

A comprehensive overview of role of combined myoinositol and D-chiroinositol (40:1 ratio) therapy in the management of PCOS

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ABSTRACT

Polycystic Ovarian Syndrome (PCOS) is one of the most common metabolic and reproductive ailment among reproductive age group women. PCOS patients present with a constellation of signs and symptoms associated with menstrual dysfunction and androgen excess, which significantly impacts quality of life. Women with PCOS is at increased risk of various morbidities, which includes obesity, insulin resistance, type II diabetes mellitus, cardiovascular disease (CVD), infertility, cancer, and psychological disorders. Exact pathophysiology of PCOS is poorly understood although studies have suggested an important role of insulin resistance and/or resultant compensatory hyperinsulinemia. Deficiency in the usage and/or tissue availability of myoinositol (MI) and/or D-chiroinositol (DCI) in PCOS patients could likely lead to insulin resistance typical of this syndrome. Recent studies have demonstrated that combined supplement containing both MI + DCI in their physiological plasma ratio 40:1 is able to improve the endocrine profile, ovarian function and the insulin resistance in PCOS patients. The aim of the present review was to summarize currently available data on the MI+DCI (40:1) combination therapy in PCOS patients.

Keywords: Polycystic ovary syndrome, myoinositol, D-chiroinositol, insulin resistance.

In modern medical era, polycystic ovary syndrome (PCOS) was first described by Stein and Leventhal in 1935, who studied seven females with amenorrhea, hirsutism and enlarged ovaries with multiple cysts.¹ PCOS is now recognized as a common, heterogeneous, heritable disease affecting females throughout their lifetime. It is most common cause of hyperandrogenism and oligo/anovulation leading to notable psychological, social, and financial consequences.² The prevalence of PCOS has

shown significant rise from 8% to almost 20% globally within the past two decades.³ Studies conducted on PCOS in India showed a prevalence ranging from 3.7 % to 22.5 %^{4,5} (with 9 % to 36% prevalence in adolescents).^{6,7} In Indian subcontinent, PCOS prevalence rate amongst infertile women is high (upto 50-60 %).⁸

Clinical symptoms and conditions associated with polycystic ovary syndrome^{9,10} (Figure 1)

As per Rotterdam criteria which is widely followed

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Figure 1: Clinical signs and symptoms of PCOS^{9,10}

Manifestations of Hyperandrogenism	<ul style="list-style-type: none">•Acne•Hirsutism•Alopecia•Acanthosis nigricans
Menstrual irregularity	<ul style="list-style-type: none">•Oligomenorrhea•Amenorrhoea
Ultrasonographic findings	<ul style="list-style-type: none">•≥12 follicles in each ovary•Follicle size between 2 to 9 mm with or without 10ml ovarian volume
Associated morbidities	<ul style="list-style-type: none">•Obesity•Insulin resistance•Type 2 diabetes mellitus•cardiovascular disease•Dyslipidemia•Metabolic syndrome•Mood disorders•infertility•psychological disorders: depression, anxiety

across Asia, Europe and Australia,¹¹ for stating the presence of PCOS, at least two of the following three criteria should be present: (i) Oligo- or anovulation (ii) Biochemical or clinical indication of hyperandrogenism; and (iii) presence of polycystic ovaries at ultrasound or presence of 12 or more follicles with a diameter of 2 to 9 mm in each ovary, and/or raised ovarian volume (>10 ml).¹²

Role of Insulin Resistance in PCOS pathophysiology

Exact pathophysiology of PCOS is still poorly understood. PCOS is a multifactorial disorder that results from complex interactions between genetic and environmental factors.¹³ Familial clustering, linkage and association studies have shown candidate genes for PCOS with autosomal dominant trait and low penetrance.³ Current knowledge of PCOS pathophysiology indicates substantial role played by insulin resistance. Insulin resistance is observed in upto 50-90 % of PCOS patients.¹⁴ Compensatory hyperinsulinemia acts synergistically with luteinizing hormone (LH) as a co-gonadotrophin within ovarian theca cells.¹⁵ Resultant activation of CYP17 encodes P450c17 α which is a very important enzyme for androgen biosynthesis.¹⁶ Acting within the ovary, insulin promotes arrest of pre-antral follicle growth and development.¹⁷

