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RESEARCH

Comparative efficacy of combined myo-inositol and D-chiro inositol versus metformin across PCOS Phenotypes: enhancing ovarian function, ovulation, and stress response in a prospective clinical trial

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Abstract

This study aimed to evaluate the comparative efficacy of Myo-inositol (MI) and D-chiro-inositol (DCI) with metformin in enhancing ovarian function, promoting ovulation, and reducing perceived stress in patients with polycystic ovary syndrome (PCOS). Women with PCOS were identified using the Androgen Excess Society's criteria, and 60 participants were enrolled and divided equally into two groups. One group received a 40:1 ratio of MI plus DCI, while the other received metformin for a 12-week period. Endocrine and metabolic parameters, insulin-resistance, stress levels, and quality of life were assessed pre- and post-treatment. Both MI plus DCI and metformin significantly improved insulin sensitivity (HOMA-IR, $p < 0.001$), SHBG levels ($p = 0.021$), ovarian volume ($p < 0.001$), and menstrual regularity ($p = 0.002$), along with BMI, quality of life, and PSS scores ($p < 0.001$). Metformin showed slightly better outcomes in certain parameters, such as insulin sensitivity and endocrine markers, probably due to a higher representation of Phenotype A. In contrast, we hypothesize that MI plus DCI may be more effective for Phenotypes C and D. Our findings support both MI plus DCI and metformin as effective treatments for PCOS, with each treatment offering specific benefits. These results highlight the potential for a phenotype-specific tailored therapeutic approach to better manage the complex metabolic, endocrine, and stress-related challenges of PCOS.
Trial Registration: clinicalTrial.gov NCT05767515. Registered 3 February, 2023.

Keywords Myoinositol-D-chiro inositol · PCOS · Insulin-resistance · Hyperandrogenism · Perceived stress · Quality of life · Hormonal parameters · BMI

Introduction

Polycystic ovary syndrome (PCOS) is the most prevalent endocrine disorder among women of reproductive age, characterized by hyperandrogenism, chronic oligo- or anovulation, and polycystic ovaries The prevalence of PCOS varies significantly worldwide, affecting approximately 5% to 20% of women, highlighting the influence of genetic, environmental, and lifestyle factors on this variability (Polycystic and Syndrome 2018). This syndrome is, often described as a multifactorial disorder with unclear pathogenesis, involving abnormalities in the hypothalamic-pituitary axis, steroidogenesis, and insulin-resistance (Moura et al. 2011). It impacts multiple body systems which lead to health issues such as irregular menstruation, infertility, hirsutism, obesity, and metabolic syndrome. Additionally, women with PCOS are at a higher risk of developing type 2 diabetes and may have an increased risk of cardiovascular diseases

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(Norman et al. 2007). Beyond these physical health challenges, PCOS is also associated with significant mental health issues, underscoring the serious psychological risks that can worsen with age (Sadeeqa et al. 2018). Studies indicate that the geographical and population-based differences significantly contribute to the prevalence rates, necessitating tailored diagnostic and management approaches to address the diverse manifestations of PCOS across different regions (Deswal et al. 2020).

Myo-inositol (inositol) is a cyclic carbohydrate found in foods like beans and citrus fruits. It presents as phytic acid in plants and in phospholipids in mammals and reduces lipolysis, enhances glucose absorption, improves insulin sensitivity, and regulates hormone levels such as TSH (Monastra et al. 2023). Recent studies show that myo-inositol (MI) significantly improves menstrual regularity, insulin sensitivity, and ovarian function, along with enhancing metabolic indices (Monastra et al. 2023). MI is a component of phosphatidylinositols, which are lipid-anchored to the cell membrane. These molecules serve as precursors to the second messengers inositol trisphosphate (IP3) and diacylglycerol (DAG) (Dinicola et al. 2021). MI acts as a crucial second messenger in the signaling pathways that regulate the activity of several hormones, including follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), and insulin. D-chiro-inositol (DCI) is a stereoisomer of inositol that complements MI by increasing insulin receptor sensitivity and maintaining euglycemia (Dinicola et al. 2021). Several studies suggest that DCI positively affects insulin-resistance, hormonal parameters, and BMI. DCI has restored menstrual regularity in 62.5% of cases, with benefits appearing after four months of therapy (Kachhawa et al. 2022). In a study, patients receiving DCI for 6–8 weeks showed a higher ovulation rate and reduced testosterone and insulin levels compared to a placebo. Further research indicates that DCI's effectiveness is dose-dependent, higher dosage being more effective in inducing ovulation than lower doses (Nestler et al. 2001).

