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Inositol and herbal substances as elements of complementary therapy in patients with PCOS

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Abstract

Introduction: Polycystic ovary syndrome is a common hormonal disorder in women and the leading cause of female infertility. Traditional therapeutic methods often do not yield the expected results, hence the need to explore new treatment strategies. Promising results have been observed in studies on inositol.

Objective: The aim of this study is to summarize the current knowledge regarding the effectiveness and safety of inositol and herbal preparations in the treatment of PCOS based on available scientific literature.

Materials and Methods: A literature review was conducted using PubMed and Google Scholar databases, using search terms: inositol, PCOS treatment, herbal medicine in PCOS.

Current knowledge: Inositol is an oral supplement used in the therapy of PCOS. It is characterised by high safety and minimal risk of side effects. Herbal extracts alleviate symptoms in patients with PCOS.

Conclusions: Analysis of scientific research has provided evidence of the effectiveness of inositol, particularly myo-inositol, in complementary therapy for PCOS. Herbal medicine also appears to be an effective supportive treatment. However, these substances should not be considered as primary therapy but rather as an adjunct. Only both - primary medications and complementary treatment methods, can yield a therapeutic effect.

Keywords: inositol, herbal medicine, PCOS.

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age. It is characterized by oligo-ovulation or anovulation, menstrual irregularities, and the development of hyperandrogenism due to high levels of circulating luteinizing hormone (LH) and an altered ratio of LH to follicle-stimulating hormone (FSH) [1]. Based on several meta-analyses, the prevalence of PCOS is estimated to be around 6-10% in the global population [2]. Other common symptoms of PCOS include hirsutism, acne, and mood disturbances. Additionally, there are several metabolic disturbances associated with this condition. These include insulin resistance and the subsequent development of type 2 diabetes mellitus (T2DM), metabolic syndrome, obesity, dyslipidemia, and hypertension. These conditions later contribute to an increased risk of cardiovascular diseases [3]. The complex pathophysiology of PCOS makes it difficult to determine its exact causes. According to the latest guidelines from the International PCOS Network in 2018, the diagnosis of PCOS is based on the absence or infrequent ovulation, clinical or biochemical signs of hyperandrogenism, and the presence of polycystic ovaries on transvaginal ultrasound (with 20 or more follicles measuring 2-9 mm in diameter and/or an ovarian volume exceeding 10 ml). Previously, the Rotterdam criteria required a minimum of 12 follicles for diagnosis, but current scientific societies lean towards a threshold of 20 follicles [4]. Based on updated information, PCOS can be classified into two main phenotypes: hyperandrogenic (H-PCOS), which corresponds to subtypes A, B, and C according to the Rotterdam criteria, and hyper-/hypoandrogenic (HH-PCOS) - subtype D according to the Rotterdam criteria. This modern classification aims to improve patient selection. H-PCOS is strongly associated with metabolic syndrome, in contrast to HH-PCOS. Furthermore, the HH phenotype of PCOS, in approximately 85% of cases, exhibits signs of immune system hyperactivity (autoimmunity and chronic inflammation). Various genetic factors contribute to the metabolic disturbances and immune system dysregulation, making it important to conduct studies that accurately define the study populations, as understanding the underlying factors of PCOS is even more challenging without this information [5].

Based on a study conducted by Gibson-Helm et al., it is evident that many patients report negative experiences related to the management of the disease, which could be avoided. This includes delayed diagnosis and insufficient information provided by healthcare professionals. There are numerous opportunities to improve awareness and knowledge about this condition among patients and healthcare workers. Education in this area appears to be

necessary [6]. PCOS is a challenging condition to diagnose and treat, given the diversity of symptoms and the continuously evolving diagnostic criteria. Traditional therapeutic approaches often yield incomplete results, highlighting the need to explore new treatment strategies, such as inositol, which has shown promising results in regulating menstrual cycles and reducing PCOS symptoms.

Current methods of diagnosis and treatment of PCOS

Various tests are used in the diagnosis of polycystic ovary syndrome (PCOS). Androgens have a biological role in the female body, including enhancing bone density and muscle mass. The ovaries are responsible for the biochemical hyperandrogenism in patients with PCOS. Testosterone, in its non-sex hormone-binding globulin (SHBG) bound form, is the most commonly elevated and most sensitive marker. Among the laboratory tests useful in detecting this condition, calculations of free testosterone or high-quality tests (using immunological methods, extraction, chromatography, or mass spectrometry) for measuring free and total testosterone are distinguished. Additionally, women with PCOS often show elevated levels of dehydroepiandrosterone sulfate (DHEA-S) [7]. Another marker of PCOS is oligo-amenorrhea (menstrual cycles occurring at intervals of >35 days or <8 cycles per year) [8]. In terms of PCOS diagnosis, the criterion that presents the most difficulties and exhibits the most common changes is the ultrasonographic (USG) criterion. This primarily stems from the variability in interpreting ultrasonograms and the lack of clearly defined diagnostic criteria regarding the number and size of ovarian follicles, leading to challenges in accurately confirming or ruling out the presence of the disease [4].

