

REVIEW

Dietary supplements for polycystic ovary syndrome

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Summary

Polycystic ovary syndrome (PCOS) is one of the most prevalent female endocrine reproductive disorders, affecting between 4 to 18% of the women in their reproductive age. It is generally characterized by several clinical aspects, among which anovulation, inflammation and infertility. Moreover, PCOS has several health implications, including increased metabolic, reproductive, and psychological risks. Previously, metformin and to some extent thiazolidinediones were considered as drug of choice for PCOS management, but they had several side-effects, and controversial results were obtained about their efficiency, especially in non-insulin-resistant non-obese patients. Thus, alternative treatment options are now being studied for PCOS, including different

natural molecules and complementary medicines (CM) for the improvement of their health, wellbeing and fertility. Recently, treatment of PCOS patients with different natural molecules, coming from nutritional supplements and herbal medicines, has attained satisfactory results with the absence of any side effects. In this review, four natural molecules, curcumin, vitamin D, inositol and CoQ10 are discussed for their therapeutic ability. These molecules proved to decrease insulin sensitivity and inflammation, to improve the restoration of ovarian function, and they could restore hormonal balance and regulate the menstrual cycle, all of which are the main features and major concerns for women suffering from PCOS.

Introduction

Polycystic ovary syndrome (PCOS) is a very prevalent heterogeneous female endocrine reproductive disorder affecting 4-18% of women during their reproductive years. It is generally characterized by anovulation and overproduction of ovarian androgens. PCOS has a wide range of health implications, including increased risk of metabolic (obesity, cardiovascular disease, type 2 diabetes), reproductive (miscarriage, infertility, neonatal and pregnancy complications) and psychological disorders (stress, depression and anxiety) [1]. It is generally agreed that besides thorough examination with medical history, the reproductive expectations of the patient should also be considered, before any therapy is decided. Tailored or personalized therapeutic approaches involving weight loss, diet and lifestyle can significantly improve ovarian function and avoid the risks associated with PCOS [2]. A hormone-based approach has traditionally used metformin or oral contraceptives, personalizing according to specific needs and clinical situations. Although oral contraceptives, like estrogen-progestin compounds, are effective, they cannot be recommended to patients who wish to restore ovulation in order to achieve pregnancy [3]. Metformin and to some extent thiazolidinediones have been considered the drugs of choice for management of PCOS in women desiring motherhood. Although metformin has improved the condition of obese insulin-resistant women with PCOS, there have been controversial results regarding its efficacy among non-insulin-resistant, non-obese patients [4]. Furthermore, metformin

causes recurrent gastrointestinal side-effects like vomiting, nausea, diarrhea, metabolic complications and abdominal bloating, while thiazolidinediones may induce fluid retention, weight gain, myocardial infarction, bladder cancer and coronary artery disease [1].

Women suffering from PCOS have been seeking alternative treatment options including natural molecules and complementary medicines [1]. A number of natural molecules have recently shown promise and an absence of side-effects in PCOS patients.

Natural molecules and sources

Studies have found that ingestible complementary medicines like nutritional supplements and herbal medicines have some positive effects in PCOS [5]. Women with PCOS show significantly higher oxidative stress and homocysteine plasma levels. Certain nutritional supplements have been found effective in these patients and in reducing the risk of PCOS in other populations [6]. The endocrine effects of the natural compounds used as supplements or medicine may improve hormonal balance and menstrual regularity [1, 7]. In this review we focus on the beneficial effects of the following natural compounds.

Curcumin

Curcumin is a dietary polyphenol derived from *Curcuma longa* (turmeric). It is a popular spice in many Asian

countries. It acts as an antioxidant that increases glutathione peroxidase superoxide dismutase and catalase activities, as well as being a free radical scavenger and regulator of the Keap1-Nrf2/ARE signalling pathway that upregulates detoxification and antioxidant genes. Curcumin is also known to induce ovulation and enhance the biochemical profile of patients with PCOS [8, 9].

