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Inositol As a Treatment for Polycystic Ovary Syndrome

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An understudied endocrine, reproductive disorder that effects the physical and mental health of women is Polycystic ovary syndrome (PCOS). PCOS is a common condition affecting a substantial number of reproductive-aged women with metabolic, reproductive, and psychological consequences. Current treatments for PCOS like Metformin, the golden standard, have a lot of side effects and it is necessary to research less adverse alternatives such as D-chiro-Inositol (DCI) and Myo-inositol (MI). Various eligible studies regarding PCOS and inositol were considered using search strategies on PubMed and Google Scholar including search terms such as "PCOS" and "Inositols". A flowchart was plotted that demonstrates the inclusion and exclusion criteria for the sources used. The literature review revealed that treatment with DCI and myo-inositol, either individually or in combination, can significantly improve metabolic and endocrine parameters in PCOS, including insulin resistance, Luteinizing hormone (LH) and androgen levels, and ovulation. This finding of this review concluded that inositol supplementation for PCOS patients can help lessen the severity of the symptoms of this metabolic disorder.

Keywords: Polycystic ovary syndrome; PCOS; Inositol; myo-inositol; d-chiro-inositol; metformin; Insulin resistance;

Introduction

Polycystic ovarian syndrome, or PCOS, is one of the most common endocrine, reproductive disorders in reproductive-aged women, impacting 4 – 18% of the at-risk population¹. According to the Rotterdam criteria, which is the gold standard for PCOS diagnosis, a diagnosis requires the presence of a minimum of two of the following criteria: ovulatory dysfunction, hyperandrogenism, or polycystic ovary morphology².

While the Rotterdam criteria have gained widespread acceptance, it has become evident that a new clinical consideration must be acknowledged-the dysmetabolic aspect of insulin resistance. A review done by Greff et al. reported that insulin resistance is common in PCOS patients, irrespective of their body mass index (BMI)³. Insulin resistance, consequently, drives androgen overproduction, which is further amplified by the bidirectional relationship between insulin resistance and hyperandrogenism⁴. Insulin resistance represents a distinct biological adaptation that leads to compensatory hyperinsulinemia in around 70 to 80% of women diagnosed with PCOS and central obesity, as well as in 15 to 30% of lean women with PCOS³.

Females with PCOS generally demonstrate symptoms including hirsutism, hair loss, excess acne, delayed periods, obesity, and infertility⁵. A review by Unluturk et al. highlights that inherited genes and mutations play a role in PCOS. These include genes involved in ovarian and adrenal steroidogenesis(*CYP11a*, *CYP21*, *CYP17*, and *CYP19*), the sex hormone-binding globulin gene, and genes related to insulin action and secretion (*INS*, *INSR*, *IRS1*, *IRS2*, *CAPN10*). However, some findings remain

controversial⁶. These genes can cause hormonal disbalances: abnormally high levels of androgens and unexpectedly low levels of estrogen produced by the ovaries⁷. This can cause growth of follicular cysts, developing during the follicular phase since ovum is not released as expected, due to excessive FSH stimulation or the absence of the typical mid-cycle LH surge preceding ovulation. These cysts persist and grow under ongoing hormonal stimulation, further producing androgens⁸. PCOS needs to be managed as soon as clinically possible since women with PCOS are more likely to develop serious health conditions such as type 2 diabetes, high blood pressure, problems with the heart and blood vessels, and uterine cancer⁹. Individuals with PCOS exhibit a notably higher prevalence of depressive disorders and anxiety disorders, experiencing three times more depressive symptoms and five times more anxiety disorders compared to those without PCOS ¹⁰. For instance Testosterone impacts brain regions like the amygdala and prefrontal cortex, which regulate emotions. High levels, like the case of hyperandrogenism in PCOS, may over activate these regions, leading to emotional dysregulation 11.

Metformin is the primary metabolic treatment for managing PCOS and is recognized as the front line treatment ¹². Metformin treats PCOS by activating AMP-activated protein kinase(AMPK), which decreases blood sugar levels, improves insulin sensitivity and reduces hepatic glucose production, thereby lowering androgen levels. Therefore it helps restore ovulation, regulate menstrual cycles, and decrease the intensity of symptoms like hirsutism and acne ¹³. Nonetheless, metformin use can lead to gastrointestinal side effects ranging from mild to severe,

including nausea, diarrhoea, vomiting, and flatulence. Consequently, seeking alternative treatments with fewer side effects would be advantageous for the care of these patients. In recent research, various studies have explored the potential benefits of inositol supplementation, proposing that inositols could serve as potent alternatives to metformin in treating PCOS ¹⁴.