Polycystic ovary syndrome (PCOS) is an endocrine disorder that requires an interdisciplinary approach to therapy. The fundamental treatment methods include interventions aimed at lifestyle changes to a more active one, pharmacotherapy, and surgical procedures. Meta-analyses confirm that weight reduction through a healthy diet and regular physical activity leads to improved insulin sensitivity, reduced insulin resistance, and regulation of the menstrual cycle. It can also lower androgen levels, improve lipid profiles, and reduce the risk of metabolic complications in patients with PCOS [9-11].

Combined oral contraceptives (COCs), which consist of estrogen and progestin, are first-line pharmacotherapy for PCOS. The estrogen component reduces gonadotropin production by the pituitary gland, thereby reducing ovarian androgen secretion. Progestins act on progesterone receptors and regulate endometrial proliferation, preventing endometrial

hyperplasia and the development of endometrial cancer in patients. COCs also have an impact on certain metabolic aspects such as changes in cholesterol distribution and adipose tissue, but their adverse effects should be taken into account [12,13].

Anti-androgen drugs, including cyproterone acetate, flutamide, finasteride, and spironolactone, block the action of androgen receptors, thereby inhibiting the effects of testosterone. Significant reduction in androgenization leads to a decrease in hirsutism (excessive hair growth) and alleviation of acne symptoms. Spironolactone has many beneficial effects in PCOS therapy, such as blocking androgen receptors, stimulating aromatase, reducing acne severity, and reducing hair loss. Additionally, it exhibits strong anti-inflammatory effects [14,15].

Metformin, belonging to the group of insulin sensitizers, has significant benefits in the context of PCOS therapy. Several reports confirm that metformin improves the hormonal profile of patients by inhibiting ovarian androgen production, thus alleviating hyperandrogenism. Furthermore, metformin acts on insulin resistance mechanisms by improving peripheral tissue sensitivity to insulin and reducing its concentration, leading to the normalization of menstrual cycles and improvement in the metabolic profile [16]. There is also increasing discussion about the effectiveness of GLP-1 receptor analogs, such as exenatide and liraglutide. Their effectiveness, which includes BMI improvement, reduction in central obesity, and insulin resistance, is most pronounced when combined with metformin [17].

The use of herbal medicine in PCOS therapy

Due to the difficulties in treating polycystic ovary syndrome (PCOS) and the limited effectiveness and long-term side effects associated with standard treatment, there is a search for new therapeutic methods. Herbal medicine, as part of complementary medicine, serves as a valuable complement in the management of patients with PCOS. There are several reports supported by scientific evidence on the beneficial effects of herbal extracts on reproduction, menstrual cycle disorders, metabolism, and hyperandrogenism in PCOS patients [18].

Among the herbs with a positive impact on improving ovarian function, menstrual cycle regularity, and subsequently fertility, Trigonella foenum-graecum L. (fenugreek) and Grifola frondosa stand out [19,20]. Cinnamon, as a bioactive substance, reduces anti-Mullerian hormone and has fewer side effects compared to metformin. At least a 6-month treatment with Cinnamonum cassia supplement normalizes menstrual cycles. Additionally, cinnamon in combination with Glycyrrhiza spp., Paeonia lactiflora Pall., and Hypericum perforatum L.

lowers the level of luteinizing hormone (LH) without affecting follicle-stimulating hormone (FSH) and free testosterone levels [21-23]. Among the herbs that reduce androgen levels and hirsutism, green tea rich in polyphenols and Matricaria chamomilla L. (chamomile) are distinguished [24, 25].

Due to their potential beneficial metabolic properties, herbs can be valuable tools in PCOS therapy. A study by Arentz et al. demonstrates that cinnamon, along with Glycyrrhiza spp., Paeonia lactiflora Pall., and Hypericum perforatum L., reduces body mass index (BMI) and insulin levels without significant impact on fasting blood sugar (FBS) levels [23]. The use of extracts from Cinnamomum zeylanicum Blume roots and Nigella sativa L. seeds led to a significant decrease in fasting blood glucose, insulin, insulin resistance, as well as cholesterol, triglyceride, and low-density lipoprotein (LDL) levels [26,27]. In a study conducted by Jamilian et al., it was shown that long-term supplementation of soy supplements containing isoflavones and soy phytoestrogens for at least 12 weeks led to a reduction in insulin resistance and serum triglyceride levels through the modification of metabolic dysfunction [28]. Furthermore, the consumption of certain food substances such as Allium cepa L. (red onion), walnuts, and almonds has been shown to have a positive impact on lipid profile and correct metabolic dysfunctions in women with PCOS [29, 30].