Polycystic ovary syndrome is a prevalent cause of infertility in women [10]. Some key features of PCOS are insulin resistance and hyperandrogenism. Increased insulin levels cause an increase in luteinizing hormone (LH) levels by activation of cytochrome P450c17. Curcumin may decrease cytochrome P450c17 activity, improving hyperandrogenism among patients with PCOS [11].

The androgen receptor signaling pathway has also been recognized as a possible mechanism of anovulation in women with PCOS. Curcumin substantially downregulates expression of ovarian androgen receptor proteins. Inflammatory factors, too, have a significant role in the pathogenesis of PCOS. Curcumin has anti-inflammatory action through reducing tumor necrosis factor- α and IL-6. It is also known to decrease LH, reduce insulin resistance, induce ovulation in PCOS patients, improve body weight and correct lipid abnormalities [12-14].

A meta-analysis by Chien *et al.* evaluated the effect of curcumin in PCOS patients, finding an improvement in glycemic control through regulation of fasting insulin, fasting glucose, HOMA-IR index and the quantitative insulin-sensitivity check index. However clinical use of curcumin is limited due to intrinsic and extrinsic factors often associated with herbal medicines. Intrinsic factors include variations in organ specificity, in chemical and pharmacological constituents, in activity between different Curcuma species and diurnal variations; extrinsic factors include storage, environmental, cultivation, manufacturing and substitution variables [8, 11].

Vitamin D

There is evidence that vitamin D deficiency could be a major cause of insulin resistance and metabolic syndrome in women suffering from PCOS [15]. A higher prevalence of vitamin D deficiency (67-85%) is observed in these women. Positive associations have also been reported between vitamin D deficiency and other diseases that co-exist with PCOS, such as insulin resistance, type 2 diabetes, cardiovascular disease and metabolic syndrome. This is sustained by the fact that vitamin D receptors control over 3% of the human genome, including genes critical for glucose metabolism [16]. Polymorphisms associated with vitamin D are linked to insulin resistance and vitamin D deficiency in PCOS. More precisely, vitamin D receptor variants as in the *DHCR7* and *Cdx2* genes are known to be associated with insulin sensitivity and insulin resistance, while variants in vitamin D receptor α -I are linked to testosterone levels in women with PCOS [17]. Hence vitamin D modulates glucose-insulin homeostasis through particular receptors in pancreatic β cells and skeletal muscle, leading to di-

rect activation of human insulin receptor gene transcription and of peroxisome proliferator activator receptor δ , as well as stimulation of insulin receptor expression and increase in insulin-mediated glucose transport *in vitro* [18]. The endorsement of vitamin D supplementation in women with PCOS is based on the role of vitamin D in glucose metabolism: it enhances insulin synthesis and release, increased expression of insulin receptors and suppression of pro-inflammatory cytokines. Vitamin D may play a significant role in the development and onset of most clinical features of PCOS [19, 20].

A research study by Daniela Menichini and showed that vitamin D supplementation may help to restore physiological serum levels of 25(OH)D in women with vitamin D deficiency. Actually, since 67-85% of women with PCOS have inadequate vitamin D levels, vitamin D supplementation is recommended for all of them [21]. Randomized controlled trials have suggested that regular low dose supplementation of vitamin D (< 4000 IU/d) in PCOS patients or consumption of vitamin D as a co-supplement improves fasting glucose concentrations and insulin sensitivity as well as HOMA-IR index [22]. Other studies suggest that better results are achieved by higher doses of vitamin D (\geq 4000 IU/d) for at least 12 weeks. With these doses, significant improvements in insulin sensitivity, glucose levels, hormonal function and hyperlipidemia have been reported [19].

Vitamin D appears to improve reproductive and metabolic impairment in PCOS through its impact on insulin resistance. As far as reproduction is concerned, insulin resistance improves hyperandrogenism by insulin-mediated stimulation of ovarian androgen production and associated reduction in sex hormone-binding globulin [19, 23]. Vitamin D is also significantly involved in facilitating successful pregnancy. Many studies have reported a correlation between vitamin D deficiency and male as well as female infertility, which can be diagnosed with genetic tests [24-26], and that vitamin D improves the outcomes of assisted reproductive techniques. Likewise, vitamin D supplementation with myoinositol and melatonin increases pregnancy rate. The association between vitamin D status and pregnancy rate varies in different ethnic groups ($p < 0.01$). In the white non-Hispanic population, pregnancy rate decreases with decreasing vitamin D levels, whereas among Asians the reverse relationship is observed. Considering the age, quality and number of embryos transferred, the pregnancy rate in non-Hispanic whites was four times greater in vitamin D-sufficient than in vitamin D-deficient patients [27, 28].