Inositol is a six-carbon ring compound with a hydroxyl group attached to each carbon atom. They are naturally present in all living beings and participate in various metabolic pathways, and MI is present more abundantly in nature with greatest amounts present in fruits, grains, beans and nuts ^{15,16}. Two specific stereoisomers of inositol, MI and DCI, act as insulin second messengers and mediate different insulin actions. MI is converted into an inositolphosphoglycan (IPG) involved in cellular glucose uptake, while DCI is converted into an IPG responsible for glycogen synthesis. At the ovarian level, MI-based second messengers are involved in glucose uptake and FSH signalling, whereas DCI-based second messengers are involved in insulin-mediated androgen production ¹⁷.

Inositol, often categorized as a pseudovitamin (sometimes referred to as vitamin B8) is taken as a vitamin supplement for glucose metabolism and insulin signalling deficiencies ¹⁸. Some people reported inositol supplementation improves insulin sensitivity and hormonal balance, therefore the scientists started researching its effectiveness on PCOS as a more natural alternative than drug therapies ¹⁹.

It is necessary to find an alternative for metformin, and this review investigates what evidence supports inositol as an alternative treatment for PCOS in women or even improved treatment option.

Methods

The review question was, 'how effective is Inositol as a treatment for polycystic ovarian syndrome in women?'. The target participants for this review are women diagnosed with PCOS. The concept of this review was a summary of topics related to the effect of inositols on PCOS. The context of this review includes menstruating women in all countries. In this review the databases which will be searched for include PubMed and Google Scholar. The criteria for inclusion were papers written in English.

Keywords and search strategy

("PCOS"(Title/Abstract) OR "PCOD"(Title/Abstract) OR "polycystic ovary*"(Title/Abstract) OR "Polycystic Ovary Syndrome"(MeSH Terms)) AND ("Inositol"(MeSH Terms) OR "Inositol"(Title/Abstract))

Extracting and charting the results

The flowchart (figure 1), depicts the process for finding studies, eliminating duplicates, choosing pertinent research, obtaining the complete article from the library, and presenting the final analysis. In the scoping review, 'charting the results' is an iterative process that involves extracting relevant data from all the studies included in the review.

Results

General criteria of studies included

Most studies included women between the ages of 18 and 50 who were diagnosed with PCOS according to the Rotterdam criteria. Twelve primary articles were identified, describing various concepts, including the effects of DCI, MI, a combined therapy of DCI and MI, and the effects of inositol versus metformin.

Ovulation

Studies showed that both MI and d-chiro-inositol administered increased ovulation mostly through serum progesterone levels 14,20,21. Nester et al. found that 19 out of 22 women who were administered 1200 mg of DCI for 6 -8 weeks, the reason for this dosage is not specified, ovulated compared to 6 out of 22 women in the placebo group 14. A study by Benelli et al. also demonstrated an increase in ovulation after 6 months of combined treatment of MI and DCI in a 40:1 ratio, since it's the physiological ratio of the two isomers in the body, through 17-beta-Estradiol and Sex Hormone Binding Globulin levels (SHBG)²⁰. In another study Özay et al. Women who had MYO + 400g folic acid for 12 weeks, the reason for this dosage is not specified, had increased ovulation which was monitored through serum progesterone levels²¹. In a double-blind trial done by Constantino et al., 16 out of 23 women treated by MI ovulated compared to 4 out of 19 in the placebo group ²². A study by Gerli et al. also demonstrated that the treated group, who received 100 mg of Inositols twice a day (reason unspecified), had greater ovulation. This was ascertained through ovulation frequency, which was measured using the ratio of luteal phase weeks to total observation week. The treated group had an 23% ovulation frequency and shorter time to first ovulation (23.6 days; 95% CI: 17–30) whereas the placebo group had a 13% frequency and a longer time to first ovulation (41.8 days; 95% CI: 28-56) (23).

