

## COMPARATIVE EFFICACY OF D-CHIRO-INOSITOL AND METFORMIN IN MANAGING POLYCYSTIC OVARY SYNDROME: A RANDOMIZED CONTROL TRIAL

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### ABSTRACT

**Background:** Polycystic ovary syndrome (PCOS) is a common endocrine disorder characterized by insulin resistance, metabolic disturbances, and menstrual irregularities. Insulin resistance IR is due to defect in post receptor mechanism of signal transduction. D- chiroinositol acts as a second messenger in insulin signalling and helps to reduce insulin resistance thereby improving metabolic and hormonal profiles. **Aim:** This study aimed to evaluate the efficacy and safety of D-chiroinositol (DCI) supplementation in PCOS management. Primary objective of the study was regulation of menstrual cycle. Secondary objectives were reduction in LH level, reduction in serum insulin level and weight reduction. **Materials and Methods:** A randomized, open-label, interventional, and comparative study was conducted at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai, from August 2016 to May 2017. Sixty women diagnosed with PCOS were randomized into three groups receiving following drugs: Group A: Tab Metformin alone (n=20) Group B: Tab D-chiro-inositol alone (n=20), Group C: Combination of metformin and DCI (n=20) ,Participants were monitored over a 12-week treatment period, and then 8-week follow-up. **Result:** All three treatment groups demonstrated improvement in menstrual regularity, reduction in BMI, reduced serum LH and fasting insulin levels. Of which, Group C showed the most substantial improvements, indicating a synergistic effect of DCI and metformin. Adverse effects, mainly gastrointestinal discomfort, were observed predominantly in the metformin-only group, whereas DCI was well-tolerated with minimal side effects. **Conclusion:** DCI supplementation, alone or in combination with metformin, significantly enhances insulin sensitivity, hormonal balance, and reproductive outcomes in women with PCOS. Its superior tolerability and clinical benefits position it as a promising alternative or adjunct therapy. Further large-scale studies with extended follow-up are warranted to confirm long-term benefits and optimize treatment strategies.

## INTRODUCTION

The most prevalent endocrine condition affecting women in their reproductive years is Polycystic Ovary Syndrome (PCOS).<sup>[1]</sup> The Rotterdam criteria state that PCOS is diagnosed when the following traits are more prevalent: polycystic ovarian morphology on ultrasound, clinical or biochemical indicators of hyperandrogenism, and irregular or absent ovulation.<sup>[2]</sup> This syndrome is a leading cause of infertility because it disrupts the regular menstrual cycle. The development of PCOS is complex, with both genetic predispositions and environmental

factors—such as stress, lifestyle habits, unhealthy diet, and physical inactivity—playing critical roles.<sup>[3]</sup> A significant proportion (approximately 60–70%) of women with PCOS exhibit Insulin resistance, primarily due to defects in the post-receptor mechanism of insulin signalling.<sup>[4]</sup> This resistance leads to compensatory hyperinsulinemia, which in turn stimulates the secretion of luteinizing hormone (LH), thereby increasing ovarian androgen production and further impairing ovulation.<sup>[5]</sup> Beyond its effects on reproduction, PCOS is linked to metabolic disorders such as obesity, dyslipidemia, atherosclerosis, cardiovascular illnesses, and type 2

diabetes mellitus, which together contribute to the metabolic syndrome.<sup>[6]</sup>

While lifestyle modifications such as improved diet and regular exercise remain the cornerstone of PCOS management, pharmacotherapy is often required. Metformin, a well-established insulin sensitizer, is frequently used.<sup>[7]</sup> But, it may cause gastrointestinal discomfort and other side effects. In light of these limitations, alternative therapies are under investigation.<sup>[8]</sup>

One such alternative is D-chiro-inositol (DCI), an important stereoisomer of inositol that functions as a secondary messenger in insulin signalling.<sup>[9]</sup> DCI contributes to the formation of key molecules like inositol triphosphate (IP3) and phosphatidylinositol 3-kinase (PI3K), which are critical for enhancing glucose uptake and improving insulin sensitivity.<sup>[10]</sup> Previous studies have demonstrated that DCI supplementation can improve both endocrine and metabolic parameters in PCOS suggesting its potential role as either a primary treatment or in combination with metformin.<sup>[11,12]</sup>

#### Aim and Objectives

**Aim:** To evaluate the efficacy and safety of D-chiro-inositol supplementation in women diagnosed with PCOS.

#### Objectives:

**Primary objective:** To assess the normalization of menstrual cycles following treatment.

#### Secondary Objectives:

1. To determine the extent of reduction in LH levels.
2. To evaluate changes in fasting serum insulin concentrations.
3. To monitor variations in body weight over the treatment period.