The role of DCI in PCOS management has been the subject of significant historical and clinical interest. In 1998, an international patent (US patent No. 5,906,979) was filed where the inventor claimed the use of DCI for the treatment of PCOS. This was based on pivotal clinical evidence, which demonstrated that treatment with 1200 mg of DCI for 8 weeks increased insulin sensitivity, improved ovarian function, and reduced serum androgen and triglyceride levels in obese women with PCOS. Remarkably, ovulation was recorded in 86% of these women within 45 days of treatment, compared to 27% in the placebo group (Nestler et al. 1999). Further studies with DCI were conducted, including one involving 600 mg doses in lean women with PCOS, confirming the initial positive results (Iuorno et al. 2002). Despite encouraging findings from early studies with lower doses of DCI, later research phases encountered challenges. A study by Cheang et al. in 2008 involving 2400 mg doses, was prematurely terminated due to the sudden unavailability of the study medication, leading to significant setbacks in the clinical investigation of DCI (Cheang et al. 2008). The scientific community has been engaged in discussions about the optimal dosing and therapeutic viability of DCI in treating PCOS. Further supporting the therapeutic potential of DCI, a 2014 study tested a lower dose of 500 mg daily over 12 weeks in obese PCOS patients (Genazzani et al. 2014). This regimen not only improved insulin sensitivity but also positively influenced hormonal levels including luteinizing hormone and insulin responses to glucose challenges. These findings collectively reinforce the therapeutic promise of DCI, emphasizing the need for optimal dosing strategies to maximize its benefits in PCOS management while minimizing risks associated with higher doses. Combined doses of myo-inositol (MI) and D-chiro-inositol (DCI) have shown superior efficacy in treating PCOS, reducing metabolic abnormalities, and enhancing ovarian function. The optimal clinical ratio of MI to DCI is 40:1 which reflects its physiological conditions with more beneficial outcomes (Kachhawa et al. 2022). MI and DCI also influence neurotransmitter levels and neuroendocrine function, potentially offering anxiolytic and antidepressant effects by modulating dopamine and serotonin levels, the key regulators of mood (Sarkisian et al. 2023). They can also affect the hypothalamic–pituitary–adrenal (HPA) axis, reducing cortisol levels and stress reactivity in PCOS patients (Awasthi and Qurish 2023).

Metformin is a biguanide class drug that has been widely acknowledged for its role in managing type 2 diabetes, and it has also become a cornerstone in the treatment of PCOS (Abdalla et al. 2020). It mainly reduces hepatic glucose production and increases insulin sensitivity, thereby improving glycemic control. On top of that, metformin has been shown to have beneficial effects on various aspects of PCOS, including aiding in weight loss, improving menstrual regularity, and reducing insulin levels, which may help with the hyperandrogenism often observed in PCOS patients (Herman et al. 2022). Its utility in PCOS treatment is further reinforced by its role in reducing the risk of diabetes and potentially mitigating cardiovascular risks associated with the syndrome.

However, metformin has limitations in its use for PCOS. Not all women with PCOS respond positively to metformin, as it is most effective in patients with documented insulin resistance and less useful in cases without significant metabolic alterations (e.g., in multifollicular ovarian disorder) (Herman et al. 2022). In cases of PCOS not associated with obesity or insulin resistance, metformin may not provide significant benefits (Melin et al. 2023). Furthermore, common side effects, such as gastrointestinal disturbances (nausea,

diarrhea, and abdominal cramps), can compromise treatment adherence (Juhász et al. 2024). Additionally, while metformin may promote mild weight loss, it is not primarily a weight-loss drug, and its effects are often modest compared to other strategies such as lifestyle modifications or targeted pharmacological interventions (Juhász et al. 2024). These limitations highlight the importance of patient-specific treatment approaches, considering individual metabolic and hormonal profiles to optimize therapeutic outcomes in PCOS management.