LH concentrations

A study by Benelli et al., found an average decrease in LH levels from 12.5 ± 8 mIU/ml to 8.5 ± 4.04 in a group of 21 women after combined therapy of MI and DCl through immune-enzymatic assays. Januszewski et al., also reported a significant decrease

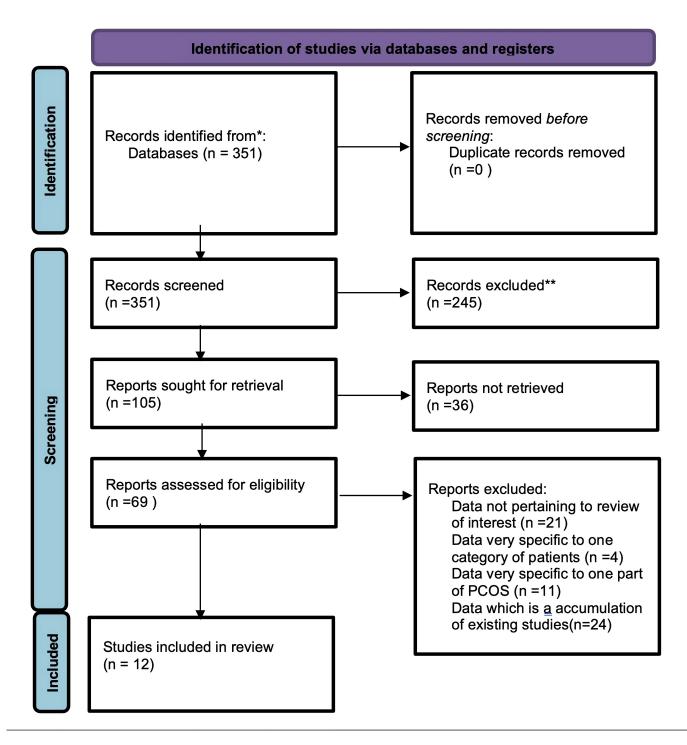


Fig. 1 351 studies were identified from the PubMed and Google Scholar search. There were 0 duplicate records removed. After screening of their abstracts and introduction, 245 records were removed, and 101 were sought out for retrieval. 36 records could not be retrieved; hence, 69 were assessed for eligibility. Out of the 69, 21 records were not focused on the topic, 4 were too specific to one category of patients, 11 were too specific to one section of PCOS, and 24 were records combining other existing records. 12 records were reviewed.

| paper source | Inositol Form | Inositol concentration | Duration | outcomes |
|--------------------|----------------------|--|--------------|--|
| Benelli et al. | MI + DCI | MI + DCI (40:1), 550 mg MI + 13.8 mg DCI + folic acid, BID | 6 months | ↑SHBG, ↑Ovulation, ↓LH, ↓Free testosterone, ↓HOMA index, ↓Fasting insulin |
| Constantino et al. | MI | 2 g/ day MI + 400 mg/day folic acid | 3 months | ↓Total testosterone, ↓Free testosterone, ↓Plasma triglycerides, ↓Systolic blood pressure, ↓Diastolic blood pressure, ↓Plasma insulin curve AUC, ↓Fasting insulin, ↑Whole body insulin sensitivity (ISI comp), ↑Ovulation rate (16/23 vs 4/19) |
| Gerli et al. | not specifie d | 100 mg Inositol, BID | 16 weeks | ↑Ovulation frequency, ↓Time to first ovulation, ↓Anovulatory patients, ↓Weight, ↓Leptin, ↑HDL, ↓Efficacy in BMI > 37 |
| Januszewski et al. | MI + DCI | MI + DCI (10:1), 1100 mg/day (2 tablets) | 6 months | ↓Body weight, ↓Free testosterone, ↓FSH, ↓LH, ↓Insulin, ↑SHBG, ↓OGTT glucose, ↑Skin condition |
| Kachhawa et al. | MI + DCI | MI + DCI (3.6:1), 550 mg + 150 mg, BID | 6 months | ↑Spontaneous menses, ↑Regular cycles post-treatment, ↓Cycle length, ↓AMH, ↓HOMA-IR, |
| Marca et al. | DCI | 1000-1500 mg/day DCI (dose based on body weight) | 15 months | ↓HOMA index, ↓AMH, ↑Regular menstrual cycles |
| Nestler et al. | DCI | 1200 mg/ day DCI | 8 weeks | ↓Plasma insulin AUC, ↓Free testosterone, ↓BP (systolic & diastolic), ↓Triglycerides, ↑Ovulation |
| Özay et al. | MI | 4 g MI + 400 mg folic acid, BID | 12 weeks | ↑Serum progesterone (day 21), ↓Fasting insulin, ↓Fasting glucose, ↓HOMA-IR, ↑Spontaneous pregnancy, ↑Clinical pregnancy rate, ↓Cycle cancellation, ↓Total rFSH dose, ↓Cycle duration |
| Zacchè et al. | MI | 2 g MI + 200 mg folic acid, BID | 6 months | ↓LH, ↓Testosterone, ↓Free testosterone, ↓Insulin, ↓HOMA index, ↓Hirsutism, ↓Acne |