## MATERIALS AND METHODS

The Institute of Pharmacology at Madras Medical College (MMC) and the Institute of Obstetrics and Gynaecology at Rajiv Gandhi Government General Hospital (RGGGH) in Chennai cooperated to perform this randomized, open-label, interventional, and comparative trial. The study was conducted between August 2016 and May 2017. Prior to enrolment, each subject gave written informed permission, and the Institutional ethics committee granted ethical clearance.

#### Inclusion Criteria:

1. Women diagnosed with PCOS experiencing irregular menstrual cycles.
2. Age between 18 and 40 years.
3. Oligomenorrhea, defined as eight or fewer menstrual cycles per year.
4. Presence of hyperandrogenism, confirmed clinically or via laboratory tests.

5. Willingness to provide informed written consent.
6. Ability to adhere to the study protocol.

#### Exclusion Criteria:

1. Women diagnosed with diabetes mellitus.
2. Significant cardiovascular, pulmonary, renal, hepatic, neurological, or psychiatric disorders, or malignancies.
3. Concurrent endocrine disorders (e.g., thyroid dysfunction, hyperprolactinemia, or adrenal abnormalities).
4. Use of any investigational drug within two months before the study.
5. Pregnant or lactating women.

Women with confirmed diagnosis of PCOS, evaluated based on detailed medical history, physical examination, systemic evaluation, as well as laboratory investigations were selected. Out of 108 women screened, 60 fulfilled the requirements for participation in the investigation. Using a randomization technique, the participants were chosen at random and divided into 3 categories:

- Group A (n=20): Received standard treatment with tablet Metformin 500 mg TDS.
- Group B (n=20): Received tablet D-chiro-inositol 600 mg BD.
- Group C (n=20): Received D-chiro-inositol and Metformin combination.

The study spanned a treatment phase of 12 weeks, then an 8weeks follow-up. Medication compliance was monitored by reviewing returned medication bottles, and all participants were given detailed instructions regarding proper drug intake and the importance of reporting any adverse effects. The biochemical parameters were evaluated statistically using SPSS software version 21. On the other hand, ANOVA has been employed to assess the variations among the Control and Study groups. A significance level of  $P < 0.05$  is deemed statistically significant.

## RESULTS

Out of 108 individuals initially screened, 60 participants fulfilled the eligibility criteria and completed the study, with no dropouts observed. The study group featured both married and unmarried women within the range of 18-40yrs.

Detailed statistical analyses revealed significant improvements in key parameters such as body mass index (BMI), LH levels, fasting serum insulin level and menstrual regularity across all groups. Notably, the group receiving combination therapy (Group C) demonstrated the most substantial benefits. Mild adverse events, including nausea, abdominal discomfort, and diarrhoea, were reported—primarily in the metformin-only group—while the DCI group experienced fewer side effects.

**Table 1: Menstrual Cycle Regularity**

Group	Patients With Regular Cycles 0 - Weeks	%	Patients With Regular Cycles 12 - Weeks	%
GROUP A	0	0	8	40
GROUP B	0	0	13	65

GROUP C	0	0	15	75
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[Table 1] shows number of patients who had regular menstrual cycles.

Menstrual cycle regularity was seen maximum in group C, followed by group B and group A.

**Table 2: Luteinizing Hormone Level (mIU/ml)**

GROUP	0 – WEEKS		12 – WEEKS		P – VALUE
	MEAN	SD	MEAN	SD	
GROUP A	14.79	2.14	14.47	2.04	0.023
GROUP B	15.60	3.28	13.82	3.03	0.001
GROUP C	16.26	2.96	11.88	3.11	< 0.001
P - VALUE	0.267		0.021		

[Table 2] shows mean LH levels in all three groups at Baseline and at the end of 12 weeks.

Statistical analysis in between the groups showed a significant decrease in the LH level at the end of 12 weeks ( $p < 0.05$ ).

**Table 3: Fasting Serum Insulin Level (µIU/ml)**

GROUP	0 – WEEKS		12 – WEEKS		P – VALUE
	MEAN	SD	MEAN	SD	
GROUP A	14.40	5.94	11.79	3.64	0.001
GROUP B	15.90	6.03	12.05	4.71	0.001
GROUP C	17.16	6.52	10.07	2.90	< 0.0001
P - VALUE	0.372		0.007		

[Table 3] shows fasting serum insulin levels in all three groups at Baseline and at the end of 12 weeks.

Statistical analysis in between the groups showed a significant decrease in the fasting serum insulin levels at the end of 12 weeks ( $p < 0.05$ ).