The treatment of PCOS is thus quite complex, due to its multifactorial nature and varying phenotypes. PCOS affects women across various metabolic, reproductive, and psychological domains, making it challenging to address with a single therapeutic approach. Metformin is another well-established treatment for PCOS. It's particularly effective in improving insulin sensitivity and managing hyperandrogenism in insulin-resistant phenotypes (Phenotype A) (Zhao et al. 2023). However, earlier studies suggests that MI combined with DCI in a 40:1 ratio may offer unique benefits in regulating insulin and androgen levels, enhancing ovulation, and improving mental health outcomes.

In this study, we evaluated the impact of MI plus DCI in women with PCOS and compared it with metformin on clinical, metabolic, and endocrine parameters. Additionally, we evaluated changes in quality of life (QOL) and perceived stress levels before and after 12 weeks of treatment, providing critical insights into the comparative benefits of these treatment modalities. These findings may support a phenotype-specific approach, optimizing PCOS treatment strategies to address individual patient profiles more effectively.

Subjects and methods

Study population

In this study a total of 60 infertile, married women aged 18 to 35, meeting the Androgen Excess Society's 2006 criteria, were recruited from a gynecology clinic at Peshawar Health Center (Azziz et al. 2009). Participants were equally divided into two groups: one group of 30 received metformin, and the other group received a combination of Myo-inositol (MI) and D-chiro-inositol (DCI) (will be referred to as MI + DCI hereafter). The sample size for the study was determined using G*power software, referencing previous luteinizing hormone values in PCOS women (Pustotina et al. 2024), with an alpha of 0.05 and a power of 0.95, resulting in a required sample size of 30 in each group.

Inclusion and exclusion criteria

Participants were included if they met at least two of the 2012 NIH revision of the ESHRE/ASRM 2003 Rotterdam criteria for PCOS: hyperandrogenism, chronic anovulation, or polycystic ovarian morphology. Exclusion criteria included current medication affecting metabolic or endocrine profiles, recent hormone therapy, conditions like congenital adrenal hyperplasia, diabetes, thyroid disease, Cushing syndrome, ovarian tumors, pregnancy, androgen-producing tumors, and a history of certain cancers or undiagnosed vaginal bleeding. Women with an infertile male partner were also excluded.

Phenotype identification

Our study uses the phenotypic classification of PCOS into A, B, C, and D, consistent with the 2012 NIH revision of the ESHRE/ASRM 2003 Rotterdam criteria. Phenotype A includes hyperandrogenism (HA), ovulatory dysfunction (OD), and polycystic ovarian morphology (PCOM). Phenotype B is characterized by HA and OD without PCOM. Phenotype C involves HA and PCOM without OD. Phenotype D is defined by the presence of OD and PCOM without HA. This classification addresses the diverse presentations of PCOS and enables a comprehensive evaluation of treatment responses across different phenotypes.

Study approval and setting

The research proposal received approval from the Advanced Study and Research Board (ASRB) after review by the Graduate Study Committee (GSC) (study approval No: DIR/KMU-AS&RB/EO/EM/001934). Additionally, ethical approval was granted by Khyber Medical University's ethical board (study approval No: KMU/IBMS/IRBE/8th/685–2). The study was conducted in the gynecology and obstetrics department of Peshawar Health Center and the physiology laboratory of the Institute of Basic Medical Sciences, Khyber Medical University. The trial was registered at clinicalTrial.gov on 3 February, 2023 with the trial registration No. NCT05767515. Here, data from only two arms of the registered trial is presented.