Similarly, because the physiological effects of vitamin D act simultaneously or in cooperation with progesterone, vitamin D is considered to be a steroid hormone with progesterone-like activity [16]. Calcitriol or bioactive vitamin D plays a significant role in promoting endometrial receptivity. It also supports implantation and the progress of pregnancy via pathways similar to those of progesterone, creating substantial synergy of action. Thus the significance of vitamin D is clear from luteal phase onwards [27, 29]. Vitamin D also regulates

follicular development by influencing anti-müllerian hormone signals, ovarian sensitivity to follicle-stimulating hormone (FSH) and progesterone production in the granulosa cells of the ovaries [30].

Inositol

Inositol (cyclohexane-1,2,3,4,5,6-hexol) is a carbocyclic sugar/polyol that accumulates in brain, kidney, liver and other mammalian tissues. It regulates cell signal transduction in response to different neurotransmitters, growth factors and hormones. Inositol may be transformed into nine stereoisomers through epimerization of its hydroxyl groups. The most clinically important isoforms of inositol are myoinositol and D-chiro-inositol (DCI). Dietary intake of myoinositol is sufficient to achieve concentrations that could improve different endocrine disorders, including insulin resistance and diabetes, in which myoinositol plays a crucial role [31]. The two isoforms work as second messengers of insulin but with different activities. Myoinositol is primarily involved in cell uptake of glucose [32]. It may therefore be regarded as a semi-essential compound, deficient in different pathological and physiological conditions [31]. Myoinositol is an insulin sensitizer commonly used to treat PCOS due to its effectiveness in reducing the reproductive and metabolic disorders that are the key features of the syndrome. Myoinositol also plays a critical role in cytotogenesis and cell morphogenesis, as well as being involved in cell membrane formation, cell growth and lipid synthesis. It is crucial for signaling pathways that operate throughout cell life to modulate various physiological processes, such as oocyte maturation, gamete development, fertilization and early embryo development [33].

Myoinositol is well established as a nutraceutical that improves insulin sensitivity and hormonal and reproductive functions [34]. Myoinositol supplementation decreases the prevalence of gestational diabetes among women at risk due to a family history of diabetes. Similarly, a recently published study reported a dramatic reduction in the prevalence of gestational diabetes among overweight pregnant women (33.6-14%) [35].

Myoinositol plays crucial roles in female as well as male reproduction. Various studies and the FDA have confirmed and approved this stereoisomer as very safe [30]. Restoration of ovarian function has been reported among women with PCOS on insulin-sensitizing myoinositol supplements, as hyperinsulinemia causes PCOS-related ovarian dysfunction. In the same way positive effects of myoinositol supplementation were found among post-menopausal women with other hyperinsulinemic disorders like metabolic syndrome [36].

Myoinositol plays a significant role in many cell pathways as it regulates hormones like insulin, FSH and thyroid-stimulating hormone and acts as a second messenger [37]. Several reviews of the literature suggest that myoinositol signaling is associated with production of anti-müllerian hormone in human granulosa cells [11].

Other studies have established that myoinositol treatment of women with PCOS decreases insulin resistance and androgen levels, inducing ovulation and regularizing the menstrual cycle [33].

Role of inositol in assisted reproductive technologies

Although assisted reproductive technologies face several bioethical issues [38], women with PCOS are the subject of several ongoing research studies. Wdowiak examined oral myoinositol activity in PCOS patients undergoing intracytoplasmic sperm injection [39]. A significant difference in the pregnancy rate was observed between women with PCOS treated with myoinositol (34.62%) and untreated PCOS controls (only 20%). Follicular fluid concentrations of superoxide dismutase (SOD) also increased significantly only in the myoinositol-treated group [32].