in LH levels, staring from 12.4 ± 6.7 mIU/ml during the first visit to 9.3 ± 4.2 mIU/ml during the third visit after the 1100 mg/day of inostiols in form of 10:1 ratio MI and DCI combined treatment (reason for dosage was unspecified) in a group of 70 women diagnosed with PCOS. Moreover, significant decrease in LH levels was also demonstrated through a study conducted by Zacchè et al., decreasing from 14.1 + 5.7 to 8.4 + 2.2 after three months of supplementation of 2g of MI with 200 mg of folic acid, the reason was not specified for this dosage 20,23,24 .

Insulin resistance/ sensitivity

majority of the studies found a significant reduction in insulin concentration and an increase in glucose tolerance. Marca et al. found that before treatment of 1000-1500 mg of DCI daily (according to body weight) for 12 months (reason for dosage not specified), 40% of 47 women had insulin resistance, defined in the study for a HOMA index> 2.2, which decreased to 16% of 31 women having insulin resistance; ²⁵. In a different study by Benelli et al., the HOMA index and fasting insulin levels, which serve as markers of insulin resistance, showed a significant reduction after the combined treatment ²⁰. In the study conducted by Özay et al. and Zacchè et al., there was a decrease in serum HOMA-IR, fasting glucose, and fasting insulin levels ^{20,26}. Increased insulin sensitivity was also found in women subjected MI and DCI treatment in a ratio of 10:1 in a study conducted by Januszewski et al²⁴. Constantino et al. also found an increase in Whole-Body Insulin Sensitivity Index (ISI Comp) 2.80 ± 0.35 to 5.05 ± 0.59 mg-2/dl-2²². Nester et al., however, found no notable difference in the decrease of plasma insulin concentration observed during fasting between the group receiving DCI and the group receiving a placebo, with both groups showing similar trends ¹⁴.

Androgen levels

As demonstrated by 5 studies, levels of androgens decreased. Nester et al. found a decrease in serum testosterone levels, serum free testosterone levels, and serum androstenedione in the group receiving DCI treatment ¹⁴. Studies conducted by Benelli et al. and Constantino et al., also showcased a decrease in free testosterone levels and Serum total testosterone after combined treatment through MI and DCI and singularly MI, respectively ^{20,21}; nevertheless, there was not a significant difference in androstenedione levels compared to the placebo group. Studies Januszewski et al , Özay et al and Zacchè et al. similarly demonstrated a decrease in Free testosterone levels ^{21,23,24}.

Other variables

In the studies conducted by Nester et al. the women who were administered DCI experienced reductions in both systolic and diastolic blood pressure, as well as plasma triglyceride levels ¹⁴.

Similarly, a study done by Constantino et al. also showcased a decrease in systolic and diastolic blood pressure in women taking MI supplementation. SHBG levels increased in all 6 studies ^{14,20,21,23–25}. According to the study conducted by Marca et al. after the treatment including DCI for 12 months, 16 out of 31 had a regular menstrual cycles (ranging from 25 to 35 days) compared to 0 out of 47 prior to treatment, therefore there was a 51.6% increase in women reporting regular menstrual cycles ²⁵. In another study by Zacchè there was a significant decrease in self-reported acne and hirsutism (according to mFG score) ²³.