Extra-ovarian pleiotropic effects of hyperinsulinemia involves augmentation of LH pulse amplitude,¹⁸ enhancing adrenal P450c17 α activity and restraint of hepatic sex hormone binding globulin (SHBG) production.¹⁹ Weight gain and obesity can worsen insulin resistance in PCOS.²⁰ Decreased insulin sensitivity is observed both in obese as well as lean PCOS patients.²¹ Insulin resistance can lead to diabetes, metabolic syndrome, thus predisposing PCOS patients to cardiovascular risk.²⁰ An overview of peripheral insulin resistance and its role in the pathogenesis of PCOS is depicted in Figure 2.^{20,22}

Role of inositol in Insulin-signaling pathways

Insulin-signaling pathways involve mediators like inositol phosphoglycans (IPGs). Phosphatidyl-myoinositol acts as precursors of phosphatidyl inositol bisphosphate/triphosphate and is important for production and activation of PI3 kinase, thus playing an important role in insulin signal transduction pathway.²³ D-chiroinositol also has a potential role as a putative mediator of insulin action. D-chiroinositol is involved in stimulation of pyruvate dehydrogenase phosphatase, protein phosphatase 2C facilitating glucose disposal.²⁴ Inositol deficiency can impair insulin action leading to insulin resistance .²⁵ The overview of importance of

inositol in insulin signal transduction pathway is shown

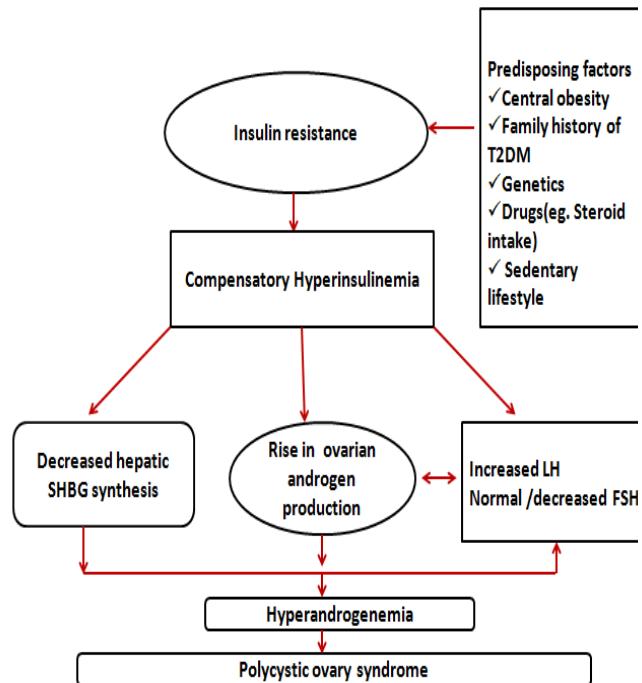


Figure 2: Role of Insulin resistance in PCOS.^{20, 22}

below Figure 3.²⁶ Available data suggest inositol deficiency in insulin-resistant women having PCOS.²⁴ These women have lower serum D-chiroinositol levels and elevated urinary loss of D-chiroinositol-IPG.²⁷ The dysregulated metabolism of inositol in PCOS highlights

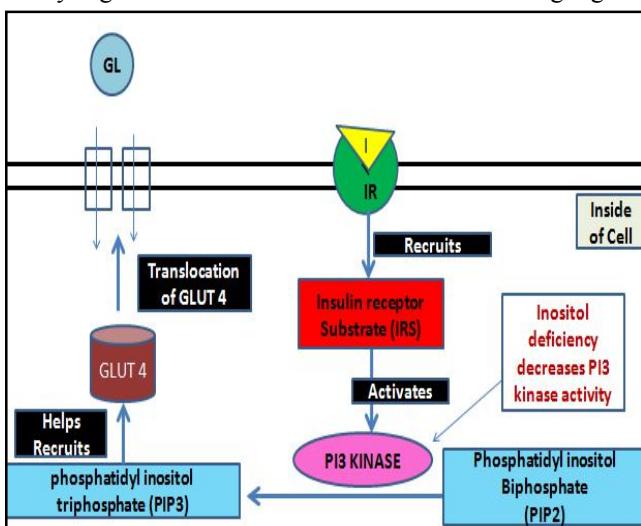


Figure 3: Insulin signal transduction pathway.²⁶

subtle connection between inositol deficiency and insulin resistance in PCOS patients.²⁸