Study design

The trial protocol was designed according to the recommendations in the CONSORT statement. It was a two-arm (1:1) trial, which was randomized and double-blinded. Both participants and the outcome assessor were blinded to the treatment intervention to minimize bias. Randomization of women with PCOS into two arms was performed by an independent researcher using a secure, online computer-generated randomization system to ensure allocation concealment. Block randomization with variable block sizes was employed to maintain balanced allocation across the two treatment groups. Allocation codes were concealed

in sequentially numbered, opaque, sealed envelopes. Participants provided written informed consent and were interviewed to collect demographic data, medical history, and menstrual irregularities. Each participant also underwent a pelvic ultrasound to assess ovarian morphology. This dual-arm approach was designed from the start to enable a direct comparison of therapeutic outcomes between the standard pharmacological treatment and the nutritional supplement regimen, thereby strengthening the validity of the trial and supporting comparative effectiveness analysis.

Patients' allocation and treatments

Before the trial commenced, all participants provided written informed consent. The 60 women with PCOS who met the eligibility criteria were randomly assigned into two pre-planned treatment arms. One group of 30 participants received a daily oral dose of 2,000 mg of Myo-inositol and D-chiro-inositol (BD, comprising 1,951 mg Myo-inositol and 49 mg D-chiro-inositol) in a 40:1 ratio for 12 weeks. The second group, consisting of 30 participants, was administered a daily oral dose of 2,000 mg metformin (BD), the standard treatment for PCOS, to serve as a comparative arm for evaluating the effectiveness of the nutritional supplements against conventional pharmacological therapy. Participants were reminded about their clinic visits and were instructed to avoid any medications that could affect their metabolic or endocrine systems. All evaluations were conducted by the same investigator at baseline and after the 3-month treatment period, with no restrictions placed on diet or routine activities throughout the study.

Treatment discontinuation

Participants were directed to stop the treatment if they became pregnant, experienced serious side effects, or developed conditions listed in the exclusion criteria. No adverse effects were reported during the study. Married participants were instructed to use a home pregnancy test after the first missed period and to inform investigators and stop the medication if pregnant. Two patients in the MI + DCI group discontinued treatment due to pregnancy, and no participants discontinued treatment due to reported side effects or lack of efficacy. However, resistance to inositol therapy was not explicitly analyzed in this study.

Clinical measures

Participants' demographic and anthropometric data were recorded using standard techniques. Their BMI was calculated as weight in kilograms divided by height in meters squared, and blood pressure was measured using an Omron Gold monitor. Hirsutism was graded with the Ferriman-Gallwey scale (Aswini and Jayapalan 2017), which scores hair growth in nine body areas from 0 to 4. Scores ≤ 8 were normal, 8–15 indicated mild hirsutism, and > 15 indicated severe hirsutism. Ovarian morphology was evaluated via transabdominal ultrasound, with participants' drinking water beforehand to aid in assessing ovarian volume and cyst number.

Venous blood sample collection

Five milliliters of blood were drawn from the antecubital vein using a disposable syringe and aseptic technique. The blood was transferred to gel tubes, which were then centrifuged at 3000 revolutions per minute for ten minutes. The resulting serum was shifted to Eppendorf tubes and stored at −80 °C until analysis. Serum levels of insulin, LH, FSH, testosterone, AMH, DHEA, SHBG, and progesterone were measured using the ELISA method.

Hormone assays

Commercially available immunosorbent assay kits were utilized for the analysis of the following biomarkers: LH ELISA Kits Germany (Cat No: H326) and FSH ELISA Kits (Cat No: H327) were purchased from Bio Active Diagnostic System, Germany. AMH ELISA Kits (Cat No: 10020), testosterone ELISA Kits (Catalog Number: 10007) and insulin ELISA Kits (Cat No: 10801) were purchased from PerkinElmer. SHBG ELISA Kits (Cat No: PRS-01391hu) from Nanjing Pars. DHEA ELISA Kits from Cal Biotech (Cat No: DH291S). Progesterone ELISA Kits from Dia Metra (Cat No: DKO004). The inter-and-intra coefficient of variance were within the range. All assays were performed according to the manufacturers' instructions.