According to three different research studies on IVF patients, myoinositol showed beneficial effects on oocytes. The effects were essential in neutralizing various endocrine and metabolic abnormalities related to PCOS. Myoinositol is known to be effective in restoring spontaneous ovarian activity, and therefore promoting fertility among PCOS patients. For example, several clinical trials have investigated the effect of oral administration of 2 g myoinositol twice a day, a dose now considered standard for PCOS treatment [40].

Another clinical IVF trial on 133 women with PCOS and 137 non-PCOS controls with conserved ovarian reserves administered oral myoinositol daily for three months during ovarian stimulation and in the preconception period. The results showed a significantly higher number of total mature oocytes in the myoinositol-treated group than in non-PCOS controls. According to the 'take home baby' index, the miscarriage and pregnancy rates for the embryo transfers were similar, suggesting that myoinositol improves oocyte quality, which in turn improves IVF outcomes [32, 41].

A clinical study by Emekçi Özay *et al.* reported a higher pregnancy rate (18.6%) in myoinositol-treated patients than controls (12.2%). Similarly, several meta-analyses and systematic reviews and eight randomized controlled trials comprising 812 subjects have established that oral supplementation of inositol during controlled ovarian stimulation and assisted reproductive technologies can reduce the quantity of gonadotropins used, as well as the period of controlled ovarian stimulation in women with and without PCOS undergoing in vitro fertilization [42, 43].

Myoinositol combined with D-chiro-inositol

Although myoinositol is the most abundant inositol isoform, another stereoisomer with great therapeutic qualities is D-chiro-inositol (DCI) [44]. Women with PCOS

have shown significant reproductive improvement when they received supplements of inositol with certain other molecules [45]. Because of the ability of both isomers to lower insulin resistance and their positive affect on metabolism, the combination myoinositol-DCI is considered to be specifically beneficial for PCOS patients. Both act as second messengers of insulin and mediate various activities of insulin [44]. The latest research studies report that this combination with a high proportion of DCI improves the pregnancy rate with respect to the physiological rate, without any difference in embryo quality or oocyte maturation. D-chiro-inositol affects oocyte quality by acting directly on the ovum or by adjusting follicular fluid composition. Oocyte quality can be further improved at genomic level and by modifying the follicular microenvironment; the latter mostly influences oocyte maturity or cytoplasmic quality [45]. Thus the combination of myoinositol and DCI improves oocyte quality by decreasing testosterone levels and increasing insulin sensitivity. Thus this combination with a high fraction of DCI may also improve oocyte cytoplasmic quality with respect to physiological concentrations [45].

Myoinositol is converted into inositol-phosphoglycan (IPG) that acts as an insulin second messenger (myoinositol-IPG) involved in uptake of glucose by cells. On the other hand, IPG derived from DCI (DCI-IPG), which also acts as an insulin second messenger, plays a significant role in glycogen synthesis. Besides, myoinositol-IPG increases ovarian uptake of glucose and plays a crucial role in FSH signaling, while DCI-IPG is involved in the production of insulin-mediated androgen. Furthermore, myoinositol and DCI can decrease plasma concentrations of testosterone and LH, and the LH/FSH ratio, thus counteracting the effects of hyperandrogenism and reducing hirsutism and acne. These specific actions of myoinositol and DCI collectively justify the use of these two stereoisomers to treat women with PCOS [44, 46]. The myoinositol/DCI ratio is 100:1 in healthy females and 0.2:1 in those with PCOS. Myoinositol and DCI are found in a specific ratio in different tissues. Unfer *et al.* suggested that as ovaries do not show insulin resistance, hyperinsulinemia causes overstimulation of epimerase activity in women with PCOS, causing poor synthesis of DCI and associated myoinositol deficiency [47]. In order to define the ideal dose of myoinositol/DCI, the myoinositol/DCI ratio in plasma was used as a standard to understand the systemic physiological balance between these two inositol stereoisomers in humans [47]. Bevilacqua *et al.* studied a mouse PCOS model, finding a pattern similar to that in humans. They treated mice with 420 mg/kg myoinositol-DCI in 2 ml drinking water per day. When myoinositol/DCI was administered in a 40:1 ratio to PCOS mice, recovery of a physiological ovarian phenotype and normal reproductive function was faster than with other formulations of myoinositol/DCI or with water alone. The 40:1 myoinositol/DCI formulation was the most effective in restoring fertility, normal uterine structure and function, and regular follicle and ovarian structure [48].