Many herbs, such as green tea, cinnamon, and turmeric, contain active ingredients like polyphenols that have anti-inflammatory and antioxidant effects. Low-grade inflammation is often present in individuals with PCOS and negatively affects glucose and lipid metabolism. The anti-inflammatory properties of herbs can contribute to the improvement of inflammation and metabolic regulation [31].

Herbal medicine in PCOS therapy can serve as a complement to conventional treatment, given the potential beneficial effects of certain herbs on hormonal imbalances. However, it is important to remember that herbs should not replace conventional treatment and should be used as an adjunct therapy. Before starting herbal supplementation, it is always necessary to consult with a doctor and pharmacist to assess potential benefits, dosages, and potential interactions with other medications.

Inositol

Inositol (Ins) is a cyclic carbohydrate containing six hydroxyl groups and was originally isolated from muscle extracts. The structure of this chemical compound allows for the distinction of its nine different isomers: cis-, epi-, allo-, myo-, neo-, scyllo-, L-chiro-, D-

chiro, and muco-inositols. Only two of them, myo-Ins and D-chiro-Ins, are biologically active [32]. Myo-Ins plays particularly important roles in cellular morphogenesis and cytogenesis and has been identified as the most common in all biological systems, hence it is considered a specific probiotic molecule [33]. It can be synthesized endogenously from glucose-6-phosphate or obtained from the diet. It serves as the main form of phosphorus storage in many plant tissues and is mainly found in bran and seeds [34]. When consumed with food, it is ingested as a phospholipid containing inositol, but primarily as phytic acid. The basic diet of an adult human provides approximately 1 g of inositol per day. Due to its partial endogenous synthesis, it is difficult to indicate the daily dietary requirement for this substance [35].

Myo-Ins is a component of cell membranes, participates in phospholipid synthesis, and acts as a precursor for hormonal messengers such as TSH, FSH, and insulin. It also serves as a mediator of intracellular signals and affects the ability of cells to uptake glucose [36]. Myo-inositol is not the only inositol that serves as a precursor for messengers. D-chiro-inositol is also involved in intracellular transmission of metabolic signals from insulin, although it operates through a different mechanism [37].

Myo-inositol and its derivatives also play other important biological functions, including glucose metabolism regulation, calcium release in cell signaling processes, chromatin and cytoskeleton structural transformation, transcriptional gene control, cell growth control, programmed cell death, and proper structural development. The inositol-related network plays a crucial role in phenotypic changes and developmental processes, enabling cells to respond appropriately to various stressful conditions. Abnormalities in myo-inositol metabolism have been observed in conditions such as infertility, metabolic disorders, thyroid dysfunction, and diabetes, among others. At the same time, it has been proven that the use of myo-inositol or its isomers brings significant clinical benefits in conditions such as PCOS, certain cancers, respiratory failure syndrome, and neurological or metabolic disorders [38].

Safety and side effects of inositol.

The safety of myo-Ins has been evaluated in several studies involving human subjects who received inositol for an extended period of time (ranging from 1 to 12 months) at doses of 4 to 30 g per day. Mild side effects (nausea or diarrhea) were reported in a small portion of the participants, but only for doses up to 12 g/day [39]. In a limited number of psychiatric patients, mild neurological discomforts (insomnia, dizziness, headaches, nausea, drowsiness) and a few cases of mania have been observed [40]. Furthermore, a prospective, randomized,

comparative clinical trial conducted in India involving 60 patients with PCOS aimed to compare the efficacy and safety of inositol with metformin. It showed a lower incidence of adverse effects in the inositol group (7% vs. 53%). The adverse effects reported in the metformin group included bloating, nausea, and general weakness [41].

Inositol in PCOS therapy

Inositols are involved in the physiology of the reproductive system in both women and men. In women, myo-inositol (myo-Ins) acts as a second messenger of FSH (follicle-stimulating hormone) and participates in the FSH-mediated cascade responsible for the regulation of granulosa cell proliferation and maturation. Additionally, myo-Ins plays a fundamental role in oocyte maturation and transport in the fallopian tube by modulating FSH-dependent anti-Müllerian hormone (AMH) production [42]. The influence of D-chiro-inositol (D-chiro-Ins) on steroidogenesis is also known. This substance stimulates ovarian androgen production by theca cells. According to recent reports, D-chiro-Ins also modulates the expression of aromatase enzyme, reducing estrogen synthesis [43].

Considering the fact that maintaining a healthy physiological state of tissues is dependent on the proper ratio of inositols, it can be presumed that the alteration in the proportion of myo-inositol to D-chiro-inositol may explain hormonal disorders observed in certain pathological conditions, such as polycystic ovary syndrome (PCOS). In line with the physiological role of inositols and the pathological implications of altered proportions of myo-Ins to D-chiro-Ins, inositol therapy can have two different aspects: restoring the physiological inositol ratio by regulating the ratio of myo-Ins to D-chiro-Ins or consciously manipulating this ratio to achieve specific therapeutic effects [44].