According to several studies inositols have been shown to have a positive impact on patients with mental disorders. In a study by Mukai et al. inositols supplementation has been demonstrated to be beneficial for depressed patients, especially ones with Premenstrual dysphoric disorder²⁷. Furthermore, In another study by Fux et al. the authors conclude that inositol is effective in treating depression, panic disorder, and obsessive-compulsive disorder²⁸. A study by Benjamin et al. also supported its efficacy in panic disorders and study conducted by Chengappa et al. demonstrated inositol's effect for bipolar depression^{29,30}. However several studies also resulted in insignificant improvement post-treatment on these parameters^{27,31}

Inositols versus metformin

In a study conducted by Shokrpour et al., it was demonstrated MI treatment, 2 g of MI plus 200 mg of folic acid two times a day, compared to treatment with metformin, 500mg three times a day, for 12 weeks, led to a significant decrease in fasting plasma glucose, serum insulin levels, HOMA-IR, serum triglycerides, and very-low-density lipoprotein (VLDL)-cholesterol levels. Moreover, MI treatment considerably increased QUICKI in comparison to metformin treatment. However, MI supplementation did not have an impact on other lipid profiles ³². A study conducted by Aggarwal et al. compared the effects of DCI and metformin supplementation over 12 weeks. The findings revealed that reductions in hormonal markers such as luteinizing hormone (LH), follicle-stimulating hormone (FSH), and anti-Müllerian hormone (AMH) were significantly greater in the group receiving DCI compared to the group treated with metformin³³. In a comparative study done by Nehra et al. participants were divided into 2 groups, Group A was given a tab MI 1g twice daily and group B was given a tab Metformin 500 mg thrice daily for 6 Months. The study concluded that Both MI and metformin both improved the biochemical parameters including LH, FSH, testosterone, HOMA-IR; moreover, the difference in parameters between the two was considered statically non-significant³⁴. In another study by Jamilian et al., it was discovered that the use of MI over 12 weeks, when compared to metformin, yielded positive outcomes in total testosterone levels, mFG scores, serum hs-CRP levels, and the gene expression of IL-1 among individuals with PCOS. However, there was no significant impact on other hormonal profiles, NO levels, or the gene expression of IL-8 and TNF- α^{35} . The reasons for the dosages in the studies were not given.

MI versus DCI

In a study conducted by Pizzo et al., group 1, consisting of 25 PCOS patients, was treated with 4 g of MI/die plus 400 mcg of folic acid/die orally for six months, and group 2, also consisting of 25 PCOS patients, was treated with 1 g of DCI/die plus 400 mcg of folic acid/die orally for six months. It was found that MI treatment, compared to DCI supplementation, significantly decreased the LH/FSH ratio, total testosterone, and HOMA index. It also lowered systolic arterial pressure, though not significantly. Comparatively, the MI treatment also significantly increased SHBG levels. Furthermore, it was also found that DCI treatment, compared to MI supplementation, reduced LH and free testosterone levels the greatest, however not significantly. Post-treatment greater menstrual cycle regularization in patients treated with DCI compared to those treated with MI was also observed, although the difference was not statistically significant ³⁶. In a study by Formuso et al., in comparison, 137 PCOS patients were randomized into three groups: group A (51 patients) : 2 g of MI twice daily with folic acid, group B (48 patients): 500 mg of DCI twice daily with folic acid, vitamin B12, and manganese, and group C (38 patients, control): placebo. Over six months, ovulation rates significantly improved in groups A (66%) and B (64%), with no significant changes in the placebo group. Additionally, inositol treatments accelerated menstrual cycle regularity, with MI showing slightly better efficacy in metabolic and hormonal improvements; however, it was not considered statistically significant³⁷. The reasons for the dosages were not specified.

Discussion

It has been demonstrated that women with PCOS who receive therapy of DCI, MI, or a combined therapy of DCI and MI supported a higher ovulation rate, lower insulin concentrations, and an increase in glucose tolerance, indicating an increase in insulin sensitivity ^{20,21,23,25}. The treatment also resulted in reduced androgen and LH levels, decreased systolic and diastolic blood pressure, and improvements in hirsutism, and acne in the women who received therapy. Inositol treatment, in comparison to metformin therapy, also yielded better outcomes in total testosterone levels, mFG scores, serum hs-CRP levels, the gene expression of IL-1, fasting plasma glucose, serum insulin levels, HOMA-IR, serum triglycerides, and VLDL-cholesterol ^{32,35}. A study comparing the effectiveness of MI and DCI found that MI significantly decreased the LH/FSH ratio, total testosterone,