Assessment of perceived stress

Stress response was assessed using the Sheldon Cohen Perceived Stress Scale (PSS-14) questionnaire (Cohen et al. 1983), which scores stress from 0 to 56 based on responses to 14 items about the frequency of stressors in the past month. Responses range from 0 (never) to 4 (very often). For positive items, scores were reversed. The total PSS score was calculated by summing all responses, with higher scores indicating greater stress. Participants were categorized as low (0–13), moderate (14–26), or high stress (27–56) based on their total scores.

Statistical analysis

Analysis was done using SPSS-22 statistical software. Demographic data of the study was analyzed as descriptive statistics which was presented as mean ± standard deviation.

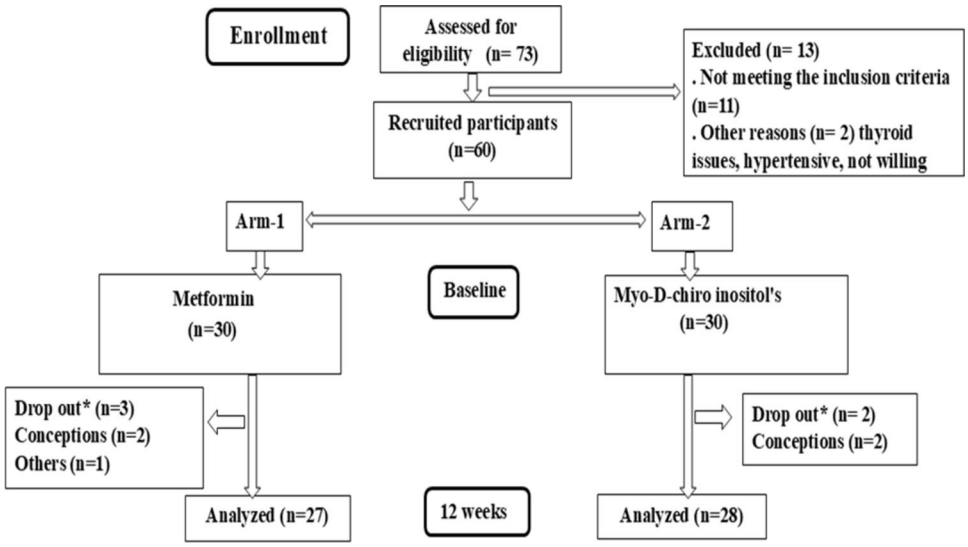

Fig. 1 Shows the participants recruitment and three months intervention till analysis

While the normally distributed variables were compared between the two treatment arms by using independent-sample t-test. Paired t-test was applied to evaluate the changes between the measurements at baseline and after 12 weeks of intervention. Categorical data was presented as percentages between the groups. $P < 0.05$ was considered significant.

Results

A total of 73 women with PCOS were initially assessed for eligibility. Of these, 13 were excluded; 11 for not meeting the inclusion criteria and 2 due to other reasons, including thyroid issues, hypertension, or unwillingness to participate. The remaining 60 eligible participants were equally divided into two pre-planned treatment arms. In the MI + DCI group, 30 women began the 12-week treatment, receiving a daily dose of 2000 mg (BD) in a 40:1 ratio. During the treatment period, two participants discontinued due to pregnancy, resulting in a final analysis of 28 participants in this group. In the metformin group, also comprising 30 women, three participants dropped out during the study phase; two due to conception and one for other reasons. This left 27 participants in the final analysis for the metformin arm. The participant flow throughout recruitment, allocation, follow-up, and analysis stages for both treatment groups is summarized in Fig. 1, which details the recruitment process flowchart.

