannot be diagnosed with a single test; rather, the condition is determined by the presence of three distinct factors: oligo-anovulation, androgen excess, and ultrasound evaluation of polycystic ovarian morphologywhich can clinically manifest as irregular menses, hirsutism, acne, and metabolic dysfunction [3,5]. As a result of metabolic dysfunction, women with PCOS are prone to insulin resistance coupled with compensatory hyperinsulinemia which puts them at high risk for developing obesity, Type 2 diabetes mellitus (T2DM), cardiovascular disease, and gynecological cancer [1,6].

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In order to improve a variety of health outcomes, lifestyle modification is one of the suggested treatment techniques for PCOS in the international evidence-based guidelines [7]. PCOS treatment should be symptom-focused, long-term, dynamic, and individualized to the patient's needs, expectations, and changing circumstances. The effects of ovarian dysfunction, hyperandrogenism, and/or related metabolic problems should all be the focus of therapeutic strategies [8]. Although there is no cure for PCOS, first-line management involves measures such as dietary changes and exercise that focus on enhancing insulin sensitivity and preventing long-term health consequences as an unhealthy diet, along with low-grade inflammation, hyperinsulinemia, and hyperandrogenism is a major contributor to the metabolic risk factors linked to PCOS pathophysiology [9,10].

Numerous symptoms, including insulin resistance, infertility, oxidative stress, hirsutism, and elevated inflammatory markers, are experienced by women with PCOS. PCOS causes infertility, which has an overall prevalence of 5% to 15% [11]. Ovarian cyst development involves a variety of negative side effects, including issues with the menstrual cycle (heavy/irregular periods/spotting) [12]. Long and irregular menstrual cycles associated with PCOS have been linked to greater levels of androgen and lower levels of Sex-Hormone Binding Globulin (SHBG), resulting in hormonal imbalance that eventually leads to infertility [13]. One of the signs of PCOS hyperandrogenism is hirsutism, which is the presence of facial terminal hair that resembles masculine facial hair. 60–80% of women with PCOS have hirsutism [14,15]. This varies between ethnic groups and is influenced by androgens (particularly, testosterone), which also affects the extent to which hair grows. Because androgen has a large influence on PCOS, folliculogenesis is diminished as a result. A rise in the number of tiny antral follicles is caused by early-stage increases in androgens, which also cause the production of primordial follicles [16].

Obesity is the primary cause of numerous metabolic disorders in our body and interacts positively with PCOS [17]. According to recent research, normal-weight women are at risk and can easily shift from being healthy to being ill, regardless of body weight, if the fat is deposited in the visceral area of the body [18]. This is true even though body weight is linked to PCOS issues. Regardless of Body Mass Index (BMI), visceral fat is common in thin women with PCOS [19]. Visceral adiposity and obesity cause inflammation and insulin resistance(IR), which in turn cause metabolic abnormalities in women's bodies in those who have PCOS [20]. Hyperinsulinemia, hyperandrogenism, IR, and greater androgen levels are all positively correlated in women with PCOS [21,22]. Acne is a significant and typical symptom of PCOS and is brought on by the inflammation of the pilosebaceous glands. Dihydrotestosterone, a powerful type of testosterone, is produced in greater amounts, which increases sebum production and disturbs follicular epithelial cells .

Nutritional interventions play a crucial role in managing and preventing complications associated with PCOS. A diet rich in whole foods, lean proteins, healthy fats, and low in refined sugars and processed foods, can help regulate insulin levels, reduce inflammation, and promote hormonal balance. These dietary adjustments can mitigate common PCOS symptoms such as weight gain, irregular menstrual cycles, and IR, thereby reducing the risk of developing more severe complications like type 2 diabetes, cardiovascular diseases, and infertility. By adopting a tailored nutritional plan, individuals with PCOS can significantly improve their overall health and quality of life. This review examines current knowledge of the nutritional components of PCOS and proposes strategies for managing food and nutritional therapy in PCOS patients. This review lays out some broad guidelines around which a customized plan for every patient can be created.