Insulin sensitizers for management of PCOS

Recently insulin-sensitizing agents have been proposed as a therapy for the treatment of PCOS. These agents act by increasing insulin sensitivity leading to decrease in hyperinsulinemia.²⁹ Since decreased insulin sensitivity is observed both in obese and lean PCOS patients²¹ use of insulin sensitizers are being advocated in most patients with PCOS. Insulin sensitizer treatment has been shown to be resulting in reduction of serum androgen levels and gonadotropins, improvement of serum lipids, metabolic comorbidities.²⁹ This therapy has also been shown to regularize the menstrual cycle, improve ovulation and fertility and decrease hirsutism and acne.²⁹ Commonly used insulin sensitizers for PCOS include metformin, myoinositol, and thiazolidinedione. Metformin although effective in counteracting hyperandrogenism in the short term in obese, insulin-resistant PCOS women³⁰ but published study reports that non obese women PCOS women had no benefit from metformin.³¹ Metformin is shown to have a detrimental effect on follicle number and quality.³² Baillargeon et al (2004) have shown that benefits imparted by metformin in PCOS can be attributed to its ability to improve insulin-mediated release of DCI-IPG mediators.³³ Nausea, diarrhoea, and weight gain observed with metformin reduce patient's compliance to therapy.³⁴ Nevertheless the use of thiazolidinediones is associated with weight gain, cardiovascular events, fragility fractures and bladder cancer.³⁵

Inositol

Inositol is polysugar alcohol that belongs to vitamin B-Complex group.²⁵ Inositol exists as nine isomers.²⁵ The myoinositol and D-chiroinositol are the two main stereoisomers present in human body.³⁶ Inositol is found concentrated in the phospholipids in many foods, such as cereals, nuts, fruits and animal tissues.³⁷ Each tissue has its own MI/DCI ratio and the relative proportion of each inositol in a particular tissue is reflective of inositol specific functions.³⁸ This ratio within the cell is maintained via direct enzymatic transformation of MI to DCI through insulin dependent enzyme epimerase as per

the tissue requirement.(39) In plasma, the physiological ratio of MI: DCI is shown to be 40:1.³⁹

Myoinositol: MI, an essential component in eukaryotic cell membranes is the most abundant inositol found in nature.⁴⁰ Myoinositol plays an important role in several biological processes like insulin mediated signals transmission, cytoskeleton assembly, gametogenesis, intracellular calcium concentration regulation, maintenance of membrane potential, regulation of gene expression.⁴¹ Myoinositol controls the activities of several hormones such as follicle stimulating hormone (FSH), insulin, thyroid stimulating hormone (TSH).³⁹ MI is involved in cellular glucose uptake, it raises ovarian energy status and hence it is able to improve oocyte quality.³⁸

D-chiroinositol (DCI). It is a product of the epimerization of the MI. DCI is important for glycogen synthesis. High concentrations of DCI is present in glycogen storage tissues, such as liver, muscles, fat and low concentration is present in those tissues with high glucose utilization such as brain, ovary, heart.³⁸

Both the isoforms of inositol individually were found to be effective in improving ovarian function and metabolism in patients with PCOS.⁴² Myoinositol showed the most marked effect on the metabolic profile, whereas D-chiroinositol caused better reduction of hyperandrogenism.⁴²

Rationale of MI +DCI (40:1) ratio supplementation in PCOS

Epimerase is an insulin dependent enzyme.⁴³ In PCOS, the insulin resistant tissues have low DCI level due to reduced epimerase activity, on the other hand insulin sensitive tissues like ovary have increased epimerase activity causing enhanced conversion of MI to DCI depleting MI level.⁴³ In follicular fluid normal MI/DCI ratio is nearly 100:1 while in PCOS women that ratio is only 0.2:1³⁵ (DCI paradox). In PCOS, peripherally reduced DCI augments insulin-resistance and worsens the metabolic features⁴⁴ while reduced MI blocks synthesis of phosphatidyl-MI that lead to lack of transmission of FSH signals which might be responsible for chronic anovulation in PCOS patients.³⁹ Reduced levels of MI decreases oocyte quality by interfering with physiological follicular maturation.⁴⁴ Hence to restore disturbed inositol balance in various tissues particularly in ovary, there is

need of MI and DCI supplementation in their physiological ratio of 40:1. As MI and DCI regulate different biological processes, concomitant administration has synergistic action which is more beneficial than MI alone and DCI alone in PCOS.^{45,46} DCI is speculated to rapidly cause reduction in the peripheral hyperinsulinemia while MI mainly cause improvement in the ovulatory function.⁴⁵ Supplementation of MI and DCI, in a physiological ratio (40:1), ensure better clinical results both at ovarian and non-ovarian level.⁴⁵