Anthropometric and demographic measures of the participants

The anthropometric and demographic of the participants are summarized in Table 1. All participating women were married and aged between 18 and 35 years. At baseline, participants in the MI + DCI group had a mean weight of 71.19 ± 12.72 kg and a BMI of 27.40 ± 4.39 kg/m^2, while those in the metformin group had a similar initial weight of 70.78 ± 9.49 kg and a BMI of 25.73 ± 2.67 kg/m^2. After the 12-week intervention, participants in the MI + DCI group experienced a significant reduction in weight to 68.98 ± 11.55 kg ($p = 0.001$) and a decrease in BMI to 26.49 ± 3.91 kg/m^2 ($p < 0.001$). In the metformin group, participants showed a more pronounced weight reduction to 67.07 ± 9.23 kg ($p < 0.001$) and a BMI decrease to 24.33 ± 2.65 kg/m^2 ($p < 0.001$). Systolic blood pressure in the MI + DCI group decreased slightly ($p = 0.300$), while diastolic blood pressure showed marginal increase ($p = 0.096$). In the metformin group, both systolic and diastolic blood pressure showed slight changes, with systolic pressure moving from 119.8 ± 5.96 mm Hg to 120.4 ± 4.98 mm Hg ($p = 0.582$) and diastolic pressure from 88.70 ± 11.73 mm Hg to 89.81 ± 10.14 mm Hg ($p = 0.386$).

Ferriman-gallwey score of the participants

Women with PCOS treated with MI + DCI showed a significant reduction in the Ferriman-Gallwey (FG) score decreasing from 13.39 ± 1.47 to 11.11 ± 1.10 ($p < 0.001$). Similarly, metformin treatment resulted in a decrease in FG scores from 13.33 ± 3.13 to 11.70 ± 2.58 ($p < 0.0001$). Both treatments effectively reduced hirsutism symptoms, offering comparable dermatological improvements (Table 1).

Metabolic parameters of the participants

The metabolic parameters of the participants are depicted in Table 1. PCOS-affected women treated with MI + DCI showed significant metabolic improvements over a three-month period. Insulin sensitivity increased, with fasting insulin levels decreasing from 13.18 ± 11.46 µU/mL to

Table 1 Comparison of anthropometric, dermatological and metabolic parameters in patients with PCOS before and after three months of treatment with MI + DCI

Parameters	Baseline Met (n = 30) M ± SD	After 3 months Met (n = 27) M ± SD	P-value	Baseline MI + DCI (n = 30) M ± SD	After 3 months MI + DCI (n = 28) M ± SD	P-value
Age (yrs)	27.82 ± 3.36	–		23.32 ± 3.31	–	**= 0.001**
Weight (kgs)	70.78 ± 9.49	67.07 ± 9.23	**< 0.001**	71.19 ± 12.72	68.98 ± 11.55	**0.001**
BMI (kg/m^2)	25.73 ± 2.67	24.33 ± 2.65	**< 0.001**	27.40 ± 4.39	26.49 ± 3.91	**< 0.001**
SBP (mm Hg)	119.8 ± 5.96	120.4 ± 4.98	0.582	119.64 ± 6.66	121.61 ± 7.82	0.300
DBP (mm Hg)	88.70 ± 11.73	89.81 ± 10.14	0.386	94.64 ± 9.12	90.89 ± 9.23	0.096
FG score	13.33 ± 3.13	11.70 ± 2.58	**< 0.0001**	13.39 ± 1.47	11.11 ± 1.10	**< 0.001**
Glucose (mg/dL)	89.26 ± 10.42	84.19 ± 7.49	**< 0.001**	94.07 ± 12.74	84.07 ± 12.41	**< 0.001**
Insulin (µU/mL)	20.95 ± 6.18	14.12 ± 5.44	**< 0.001**	13.18 ± 11.46	5.60 ± 4.98	**0.001**
HOMA-IR	4.80 ± 1.71	3.252 ± 1.70	**< 0.001**	3.02 ± 2.40	1.26 ± 1.12	**0.001**
LH (mIU/mL)	20.06 ± 11.85	10.29 ± 4.696	**= 0.0001**	39.52 ± 21.98	37.39 ± 21.59	0.650
FSH (mIU/mL)	11.43 ± 4.324	9.55 ± 2.405	**= 0.026**	16.62 ± 5.084	17.20 ± 5.36	0.608
Testosterone (ng/mL)	0.96 ± 0.25	0.57 ± 0.20	**< 0.0001**	1.05 ± 0.56	1.23 ± 0.81	0.168
SHBG (ng/mL)	3.01 ± 3.72	13.44 ± 3.41	**< 0.0001**	8.78 ± 2.67	11.26 ± 5.20	**0.021**
DHEA (ug/mL)	3.07 ± 2.804	1.69 ± 0.73	**< 0.0001**	1.60 ± 0.79	1.41 ± 0.72	0.320
AMH (ng/mL)	10.58 ± 2.91	8.34 ± 3.38	**= 0.0034**	9.49 ± 3.84	10.18 ± 3.52	0.395