Methods

To ensure a thorough review of the existing research on PCOS symptoms and dietary interventions, the literature search for this article was conducted using multiple databases such as PubMed/MEDLINE, Scopus, and Web of Science. A combination of keywords and Medical Subject Headings (MeSH) words such as "polycystic ovary syndrome", "PCOS", "dietary interventions", "intermittent fasting", "low-carbohydrate diet", "ketogenic diet", "Mediterranean diet", "vitamin D", "inositol", "selenium", "omega-3", "probiotics" and related terms were used. Boolean operator "AND" was utilized to refine the search and obtain the most relevant studies. In addition, studies cited in the articles referenced in this paper were reviewed to identify relevant articles that might have been missed and ensure a comprehensive and thorough review of the topic. Peer-reviewed original research, systematic review articles and meta-analyses were included in this paper. Multiple researchers were involved in performing the literature review to screen and identify the relevant articles.

This study does not require Institutional Review Board approval as there were no human subjects involved. This review summarizes the results of existing research done on this topic .

Results

Low-carbohydrate diet

Low-carbohydrate diets (LCDs) are of many types, with the difference being the amount of carbohydrates (CHO) consumed and whether protein and fats are restricted or increased. LCDs typically allow 10-25% of total daily energy (TDE) to be obtained from CHO, 10-30% from protein, and 25-45% from fats. A popular form of LCDs called the ketogenic diet (KD) is a type of low-carb high-fat diet where CHO are severely restricted to <10% of TDE, protein to about 10% of TDE, and fats to an increased quantity of 70-80% of TDE. KD restricts protein to 10% of TDE to prevent gluconeogenesis and can also be hypocaloric to promote weight loss[23]. Another popular form of LCD is the Atkins diet which restricts CHO to 20-100g/day but does not restrict protein and fats[24]. Despite the LCDs and specifically KD being highly restrictive, they have been rapidly gaining popularity due to their association with improved glycemic control, improvement in hyperlipidemia, increased weight loss, and especially reduction in abdominal obesity. In addition to that, LCDs increase satiety and lead to the consumption of fewer calories naturally. Healthy fats such as omega-3 fatty acids (found in fish, flaxseeds, and walnuts) have anti-inflammatory properties that can help reduce the inflammation associated with PCOS.Monounsaturated fats (found in olive oil, avocados, and nuts) can improve lipid profiles and

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reduce cardiovascular risks, which are higher in women with PCOS. Fats promote satiety and help maintain a stable blood sugar level, reducing cravings and overeating, which is beneficial for managing PCOS symptoms.They also provide essential fatty acids necessary for hormone production and regulation.

Adequate protein intake helps maintain muscle mass, which is crucial for a higher metabolic rate. This helps in managing weight and improving overall metabolic health in women with PCOS.Proteins aid in the repair and growth of tissues, which can be beneficial for women experiencing hair loss and other tissue-related symptoms of PCOS. Proteins have a lower glycemic index and help in stabilizing blood sugar levels, reducing insulin spikes and improving insulin sensitivity. Improved insulin sensitivity helps in reducing the hyperinsulinemia and hyperandrogenism commonly seen in PCOS. It is due to this reason that KD, which was originally developed for the management of epilepsy, gained popularity for weight loss[23]. LCDs have been hypothesized to be helpful in the management of symptoms of PCOS such as hyperinsulinemia, IR, hyperlipidemia, and acne.

Studies have reported that LCDs can lower blood glucose, insulin, and hemoglobin A1c (HbA1c) levels and increase insulin sensitivity. They can also improve hyperlipidemia by reducing elevated LDL and triglyceride levels. High-glycemic foods and a high-glycemic-load diet can play a role in the development of acne through their effect on insulin, androgen hormones, and insulin-like growth factor-1 (IGF-1) activity [25]. It has been shown that replacing CHO with fat, preferably mono and polyunsaturated fats, can have beneficial effects on insulin levels in PCOS [26]. Restricting CHO can therefore reduce the spike in insulin and IGF-1 levels and reduce the development of acne mediated by androgen hormones. There are limited studies evaluating the effects of LCDs in women with PCOS. In the studies that exist, the sample size is often small.