Potential benefits of supplementation of MI/DCI in ratio 40:1

- ✓ There is better reduction of insulin resistance, androgens levels, and cardiovascular risk.³⁹
- ✓ There is better restoration of spontaneous ovulation and menstrual cycle.³⁹
- ✓ Improvement with combination is more quicker compared to MI alone.⁴⁶
- ✓ Better results in terms of weight reduction, resumption of spontaneous ovulation, and spontaneous pregnancy compared with metformin.⁴⁷

The 2013 Florence International Consensus Conference on myoinositol and D-chiro-inositol in obstetrics and gynaecology have answered many research questions pertaining to the use of these two stereoisomers. Overall evidence from the literature analyzed by the Conference scientific Committee points out that for PCOS, treatment based on the association of MI and DCI in the physiological ratio(40:1) can be the most appropriate and, could be a predictive factor in improving assisted reproductive technology (ART) outcome.^{48,49}

Clinical outcomes of the MI +DCI combination in ratio 40:1 in PCOS patients.

The available studies of MI+DCI combination are summarized in below.^{45-47, 50-52} (Table 1).

Safety

Being a naturally occurring substance in the human body as well as in plants, both myoinositol and D-chiroinositol are considered as safe drugs. Inositols are better tolerated.⁵³ The safety data of the myoinositol trials report mild side effects such as, nausea and one of flatulence and mild insomnia only at 12 g/day or higher.⁵⁴ Isabella et al. (2012) showed that a safety threshold for DCI