Human preclinical and clinical studies sustain the results of Bevilacqua *et al.*, showing that a myoinositol/DCI ratio of 40:1 is the most effective in restoring ovulation in women with PCOS. The activity of DCI proved most beneficial at a particular ratio with myoinositol, while increase in DCI concentrations could cause loss of its beneficial reproductive effects [44, 48].

Myoinositol combined with melatonin

Recent research has established that plasma concentrations of myoinositol and melatonin are predictors of oocyte quality: higher levels of these two molecules are positively correlated with good oocyte quality [33, 49]. Many clinical trials show that myoinositol supplements, alone or in combination with melatonin, improve oocyte quality and IVF outcomes in patients with PCOS as well as normal women. Chiu *et al.* showed a direct association between follicular fluid concentrations of myoinositol and oocyte quality; thus high myoinositol concentrations are a marker of high quality oocytes [50]. In the same way, myoinositol or melatonin supplementation affects oocyte and embryo quality. Particularly, in cases of ovarian stimulation, myoinositol supplementation reduces the number of FSH units (IU) administered which increases the chances of pregnancy. Moreover, the effects of gonadotropins on ovulation, follicular growth and luteinization are linked to differences in FSH and LH receptor concentrations [32, 51, 52].

Myoinositol combined with alpha lipoic acid

Insulin sensitizers are currently being used to treat obese and lean women with PCOS. Different isoforms of inositol without the side-effects of metformin are being compared with the latter for insulin-sensitivity-enhancing activity. Alpha lipoic acid (ALA) is a naturally occurring antioxidant derived from octanoic acid, considered effective and safe [53, 54]. Alpha lipoic acid exhibits anti-inflammatory activity, inhibiting NF- κ B translocation to the nucleus and reducing release of proinflammatory cytokines. The combination of inositol derivatives and ALA is a therapeutic option to improve insulin sensitivity, ovulatory rhythm and hyperandrogenism. The combined action of myoinositol and ALA can therefore improve insulin resistance and chronic low grade inflammation in PCOS patients [55, 56].

In myoinositol-resistant patients, treatment with myoinositol and ALA leads to significant improvement in PCOS. This combination re-establishes ovulation, with substantial changes in metabolic and hormonal parameters, thus significantly increasing the chances of pregnancy in women with fertility issues. The bioavailability of myoinositol increases significantly when administered with ALA rather than alone [40].

Inositol and high-mobility-group-box-1 (HMGB1)

The best treatment option for PCOS should be determined on the basis of pathophysiology. High-mobility group box 1 (HMGB1) is a highly conserved non-histone chromatin-associated protein that plays a vital role in chromatin remodelling at nuclear level, as well as acting as a pro-inflammatory mediator in the extracellular environment. Plasma concentrations of HMGB1 are reported to be elevated in PCOS patients due to reduced ovarian expression of cystic-fibrosis-transmembrane-conductance-regulator, and are associated with inflammation and insulin resistance, both features of PCOS. Women with PCOS have considerably elevated circulating levels of inflammatory markers like hs-CRP (high sensitive c-reactive protein), IL-6 (interleukin -6) and TNF- α (tumor necrosis factor- α). Chronic low grade inflammation may contribute to different ovarian alterations as well as insulin resistance [34, 57-59].

PCOS patients have higher plasma concentrations of HMGB1, insulin and insulin-like growth factor I, and a higher HOMA-IR index and triglyceride/high-density lipoprotein-cholesterol ratio than controls. In adolescent girls with PCOS, combined inositol treatment significantly reduced concentrations of HMGB1 and insulin to levels almost similar to those of controls. In obese adults with PCOS, combined treatment with myoinositol-ALA lowered serum concentrations of insulin. Inositol treatment therefore had positive biochemical and clinical effects [34].