However, these studies show that LCDs, specifically KD, have a positive effect on anthropometric measurements and biochemical parameters such as free testosterone, luteinizing hormone levels (LH), Follicle stimulating hormone (FSH) levels, LH/FSH ratio (LH and LH/FSH ratio are elevated in women with PCOS), blood glucose, insulin level, etc. In a study by Paoli et al. [27] women who were fed a ketogenic Mediterranean diet for 12 weeks observed a reduction in body weight with a mean reduction of 9.4 kgand a reduction in glucose and insulin levels, free testosterone, LH, LH/FSH ratio, triglycerides, and cholesterol. In another study, women who consumed <20g of CHO/day for 24 weeks observed a mean weight loss of 12%, a 22% reduction in free testosterone, and a 36% reduction in LH/FSH [28]. A study by Cincione et al. showed that KD improved insulin sensitivity in obese women with PCOS and also lowered LH levels and LH/FSH ratio [29]. In a study by Li et al., apart from improvement in anthropometric measurements and menstrual cycle, KD also had a beneficial effect on liver function [30]. Overall, it can be summarized that KD is associated with an improvement in anthropometric characteristics, reproductive hormone levels, glycemic control, insulin sensitivity, blood lipid levels, and liver function.

Mediterranean diet

According to Lluis Serra-Majem et al. [31] the Mediterranean diet is thought to have its roots in the early 1950s and 1960s eating habits of the civilizations that surrounded the Mediterranean Sea, primarily Greece and Italy but also includes about 20 other countries that are dispersed throughout the region. Whole grains, legumes, fruits, and vegetables are all part of the Mediterranean diet, along with cold-pressed olive oil as the main source of fat. Seafood, meat, and dairy products are consumed in moderation, while eggs, saturated fats, and red meat are consumed in smaller amounts. Some foreign foods have been included in the conventional dietary pattern as a result of various cultural interactions. Over time, the Mediterranean diet has evolved and adapted, incorporating various foreign foods into the traditional dietary pattern. This evolution is largely due to the diverse cultural interactions and exchanges within the region, bringing in new ingredients, cooking methods, and culinary influences from different parts of the world. For example, foods such as quinoa from South America, avocados from Central America, and spices like turmeric and curry from Asia have been integrated into the Mediterranean culinary tradition, enriching and diversifying it while maintaining its core principles.Ancel Keys, an American scientist who developed the Seven Countries Study, discovered a positive correlation between the Mediterranean eating pattern and a low incidence of cardiovascular diseases when compared to the Northern European Countries after a 25-year follow up, which led to increased attention to the Mediterranean diet's health benefits [32].

In the Prevención con DietaMediterránea (PREDIMED) study, which was conducted over a 4-year period, the effects of a Mediterranean diet over a 3-month period on circulating inflammatory biomarkers like Interleukin-6 (IL-6) and C-reactive protein (CRP) were compared to those of a low-fat diet [33]. It was discovered that the fasting insulin levels, blood glucose levels, IL-6, and Homeostatic Model Assessment (HOMA) score decreased in the group that adhered to a Mediterranean diet that was supplemented with olive oil and nuts. In another study, the intervention group was advised to follow a diet that included at least 250–300 g of fruits, 125–150 g of vegetables, 25–30 g of walnuts per day, and increased consumption of olive oil over the course of 24 months. The study examined the effects of a Mediterranean diet on vascular inflammatory markers and endothelial function. The Mediterranean diet, which contains 50 to 60% CHO, 15 to 20% protein, and less than 30% fat, was also advised, as was daily exercise for 30 minutes. After following the diet for two years, it was seen that hs-CRP levels, IL-7 and Interleukin-18 (IL-18), IR, and the HOMA score were decreased. The experimental group also had a substantial decrease in body weight, BMI, and waist circumference [34].

Although the precise mechanism by which a Mediterranean diet produces health benefits is not fully understood, several approaches have been proposed to play a major role. These include a reduction in saturated fat intake as the Mediterranean diet involves a lesser intake of red meat and dairy products, by the quenching of free radicals, by the antioxidant vitamins and phytochemicals coming from a variety of whole grains, legumes, nuts, and seeds, weight reduction, and by impairing the production of free radicals.Although the precise mechanism by which a Mediterranean diet produces health benefits

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is not fully understood, several approaches have been proposed to play a major role. These include reducing saturated fat intake, as the diet involves eating less red meat and fewer dairy products. The diet also provides antioxidant vitamins and phytochemicals from whole grains, legumes, nuts, and seeds, which help quench free radicals. Additionally, weight reduction and impaired production of free radicals are believed to contribute to the health benefits of the Mediterranean diet.One of the ways the Mediterranean diet may aid in weight loss is through the production of short-chain fatty acids by the gut microbiota from a variety of resistant starches and oligosaccharides consumed on the Mediterranean diet. These short-chain fatty acids aid in promoting a sense of satiety by increasing the production of hormones like glucagon-like peptide-1 (GLP-1) and peptide-YY, which inhibit gastric emptying [35].