supplementation in PCOS patients may be set at 300

patients⁵⁴ showed that no relevant side effects of MI+DCI^{45-47, 50-52}

Table 1: The available studies of MI+DCI combination

Author	Study design & Study size	Population Characteristic	Type of treatment	Main findings
Nordio et al 2012 ⁴⁵	Randomized controlled trial in 50 women with PCOS.MI+DCI group: 26 MI only group: 24	Women with PCOS (BMI > 27 kg/m ² , Mean age 28 years range (18-41)	MI+DCI group: 550 mg of MI + 13.8 mg of DCI twice daily for 6 months. MI only group: 2g of MI for 6 months.	At 3 months, compared to MI group in MI +DCI group ,there was significant reduction in Fasting glucose(p<0.05), Glucose AUC(p<0.05).Fasting insulin (p< 0.03) and Insulin AUC(p <0.05).Compared to the MI group, the decrement of total testosterone and the increment of the serum sex hormone binding globulin were more relevant in MI+DCI group both at 3 month and at 6month. In both groups there was a striking improvement of the ovulation function.
Colazingari et al 2013 ⁴⁶	Randomized controlled trial in 100 women with PCOS. MI+DCI group=47patients. DCI only group=53Patients.	BMI<28 and FSH <10 IU/L with a diagnosis of PCOS and a normal uterine cavity.	MI+DCI group: 550 mg of MI + 13.8 mg of DCI orally twice daily for 12 weeks. DCI only group: 500 mg orally twice a day for 12 weeks.	Less IU of rFSH was administered in the MI-DCI group. In ≤ 35 years category, the difference was statistically significant.(<0.05)E2 levels before hCG administration were significantly lower in > 35 yrs women. (p<0.05). No differences were found in the number of oocytes retrieved between the groups in the ≤ 35 age category. In the >35 age category, significantly higher number of oocytes were higher retrieved in the DCI group (p<0.05) MI-DCI treatment reduced the number of degenerated oocytes in both the younger and the older age groups In the ≤ 35 category: The fertilization rate was significantly higher in the MI-DCI treated group(<0.05) and significantly higher number of oocytes were transferred in the MI-DCI treated group (P <0.05).MI-DCI group had higher embryo quality compared to DCI patients(p<0.05). In the patients >35 years old, although there was no difference between the fertilization rate and the number of transferred embryos, there was a significant difference in embryo quality.(p <0.05).
Abdelhamid et.al 2015 ⁴⁷	Case-control study in 128 PCOS Patients MI+DCI group:62 patients Metformin group:66 Patients	Diagnosed PCOS females with clomiphene resistance Age:20-35 yrs BMI less than 30kg/m ² , Failed caloric diet.	MI+DCI group: 1 g MI + 25 mg DCI + 200 mg Folic acid; 2 tablets per day for 3 months Metformin group: Metformin 500 mg tablets 3 times per day for 3 months	Compared to metformingroup,in MI+DCI group significantly higher number of patients achieved spontaneous menstruation (p<0.05) and spontaneous pregnancy. (p<0.05). Number of patients with >10% weight loss were significantly higher in MI+DCI group than metformin group.(p<0.05). There was significant difference in progesterone level, which was >12 ng/ml (p<0.05).There was no statistically significant difference in terms of AMH decrease and HOMA-IR. Results of the paired t-test performed to compare each outcome in both groups showed significant results in the other outcome parameters, such as weight loss, spontaneous ovulation and spontaneous pregnancy, in favor of the MI+DCI group. p<0.05
Benelli et al 2016 ⁵⁰	Randomized controlled Trial in 46 obese PCOS Women MI+DCI group:21 patients Folic acid group: 25 patients	PCOS Women With BMI>30 kg	MI+DCI group: MI (550 mg)+DCI (13.8mg)+ folic acid (200 mcg) capsules twice a day for 6 months Folate group: 200 mcg of folic acid, twice a day for 6 months	Only in the group treated with the MI + DCI ,there was statistically significant reduction from baseline in ✓ LH (p<0.05) , ✓ free testosterone (ng/dl) (p<0.05), ✓ fasting insulin(p <0.001) ✓ HOMA index (p<0.05). Statistically significant increase of 17-beta-Estradiol levels in MI+DCI group.
Minozzi et al.2013 ⁵¹	Longitudinal observation study in 20 women with PCOS.	Obese, caucasian PCOS women.	Patients received 550mg MI+ 13.8mg DCI twice a day for 6 months.	After 6 months of combined therapy, LDL levels were significantly reduced compared with baseline levels (p <0.05). There was significant increase in HDL (p<0.05) and significant decrease in triglycerides (p<0.05). There was significant reduction of the HOMA index (p<0.05) and glucose (p<0.05) and insulin levels.(p<0.05).
Pande M et al. 2017 ⁵²	Randomized controlled Trial in 140 obese PCOS Women MI+DCI group:70 patients Myoinositol group: 70 patients	Overweight (BMI>27) women satisfying Rotterdam criteria for diagnosis of PCOS.	MI+DCI group: MI (550 mg)+DCI (13.8mg) one tablet twice a day for 6 months Myoinositol group: Myoinositol 1 gm twice a day for 6 months	✓ Combination provided significant decrease in BMI, W:H ratio, Diastolic BP, Fasting blood sugar at end of both 3rd and 6th month,]for LDL it was at the end of 3 months. ✓ This combination also increased the HDL level significantly in both the occasions

mg DCI/day, the highest dose that will not reduce oocyte maturation.³⁸ Benelli et al.(2016) study in PCOS patients⁵⁰ and Pintaudi et al (2016) study in type 2 diabetes

combination in ration 40:1 during therapy providing further evidence of the safety of the usage of these inositol in combination.

Conclusion

Myoinositol, a second messenger regulating many hormones such Follicle Stimulating Hormone (FSH) and insulin, positively affects different pathways at both ovarian and non-ovarian level ,while D-chiroinositol by inhibiting the negative consequences of hyperinsulinemia exerts beneficial effects mainly in non-ovarian tissues. Synergistic action of concomitant administration of MI and DCI in their physiological plasma ratio (40:1) seems to be more beneficial than MI alone or DCI alone in PCOS women. Available clinical data demonstrates combined inositol supplementation in their physiological ration could fruitfully affect different pathophysiological aspects of PCOS and improves endocrine ,metabolic ,ovarian and ,reproductive disturbances of PCOS .Owing to better therapeutic efficacy, safety and tolerability profile, MI+DCI (40:1) combination can be an attractive option in management of PCOS .

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