and HOMA index while increasing SHBG levels. It also lowered systolic arterial pressure, although this reduction was not statistically significant. Treatment with DCI resulted in a more substantial reduction in LH and free testosterone levels and greater regularization of the menstrual cycle compared to MI; however, these findings were not statistically significant ³⁶. Both, MI and DCI act as insulin second messengers and mediate different actions of insulin. Specifically, MI facilitates glucose uptake and DCI catalyses glycogen synthesis. In reproductive organs like the ovary, MI regulates follicle-stimulating hormone (FSH) signalling and glucose uptake, whereas DCI is mainly involved in insulin-mediated androgen production ³⁸. MI support insulin signalling and reduce androgens by enhancing follicle maturation by improving FSH signalling since it is a second messenger; therefore, increasing aromatase activity, and lowering total androgen production, and also by stimulating SHBG production, which decreases free androgen levels. Therefore MI addresses one of the root causes of PCOS-related hyperandrogenism and its associated symptoms, such as irregular menstruation and hirsutism. However, DCI acts as an aromatase inhibitor, suppressing the conversion of androgens to oestrogens. This inhibition, especially at high doses or with prolonged use, can lead to androgen build-up and oestrogen deficiency, potentially increasing the intensity of PCOS symptoms ³⁹. Neverthless, in short-term DCI seemed to cause improvement in metabolic and ovulatory parameters of PCOS patients. In such instances, DCI decreases insulin levels, consequently increasing the level of MI, leading to increase FSH production therefore ovulation 40. This can correct the elevated LH/FSH ratio found in PCOS patients; moreover, anovulation⁴¹. The imbalance in the ovarian MI o DCI ratio may contribute to the development of PCOS in insulin-resistant patients. Increased DCI levels promote androgen production, while a depletion of myo-Ins impairs FSH signalling and oocyte quality. Studies have shown that healthy women's ovaries maintain a higher MI to DCI ratio (around 100:1), whereas women with PCOS exhibit lower MI levels and increased DCI, resulting in a ratio as low as 0.2:142. Additionally, MI and PLP-C facilitate the release of InsP3, which controls intracellular calcium (Ca2+) levels. The final stages of oocyte development are Ca2+-dependent, with InsP3 binding to its receptor 1 (IP3-R1) playing a critical role in the maturation of oocytes and the progression of meiosis, both of which are characterized by elevated Ca2+ levels³⁸. Moreover, MI-IPG appears to influence the cytoskeleton 43,44 and contributes to FSH-induced anti-Müllerian hormone (AMH) production. AMH modulates follicular sensitivity to FSH, thus regulating follicle maturation ⁴⁵. The regulatory pathway involving AMH and FSH sensitivity is often found to be disrupted in anovulatory disorders such as PCOS. Specifically, elevated AMH levels found in PCOS patients in turn prevent FSH action, impairing follicular maturation therefore contributing to anovulation, which is a common parameter of the condition ⁴⁶. Apart from in-