Intermittent Fasting in PCOS

Intermittent fasting (IF) is the practice of alternating between eating and fasting, and it is growing in popularity as a replacement for continuous calorie restriction due to new research demonstrating similar benefits for weight loss and cardiometabolic health [36,37]. Time-restricted feeding (TRF), alternate-day fasting (ADF), and the 5:2 diet (eating normally for 5 days and restricting calories to 500-600 for 2 non-consecutive days)are all included under the broad term of "intermittent fasting"36. TRF entails limiting the eating window to a predetermined number of hours per day (often 4 to 10 h) and fasting with calorie-free liquids for the remaining hours. Participants in ADF shift between "feast days" where they eat without restriction and "fast days" where they only consume water or < 25% of their daily energy needs. The 5:2 diet, on the other hand, is a modified variation of ADF that allows for five feast days and two fast days each week [38].

The majority of clinical research has concentrated on applying intermittent fasting regimens in the obese population with metabolic syndrome to reduce weight and improve health by delaying the progression of cardiovascular disease, hypertension, and T2DM [39]. Through a variety of mechanisms, metabolic switching induced across these various models of IF increases longevity, reduces body mass, and enhances metabolism39,40. IF is also found to be advantageous in lowering IR along with improving leptin and adiponectin levels [39]. There are limited studies evaluating the effects of IF in women with PCOS. TRF entails a period of fasting, allowing a decline in insulin levels with an increase in insulin sensitivity, and concurrent improvement in glucose control [41]. This is consistent with a study by Li et al. [42] in which 15 women with PCOS with anovulation between the ages of 18 and 31 took part in a 6-week trial that was split into two separate phases of a 1-week baseline weight stabilization period and a 5-week TRF period. The eight-hour TRF reduced weight, particularly body fat, and increased SHBG, with decreased total testosterone and free androgen index (FAI), which improved menstrual cycle irregularity in 11 out of 15 patients [42].

Similar to this, premenopausal women with obesity participated in a trial by Harvie et al. and followed a 5:2 diet where they fasted with 500 kcal two days each week. After a 7% weight loss compared to baseline, the FAI dramatically decreased after 24 weeks of the 5:2 diet. On the other hand, Dehydroepiandrosterone Sulfate (DHEA-S), testosterone, and androstenedione did not change [43]. These studies further established the connection between hyperandrogenism and metabolic abnormalities by showing that changes in androgen indicators were associated with decreases in body weight, inflammation, and IR38. Furthermore, it has been claimed that a time-restricted eating plan that limits nighttime food intake enhances postprandial insulin and glucose handling as it aligns circadian rhythm with diurnal food intake [44]. The study by Floyd et al.44demonstrated that an early time-restricted feeding (eTRF) regimen, where participants consumed all their meals in a 6-hour window ending before 3 p.m., significantly improved various cardiometabolic health markers. Specifically, eTRF enhanced postprandial insulin sensitivity, increased beta-cell responsiveness, and lowered blood pressure. All participants except one experienced an improvement of at least 5 mU/L in mean postprandial insulin levels. Overall, these findings, though limited, suggest that fasting can considerably lower androgen markers in premenopausal women with PCOS, especially if calories are ingested earlier in the day [38].

Inositol

Inositol is a sugar alcohol that belongs to a group of natural polyols called cyclohexanols, containing six carbon units with each carbon attached to a hydroxyl group. Epimerization of the hydroxyl groups using specific epimerases or phosphorylation using specific phosphorylases leads to the formation of 9 different forms of inositol, including the two main forms - Myo-inositol (MI) and D-chiro-inositol (DCI). MI and DCI are the most common and abundantly present forms in the human body[45]. Humans can synthesize MI in the body (up to 4 g/day), mainly in the kidneys, but can also obtain it through diet (about 1 g/day) from food sources such as citrus fruits, beans, grains, nuts, and seeds [46]. MI is biosynthesized in the body through the process of isomerization of glucose-6-phosphate to form inositol-3-phosphate which is then converted to free MI through dephosphorylation. Free MI can be converted to DCI through epimerization of the hydroxyl groups but only a fraction of free MI is converted to DCI through this process [47]. MI and DCI are present in the plasma in a 40:1 ratio.