**Table 4: body mass index (kg/m<sup>2</sup>)**

GROUP	0 – WEEKS		12 – WEEKS		P – VALUE
	MEAN	SD	MEAN	SD	
GROUP A	27.84	2.33	26.63	3.51	0.032
GROUP B	28.31	2.65	27.31	3.50	0.049
GROUP C	28.81	2.73	24.62	3.25	< 0.001
P – VALUE	0.499		0.042		

[Table 4] shows mean body mass index in all three groups.

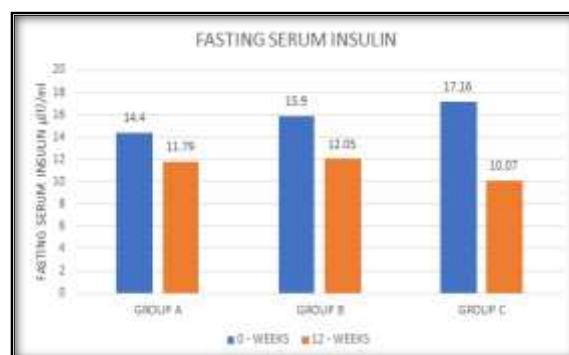
Statistical analysis in between the groups showed a significant reduction in BMI at the end of 12 weeks ( $p < 0.05$ ).



**Figure 1: Menstrual Cycle Regularity**



**Figure 2: Luteinizing Hormone Level**



**Figure 3: Fasting Serum Insulin Level**

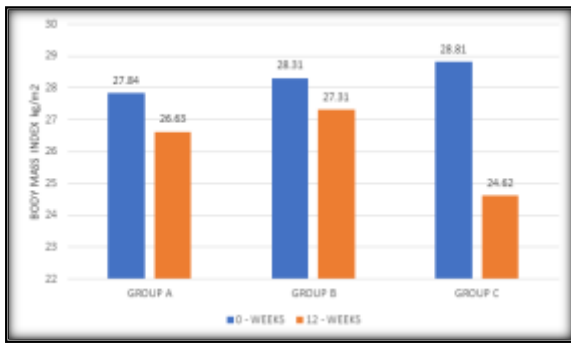


Figure 4: Body Mass Index

## DISCUSSION

The outcomes of this study highlight multifactorial nature of PCOS, especially emphasizing the role of insulin resistance due to impaired insulin receptor signalling. A deficiency in D-chiro-inositol-containing inositol phosphoglycan (DCI-IPG) was postulated as a contributor to the insulin resistance observed in PCOS.<sup>[13]</sup> In this context, DCI supplementation appears to enhance insulin sensitivity, thereby improving both metabolic and hormonal profiles.<sup>[14]</sup>

The data suggest that DCI is effective not only as a monotherapy but also as a complementary agent when combined with metformin, leading to improved outcomes such as reduction in BMI, LH, and fasting insulin levels, with normalization of menstrual cycles. Our study results are in concordance with previous studies.<sup>[15]</sup> The favourable tolerability profile of DCI, with fewer gastrointestinal side effects compared to metformin, further supports its potential utility in managing PCOS.

At baseline, all 60 patients had irregular cycles. By 12 weeks, regular cycles resumed in 40% (group A), 65% (group B), and 75% (group C), with significant intergroup differences. Metformin + DCI showed superior outcomes across all parameters.

Serum LH levels, initially similar in all groups ( $p=0.26$ ), decreased significantly in Group A (14.47 mIU/ml,  $p=0.02$ ), Group B (13.82 mIU/ml,  $p=0.001$ ), and Group C (11.88 mIU/ml,  $p<0.001$ ), with intergroup significance ( $p=0.02$ ).

Fasting insulin levels of three groups were comparable at baseline ( $p=0.37$ ) and later reduced significantly in Group A (11.79  $\mu$ IU/ml,  $p=0.001$ ), Group B (14.05  $\mu$ IU/ml,  $p=0.001$ ), and Group C (10.07  $\mu$ IU/ml,  $p<0.001$ ), with intergroup significance ( $p=0.007$ ).

At baseline, the mean BMI was comparable across groups ( $p=0.49$ ). After 12 weeks, BMI significantly reduced in Group A (26.63 kg/m<sup>2</sup>,  $p=0.03$ ), Group B (27.31 kg/m<sup>2</sup>,  $p=0.04$ ), and Group C (24.62 kg/m<sup>2</sup>,  $p<0.001$ ), with intergroup significance ( $p=0.04$ ), indicating greater weight reduction with metformin + DCI.

## CONCLUSION

This research concludes by supporting the use of D-chiroinositol as a promising therapeutic option for PCOS patients. When administered in combination with metformin, DCI effectively improves insulin sensitivity, hormonal balance, and reproductive outcomes, while also demonstrating a lower incidence of adverse effects. These encouraging results pave the way for additional investigations with bigger sample sizes as well as longer follow-up intervals to completely prove long-term advantages of DCI supplementation in PCOS treatment.

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