It is increasingly suggested that insulin resistance and compensatory hyperinsulinemia play a fundamental role in the pathogenesis of PCOS, contributing both directly and indirectly to hyperandrogenism and the associated clinical manifestations [45]. In fact, insulin directly stimulates ovarian follicular cells to produce increased amounts of androgens while inhibiting the synthesis of sex hormone-binding globulin (SHBG) in the liver, leading to elevated circulating free androgens. Altered myo-inositol to D-chiro-inositol ratio in the ovaries may be significant in the pathogenesis of polycystic ovary syndrome in patients with insulin resistance. In reality, increased levels of D-chiro-Ins promote androgen production, while a deficiency of myo-Ins negatively affects FSH signaling and oocyte quality. Healthy ovaries in women exhibit a higher level of myo-Ins and a lower level of D-chiro-Ins (at a ratio of

approximately 100:1). In contrast, the ovaries of PCOS patients are characterized by a significant deficiency of myo-inositol and an increased content of D-chiro-inositol (with a decreasing ratio of 0.2:1) [46, 47].

Over the past 20 years, numerous studies have been conducted regarding the effectiveness of inositol (mainly myo-inositol and D-chiro-inositol) in improving pathological conditions associated with polycystic ovary syndrome. In a study conducted by Genazzani et al., PCOS patients were treated with Myo-Ins and folic acid or folic acid alone. Consistent and significant changes were observed in the first group. The ratio of prolactin (PRL) to follicle-stimulating hormone (FSH) in the serum significantly decreased, while the insulin sensitivity index, expressed as the ratio of glucose to insulin, significantly increased [48]. Another study compared the therapeutic effect of metformin and Myo-Ins in women with PCOS. In the inositol group, 65% of patients compared to 50% in the metformin group regained spontaneous ovulatory activity after an average of 14.8 (±1.8) and 16.7 (±2.5) days from the first day of the menstrual cycle, respectively [49]. Constantino et al., in their double-blind study, observed a decrease in systolic and diastolic blood pressure (SBP and DBP) values in patients treated with Myo-Ins, while these values increased in the placebo group. Additionally, in the Myo-Ins group, serum triglyceride and cholesterol levels significantly decreased. Insulin sensitivity index significantly increased in the Myo-Ins group, while it did not change in the placebo group. Ovulation was restored in 69.5% of women in the Myo-Ins group and 21% of women in the placebo group. After treatment, peak progesterone levels were higher in patients with Myo-Ins compared to the placebo group [50]. Another study demonstrated improved insulin resistance and ovulation function after treatment with Myo-Ins and D-chiro-Ins, restoring the balance of hormonal and metabolic profiles [51]. Papaleo et al. expanded the clinical application of Myo-Ins by evaluating its impact on oocyte quality and ovarian stimulation protocol in women with PCOS. Patients using Myo-Ins showed a lower number of immature and degenerated oocytes. This, along with several other studies, indicates the role of Myo-Ins in improving oocyte quality [52, 53].

There is a body of research suggesting that using myo-Ins and D-chiro-Ins in a ratio of 40:1, similar to that found in the serum of healthy women, is effective and safe. In light of the latest research, inositol supplementation clearly reduces clinical symptoms of PCOS, including reducing insulin resistance [54, 55]. It also restores spontaneous ovarian activity, menstrual regularity, and ovulation, resulting in improved fertility in women with PCOS [48].

According to the position of the Expert Team of the Polish Gynecological Society, the use of inositol also restores appropriate metabolic and endocrinological parameters, with a

high safety profile and significant patient acceptance [56]. Therefore, it can be concluded that inositol supplementation has a place in PCOS therapy. Many scientific communities support this in their recommendations. Currently, several preparations containing inositol in various forms and combinations with folic acid, zinc, or vitamins (e.g., B12) are available on the market.

Summary

Summarizing the research on the use of inositol and herbal medicine in PCOS therapy, there is promising evidence for the beneficial effects, especially of myo-inositol and certain herbs, in reducing symptoms and improving metabolic parameters in women with PCOS. Although they show potential benefits, further research is needed to confirm their safety and establish optimal dosages. It is important to consult with a doctor before taking these supplements to assess the risks and potential interactions with other medications. Any complementary therapy should be based on an individualized approach that takes into account a holistic assessment of the patient's health. It is necessary to understand that the approaches discussed in the article, involving herbal extracts and inositol, should not be regarded as standalone primary therapy but as complementary to it. Only the use of a comprehensive approach, incorporating both primary medications and additional therapeutic methods, can bring beneficial effects in alleviating symptoms and improving the quality of life for patients with PCOS.

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