MI plays an important role in the uptake of glucose and transduction of cellular signals including endocrine signals such as insulin, FSH, and thyroid-stimulating hormone (TSH) while DCI plays an important role in androgen synthesis in the ovaries [47]. Inositol has been shown to improve the quality of oocytes and embryos and increase ovulation frequency and rate of pregnancy [48]. Moreover, deficiency of inositol has been linked to the pathogenesis of conditions such as diabetes, metabolic syndrome, spina bifida, and PCOS. MI and DCI have been shown to be helpful in the management of PCOS, especially in the ratio of 40:1 at a dose of 2 grams twice a day[49,50]. In a study by Nordio et al.[49, 56] participants aged 18-45 years diagnosed with PCOS were studied. MI and DCI were administered in different ratios keeping the total MI + DCI dose at 2 grams twice a day for all groups for three months. The results showed that there was an improvement in ovulation in the 40:1 group compared to the other groups and that the other ratios did not have beneficial effects.

In a study by Bevilacqua et al.[51]using a mice model, an experimental group of C57BL/6N mice was induced to develop

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PCOS and were treated with inositol at a dose of 420 mg/kg body weight with different ratios of MI: DCI. The group that received a 40:1 ratio showed faster recovery of fertility compared to the control group and the groups that received MI and DCI at 5:1, 20:1, and 80:1 ratio. Surprisingly, a high dose of DCI such as the 5:1 ratio seemed to impact fertility negatively. While metformin seems to be the first line of therapy for IR in women with PCOS, it has been demonstrated that MI has a similar function and can also improve the impact of insulin sensitizers such as metformin and clomiphene in those who are trying to conceive[52]. Thus, it can be established that inositol can play an important role in improving fertility in women with PCOS and the optimal dosage of inositol for PCOS is 2 grams twice a day at a ratio of 40:1 (MI: DCI) to improve fertility. Furthermore, inositol can also be considered an adjunct therapeutic agent for IR and can be combined with other insulin-sensitizing agents.

Adequate dietary intake of MI has been shown to have significant effects on various health conditions. MI plays a crucial role in insulin signaling and glucose metabolism, making it beneficial in managing insulin resistance and type 2 diabetes [47]. MI has been linked to improved fertility outcomes in women with PCOS due to its impact on ovarian function and hormone regulation. Incorporating MI-rich foods into the diet can support overall metabolic health and specific conditions such as diabetes and PCOS[49,50]. Consuming a diet rich in MI, through foods like citrus fruits, beans, grains, nuts, and seeds, can provide a natural source of this essential nutrient, potentially enhancing its beneficial effects. The dietary inclusion of MI-rich foods can complement medical treatments and lifestyle interventions aimed at managing these conditions, leading to a more holistic approach to health maintenance and disease prevention.

Probiotics

Probiotics are defined as "live microorganisms which, when administered in adequate amounts confer a health benefit on the host "[53] by the FAO of the UN and the WHO. Bifidobacteria and Lactic Acid Bacteria (LAB), which include the Lactobacillus, Lactococcus, Enterococcus, Streptococcus, and Leuconostoc species, are two of the most popular probiotic strains [54]. Aspergillus niger, Saccharomyces boulardii, and a few other yeasts and molds also function as probiotics. Hexose carbohydrates may be turned into lactic acid by LABs, which results in an environment that is acidic and inhibits the growth of dangerous microbes54. Although the precise mechanism of probiotic action is unclear, some significant ways in which probiotics have been shown to be beneficial include immune system stimulation, toxin inactivation, competition for adhesion sites, and secretion of antimicrobial substances[55].