Coenzyme Q

Coenzyme Q10 (CoQ10) is a lipid-soluble antioxidant naturally synthesized by human cells and required for cell growth and maintenance. It is a mobile electron carrier essential for adenosine triphosphate synthesis by oxidative phosphorylation. CoQ10 acts as an intracellular antioxidant and effectively prevents the oxidation of lipids, proteins and DNA. Numerous randomized controlled trials have established significant beneficial effects of CoQ10 supplementation as an adjuvant in different clinical conditions [60].

The inflammatory state common in PCOS patients is demonstrated by higher plasma concentrations of inflammatory cytokines such as TNF- α , interleukin-6 and C-reactive protein [61]. Release of cytokines and chemokines promotes macrophage recruitment and adhesion molecule production. Enhanced circulation of adhesion molecules like vascular cell adhesion molecule-1, E-selectin and intercellular adhesion molecule-1 are prominent signs of impaired endothelial function [62]. In women with PCOS, increased plasma levels of these three biomarkers of endothelial dysfunction have been reported [7, 8]. Farsi *et al.* reported that CoQ10 supplementation for 12 weeks had major effects on plasma concentrations of high-sensitivity C-reactive protein and TNF- α in patients with non-alcoholic fatty liver dis-

ease [63]. Likewise Shiva Taghizadeh *et al.* found that CoQ10 supplementation (200 mg/day) for eight weeks had many beneficial effects and significantly reduced serum concentrations of the above three inflammatory and endothelial dysfunction markers in overweight patients with PCOS compared to placebo-treated controls [60].

Although the precise mechanism by which CoQ10 reduces inflammatory factors is unclear, there is evidence that CoQ10 can downregulate expression of genes encoding inflammatory cytokines in patients with PCOS or with diabetic nephropathy. Furthermore Schmelzer *et al.* showed that the anti-inflammatory effects of CoQ10 may be caused by lower expression of nuclear factor- κ B-dependent genes [64]. This factor may be activated by reactive oxygen species and may increase pro-inflammatory cytokine expression. Antioxidants like CoQ10 could inhibit this NF- κ B-activating cascade [65] and CoQ10 also activates the PPAR (peroxisome proliferator-activated receptor)-mediated anti-inflammatory response, that acts as PPAR agonist. Other mechanisms including attenuation of miR-146a, modulation of interleukin-1 receptor-associated kinases, reduced secretion of macrophage inflammatory protein-1 alpha and RANTES (regulated upon activation normal T-cell expressed and secreted) by CoQ10 are proposed. Further long-period studies are required to confirm the effects of CoQ10 supplementation on inflammatory factors in PCOS [60, 66, 67].

Conclusion

Polycystic ovary syndrome is one of the most prevalent endocrine disorders affecting women of reproductive age and is generally characterized by anovulation, overproduction of ovarian androgens, insulin insensitivity, inflammation, infertility and other reproductive complications. Metformin and to some extent thiazolidinediones have been considered drugs of choice for PCOS management but they have side-effects and their efficacy in non-insulin-resistant non-obese patients is controversial. In this review we discussed the therapeutic effects of four natural molecules. Curcumin has anti-inflammatory effects, improves hyperandrogenism, lowers LH, reduces insulin resistance and induces ovulation in women with PCOS. Vitamin D plays a crucial role in glucose metabolism, improving insulin sensitivity, decreasing insulin resistance and suppressing pro-inflammatory cytokines. Inositol lowers insulin resistance, improves reproductive function, improves oocyte quality and restores ovulation in patients with PCOS. CoQ10 exerts anti-inflammatory effects by downregulating expression of genes encoding inflammatory cytokines in PCOS. Hence these substances should be considered for treatment of PCOS. Additional research could provide further evidence of the beneficial effects of using these natural molecules in the treatment of PCOS. More natural molecules should be explored and analysed for their therapeutic activity in this syndrome.

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Conflicts of interest statement

Authors declare no conflict of interest.

Author's contributions

MB: study conception, editing and critical revision of the manuscript; AKK, Kevin D, Kristjana D, LS: literature search, editing and critical revision of the manuscript. All authors have read and approved the final manuscript.

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