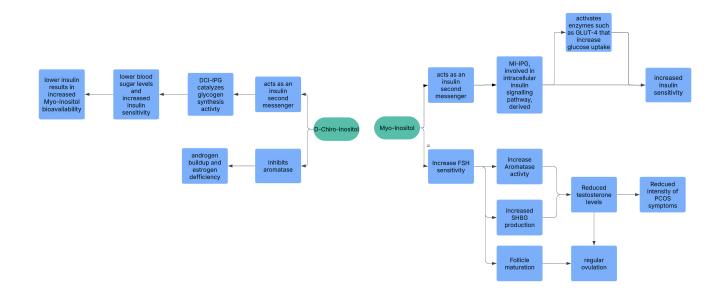


Fig. 2 D-Chiro Inositol vs Myo-Inositol

ositol, FSH activates the cAMP/PKA pathway, which promotes steroidogenesis by inducing aromatase activity ⁴⁷. Interestingly, MI concentrations in the female reproductive tract are significantly higher than in plasma, suggesting that MI has specific ovarian functions, such as enhancing oocyte transport through the oviducts ⁴⁸. In humans, inositols are primarily sourced from the diet in the form of MI (MI)²⁸. It is feasible to meet the 2g of MI (daily) requirements for treatment of PCOS through diet alone, since the intake of MI can range from 250mg to 1650mg/day from a 2000 kcal diet, depending on the foods that are consumed ^{19,49}. Consumption of whole grain foods, legumes, and nuts, rich in phytic acid, are the main source of inositol so altering diet to increase amounts of these foods achievable and can contribute to decreasing the PCOS symptoms ⁴⁹. Although a well-balanced diet can provide similar amounts of inositol as the treatment, taking an inositol supplement helps ensures consistently meeting the minimum levels recommended by research to reduce PCOS symptoms. MI can be converted into DCI through enzymes by the action of an NAD-NADH-dependent epimerase, which is activated by insulin⁴². This conversion allows organs and tissues to regulate inositol levels and alter the MI/DCI ratio to suit the specific metabolic requirements. Under normal physiological conditions, the MI/DCI ratio is approximately 100:1 in follicular fluid (FF) and 40:1 in plasma ⁵⁰. Perhaps due this ratio being present in the plasma of healthy women, the supplementation of MI and DCI in this ratio shows the most promising clinical results 40. Since it is naturally produced by the body; moreover, is a part of existing metabolic pathways, may be the reason patients taking this supplement exhibit fewer side effect than Metformin, which commonly causes Nausea, vomiting, stomach upset, diarrhoea and weakness 51. Clinical trials have shown that mild gastrointestinal symptoms such as nausea, flatulence, and mild insomnia may occur at doses higher than 12 g of MI per day⁵². However, in rodents, higher doses of DCI (10 mg/day and 20 mg/day) were seen to cause ovarian lesions similar to those seen in pre-menopausal or menopausal states, along with a significant decrease in serum testosterone levels⁵³. The allowed maximum daily inositol intake is presently up to 4 g. Furthermore, MI and DCI supplementation in pregnant women, preterm infants, and the general population has been shown to be generally safe, with adverse side-effects being limited to mild gastrointestinal symptoms such as nausea, flatus, and diarrhoea which is supported by both animal model studies and clinical trials. Furthermore, inositol is also generally recognized as safe by the FDA⁵⁴. Even though inositols shows non-inferiority in most outcomes compared to metformin, the golden standard, metformin still remains as the first-line of medication³. This may be due to its established efficacy by a large body of evidence and long-term safety profile, compared to which Inositols are relatively new and not explored to such an extent. The strength of this review is that each study was methodologically assessed. Furthermore, each paper went through 2 thorough rounds of screening. A strict protocol was followed, and Inositols were compared not only to placebo but also to Metformin, a golden standard in the industry. The review's main limitation was that the included studies may vary widely in terms of participant characteristics, dosages, durations, ethnicities; furthermore, may not control external facts such as diet and exercise making it

challenging to draw unified conclusions and leading to the reduced validity of results . Even though the results show that inositols are majorly beneficial to women with PCOS, a study conducted by Unifer et al. demonstrated that inositols may not be as effective in improving all the parameters of PCOS in its phenotypes. Specifically, The study conducted by Unifer et al. found that administration of treatment involving MI caused significant improvement in metabolic and endocrine metrics among individuals with H-PCOS(hyperandrogenic PCOS), whereas its impact on NH-PCOS(non-hyperandrogenic PCOS) was minimal. This could be because in NH-PCOS the women do not have the hyperandrogenism parameter, consequently are less dysmetabolic compared to H-PCOS; therefore, the effect of MI, which works to alter hormone levels, is minimal ⁵⁴.

Future Work

Future studies are needed to investigate the long-term safety and efficacy of inositol treatment in combination with other treatment alternatives. Furthermore, Investigate the impact of inositol therapy on quality-of-life metrics, such as mental health, body image, and overall well-being, in addition to metabolic and reproductive outcomes. Studies should also be conducted to investigate the safety and benefits of inositol supplementation in pregnant women with PCOS, focusing on maternal and neonatal outcomes and the maximum tolerance dosage for humans, rodents and non-rodents also needs to be explored. Moreover, formal, large-scale clinical trials are also required to support the efficacy of inositol in women with PCOS compared to Metformin. In future studies the effect of MI and DCI on all phenotypes of PCOS needs to be ascertained in a detailed manner. Future studies are required to study the positive and negative interactions of inositols with various drugs in a more comprehensive manner.

Conclusion

To conclude, treatment including DCI and MI singularly or in a combination can cause significant improvement in metabolic and endocrine parameters of PCOS including insulin resistance, LH and androgen concentrations, ovulation etc. Furthermore, inositols have demonstrated comparable efficacy in nearly all aspects when compared to metformin, suggesting they offer a promising alternative treatment option for PCOS.

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