It has been demonstrated that the diversity of the gut microbiota is correlated with IR and hyperandrogenism, which are frequent symptoms of PCOS [56]. According to the "dysbiosis of gut microbiota" theory put forth by Tremellen et al.[57], a high sugar and fat diet-induced imbalance in the gut bacterial flora causes hyperandrogenism by increasing the gut mucosal permeability, which allows for the passage of lipopolysaccharide (LPS), an endotoxin produced as a result of Gram-negative bacteria rupturing. This generates an immunological response that disrupts the operation of insulin receptors and causes IR. Both of these crucial PCOS markers—increased androgen synthesis in ovarian theca cells and disruption of follicle development—are caused by an elevated amount of circulating insulin[58]. When compared to healthy women, women with PCOS have been found to have elevated levels of several inflammatory mediators, including hs-CRP, a marker of low-grade chronic inflammation, tumor necrosis factor (TNF), and interleukins like IL-6, which promotes the production of CRP in the liver[59].

Probiotic supplementation with Lactobacillus acidophilus, Lactobacillus casei, and Bifidobacterium bifidum (2*109 CFU/g each) for a period of 12 weeks among 60 women with PCOS who were diagnosed according to the Rotterdam Criteria showed a significant increase in SHBG and plasma TAC (Total Antioxidant Capacity) and a significant decrease in serum TT (Total Testosterone), serum hs-CRP, and plasma MDA (malondialdehyde) which serves as an indicator for lipid peroxidation concentrations [60]. In another study, 60 women with PCOS received supplements containing strains of Lactobacillus acidophilus, Lactobacillus casei, and Bifidobacterium bifidum (2*109 CFU/g each) for 12 weeks. The results were analyzed for changes in Fasting Plasma Glucose (FPG), lipid profile, and markers of IR. In the experimental group receiving probiotics, there seemed to be a significant decrease in FPG, serum insulin levels, HOMA-IR, HOMA-B, and a significant increase in Quantitative Insulin Sensitivity Check Index (QUICKI) [61]. Along with cyproterone acetate therapy, the administration of probiotic capsules containing Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus fermentum, and Lactobacillus gasseri (1*109 CFU each) to women with PCOS has also demonstrated a significant reduction in IL-10 levels, an anti-inflammatory cytokine [62].

Selenium

According to Lu and Holmgren [63], selenium (Se) is an important micronutrient and trace element that is crucial for redox processes such as those involving glutathione peroxidase (GPx) and thioredoxin reductase (TrxRs). By serving as a cofactor for GPx during cellular metabolism, se helps to reduce oxidation. It also interacts with other proteins to generate selenoproteins [64]. There are 25 selenoproteins in humans, and each one performs a specific role [65]. Selenoprotein P (SELENOP) is a plasma protein that contains Se that is made in the liver. It has a variety of purposes, but its main one is to transport Se from the liver to other tissues. It also plays a significant part in Se metabolism and antioxidant defense. If SELENOP declines, Se shortage results in certain dysfunctions and oxidative damage, while IR is caused by an increase in SELENOP [66]. Se is necessary and performs a crucial role in the endocrine system, particularly in the production of active thyroid hormone through interaction with iodothyronine deiodinase (an enzyme that converts T4 to T3) [67]. Se's ability to imitate the activities of insulin is one of its key functions [68]. When Se is supplemented, it will improve lipid profiles and glucose homeostasis by reducing the expression of P-selectin and cyclooxygenase-2 (COX-2) [69].

Se has an impact on the metabolism of fats and CHO, according to previous studies. In addition, Se can reduce IR by preventing the production of inflammatory cytokines such IL-1 and TNF-α [70]. Se is essential for human health and well-being since deficiencies can lead to infertility in women and problems throughout the reproductive

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process in males [71]. As a result, Se supplementation has several positive benefits on stress, inflammation, and reproduction in women with PCOS72. Additionally, Se sulfide supplementation has several benefits for dermatology [73]. In rats with diabetes, inducing Se deficiency causes a significant rise in plasma glucose levels[74]. Serum insulin and HOMA-IR values in women with abdominal obesity dramatically decreased after receiving 200 µg of Se per day for six weeks [75]. Contrarily, after receiving 200 µg/day of Se supplementation for three months, diabetic individuals' FPG levels increased without changing their blood insulin levels [76]. Furthermore, Se supplementation significantly reduced the levels of triglycerides and total cholesterol in research done on male white rabbits in New Zealand[77]. The positive impact of Se supplementation enhances metabolic profiles and oxidative stress indicators in women with PCOS [78].

In a different study conducted in women with PCOS, supplementing with 200 µg/day of Se led to lower levels of serum insulin, HOMA-IR, HOMA-B, and QUICKI as well as a significant drop in serum triglycerides and very low-density lipoprotein (VLDL) without affecting other lipid parameters and FPG79. In a different trial, Se supplementation with high doses of 1000 µg on day 1 and 500 µg/day for 2–14 days reduced CRP plasma levels in sepsis patients [80]. Se is regarded as a non-toxic supplement, however, exceptionally high doses of Se supplementation, which is an uncommon condition, can cause unpleasant symptoms including nausea, joint discomfort, hair loss, weariness, diarrhea, and/or brittlenesss [81]. In a different study, 3200 g/day of Se supplementation caused participants to exhibit symptoms of Se toxicity [82]. Se can be consumed in moderation at 400 mcg per day, according to the Institute of Medicine's reference consumption [83]. Patients with certain comorbidities, such as gastrointestinal dysfunction and renal failure, which result in diarrhea and vomiting, must take the appropriate precautions before receiving Se supplementation [81].

Vitamin D

Vitamin D is categorized as a secosteroid structurally because one of its four rings is broken [84]. It comes in two forms: cholecalciferol (vitamin D3) and plant-derived ergocalciferol (vitamin D2). The skin's sebaceous gland produces the steroid 7-dehydrocholesterol, which is transformed to cholecalciferol by exposure to sunshine and ultraviolet B radiation. Exogenous sources of cholecalciferol include egg yolk and fatty fish. The liver and kidneys convert vitamin D2 and vitamin D3 to calcitriol, which is the active form of vitamin D. The 25-hydroxylase enzyme in the liver first hydroxylates vitamin D3 to create 25-OH D, also known as 25-OH cholecalciferol. The active form, 1,25(OH)2 D, also known as 1,25 dihydroxycholecalciferol or calcitriol, is produced by the second hydroxylation of 25-OH D in the kidneys. Two primary mechanisms—genomic action and non-genomic action—allow calcitriol to carry out its function. Although vitamin D receptors (VDR) play a major role in the genomic action of calcitriol, this hormone also exerts rapid cellular action through non-genomic paths [85]. Although it was previously believed that vitamin D's activity was restricted to skeletal development, the widespread distribution of vitamin D receptors (VDR) in the body now supports the notion that it performs diverse functions in the body [86].

According to studies, between 67 and 85% of women with PCOS have low levels of vitamin D, which is associated with the severity of the symptoms. Reproductive, metabolic, and mental health functions are all impacted by vitamin D status. Vitamin D deficiency is believed to make PCOS symptoms including hyperandrogenism, IR, and menstrual irregularities worse [87]. A typical feature of PCOS is IR, which is primarily seen in women with higher BMIs, showing a synergistic influence of both PCOS and obesity on hyperinsulinemia. The association, according to Bikle [86], is brought about by the pancreas cells' expression of the VDR and the promotion of insulin production by vitamin D. By promoting the development of insulin receptors and activating PPAR-δ (peroxisome proliferator-activated receptor delta), vitamin D may also increase insulin sensitivity [88]. A member of the nuclear receptor superfamily, PPAR-δ controls cellular metabolic processes such as insulin production, sensitivity, and absorption, transport, and beta-oxidation [89].

As hyperinsulinemia in PCOS prevents the liver from producing SHBG, freer androgen is circulated in the body88. Insulin and LH work together synergistically to increase androgen production by theca cells and decrease liver synthesis of the major binding protein for testosterone, SHBG, causing testosterone to circulate in the unbound, active form. According to Morgante et al. [90], obese PCOS patients had lower 25 OH-D concentrations, which are linked with higher HOMA-IR, BMI, triglycerides, and total testosterone levels. According to a comprehensive review and meta-analysis of randomized controlled trials by Lagowska et al. [91], the type, dosage, and frequency of vitamin D had a substantial impact on the HOMA-IR score. When combined with micronutrients including calcium, magnesium, zinc, and vitamin K, a lower dose of vitamin D (]4000 IU/day) had a favorable effect compared to a greater dosage (50,000 IU) given once a week. Jamailian et al. [92] reported a similar finding regarding the impact of vitamin D (calciferol) when administered in two dosages of 4000 IU and 1000 IU over the course of 12 weeks to 90 PCOS patients taking metformin. The group receiving 4000 IU of vitamin D daily in addition to metformin exhibited a significant improvement in SHBG and TAC, as well as a substantial decrease in FPG, serum insulin, HOMA-IR, hirsutism, and increase in SHBG. The HOMA-IR and other indicators were unaffected by the placebo group with metformin. Ovulation and menstrual regularity improved in women taking metformin when vitamin D and calcium supplements were combined [93]. It is well-established that supplementing with a lower daily vitamin D intake helps with hyperandrogenism, IR, BMI, menstrual irregularities, and infertility in women with PCOS.

Omega-3 fatty acids

A class of fatty acids known as omega-3 fatty acids have double bonds forming between the third and fourth omega carbon atoms. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are two of the main dietary sources of long-chain omega-3 fatty acids for humans, and they can be found in fish and algae. Additionally, ALA, which is typically found in plant sources, can be converted to EPA and DHA in the body. The conversion is often 10–14% lower than what is needed [94]. Omega-3 fatty acids like EPA and DHA, which are widely known for improving insulin and lipid metabolism in inflammation and obesity and preventing adiposity, dyslipidemia,

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IR, and cardiovascular disease [95], have been demonstrated to be effective at performing these functions. Yang et.al. [96] conducted a meta-analysis of nine randomized controlled trials that showed that women with PCOS who were supplemented with a dosage of 900–4000 mg for a period of 6–24 weeks (mostly 12 weeks) found a significant improvement in IR, the HOMA index, and a reduction in inflammation. But a meta-analysis of 3 randomized controlled trials with doses ranging from 1.2 g to 3.6 g of omega-3 fatty acid supplements for a duration of 6–8 weeks found no significant improvement in IR or HOMA-IR [97].

Studies have shown that omega-3 fatty acid supplementation affects testosterone levels and gonad function. According to a systematic review of clinical trials and cohorts, supplementing with omega-3 for 12 weeks at doses of 800 mg and 1500 mg for 24 weeks significantly decreased serum levels of total testosterone, free testosterone (the active form of testosterone), androgen, LH, and hirsutism score in women with PCOS [98]. Another double-blind randomized clinical trial on 78 women with PCOS receiving a dosage of 3g for 8 weeks as opposed to a placebo showed a similar finding [99]. The results showed both a significant improvement in menstrual regularity and a decline in testosterone levels. However, neither the FAI nor the SHBG showed any appreciable variations. In a similar trial, women with PCOS who took 2 g of omega-3 fatty acids each day for six months saw a significant increase in monthly regularity and a decrease in waist circumference [100]. Although studies have shown that omega-3 fatty acid supplementation can be used in conjunction with PCOS treatment to reduce IR, elevated TC, and TG, the long-term efficacy of omega-3 is unknown due to the short study duration and small sample sizes.

Conclusion

PCOS is a complex endocrine disorder affecting women of reproductive age and can result in infertility. There are several symptoms of PCOS including elevated androgen levels, mainly testosterone, acne, excessive hair growth on body, and insulin resistance. This review summarizes the current evidence regarding the association of these dietary patterns and nutrients and symptoms of PCOS and provides interpretation for clinical practice for dietitians including the appropriate dosage for supplementation. Based on the existing research on this topic, it can be summarized that dietary patterns such as low-carbohydrate diets, Mediterranean diet, and intermittent fasting appear to have positive effect on the symptoms of PCOS such as improvement in hormone levels, improved glycemic control, improved insulin sensitivity, improved blood lipid levels, decreased wait circumference and reduction in inflammation. In addition, inositol, vitamin D, probiotics, omega-3 fatty acids, and selenium which have also been studied in relation to PCOS, are shown to have positive health benefits such as improvement in hormone levels, improved fertility and menstruation regularity, improved blood glucose and serum insulin levels. There are some limitations to this study. The review primarily focuses on specific dietary interventions such as low-carbohydrate diets, intermittent fasting, and certain nutrients like inositol and omega-3 fatty acids. It does not comprehensively cover all possible dietary patterns or nutrients that might affect PCOS.This is an emerging area of research and therefore, limited studies are available on this topic. Long-term studies are necessary to understand the sustained effects of these dietary patterns and nutrients on PCOS symptoms.

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Conflict of Interest

The authors declare that there was no conflict of interest from preparation to publication of this manuscript.

Authors' Contributions

BR, FRARI, TSA, JG, AMJ- wrote paper; BR - had primary responsibility for final content.

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