5.60 ± 4.98 µU/mL (p = 0.001) and the HOMA-IR index dropping from 3.02 ± 2.40 to 1.26 ± 1.12 (p = 0.001). Additionally, glucose levels improved, decreasing from 94.07 ± 12.74 mg/dL to 84.07 ± 12.41 mg/dL (p < 0.001). In comparison, metformin-treated PCOS women demonstrated even greater metabolic improvements. Glucose levels reduced from 89.26 ± 10.42 mg/dL to 84.19 ± 7.49 mg/dL (p < 0.001), while fasting insulin levels dropped from 20.95 ± 6.18 µU/mL to 14.12 ± 5.44 µU/mL (p < 0.001). The HOMA-IR index, a measure of insulin-resistance, also showed a more substantial improvement, decreasing from 4.80 ± 1.71 to 3.252 ± 1.70 (p < 0.001).

Hormonal parameters of the participants

PCOS-affected women treated with MI + DCI demonstrated variable trends in endocrine parameters over the treatment period, as shown in Table 1. Luteinizing Hormone (LH) levels showed a slight, non-significant decrease from 39.52 ± 21.98 mIU/mL to 37.38 ± 21.59 mIU/mL (p = 0.650), and no significant differences were observed in Follicle Stimulating Hormone (FSH) (p = 0.608), Testosterone, Anti-Müllerian Hormone (AMH), and Dehydroepiandrosterone (DHEA) levels. However, Progesterone levels decreased significantly from 1.94 ± 0.87 ng/mL to 1.30 ± 0.63 ng/mL (p = 0.008), and Sex Hormone Binding Globulin (SHBG) increased significantly from 8.78 ± 2.67 ng/mL to 11.26 ± 5.20 ng/mL (p = 0.021).

In contrast, metformin-treated PCOS women showed notable improvements across several endocrine parameters, summarized in Table 1. LH levels significantly decreased from 20.06 ± 11.85 mIU/mL to 10.29 ± 4.696 mIU/mL (p = 0.0001), while FSH levels also dropped from 11.43 ± 4.324 mIU/mL to 9.55 ± 2.405 mIU/mL (p = 0.026). Significant reductions were observed in Testosterone (0.96 ± 0.25 ng/mL to 0.57 ± 0.20 ng/mL, p < 0.0001), DHEA (3.07 ± 2.804 ug/mL to 1.69 ± 0.73 ug/mL, p < 0.0001), and AMH (10.58 ± 2.91 ng/mL to 8.34 ± 3.38 ng/mL, p = 0.0034). Additionally, SHBG levels significantly increased from 3.01 ± 3.72 ng/mL to 13.44 ± 3.41 ng/mL (p < 0.0001).

Ovarian morphology of the participants

Before treatment, the mean ovarian volume for both ovaries was elevated in the study population. After 12 weeks of therapy, both the MI + DCI and metformin groups showed a significant reduction in ovarian volume. Figure 2A presents a side-by-side comparison of the right ovarian volume (ROV) between the MI + DCI and metformin groups, and Fig. 2B compares the left ovarian volume (LOV) for both groups. All reductions were statistically significant, with p < 0.0001 for both ROV and LOV in the MI + DCI group and for the ROV in the metformin group. The LOV reduction in the metformin group was also significant, with p = 0.0107.

Stress and quality of life of the participants

The perceived stress scores (PSS) at baseline and after 3 months are illustrated in Fig. 3A. At baseline, the mean PSS was 28.50 ± 3.48, indicating high levels of perceived stress among women with PCOS. After 12 weeks

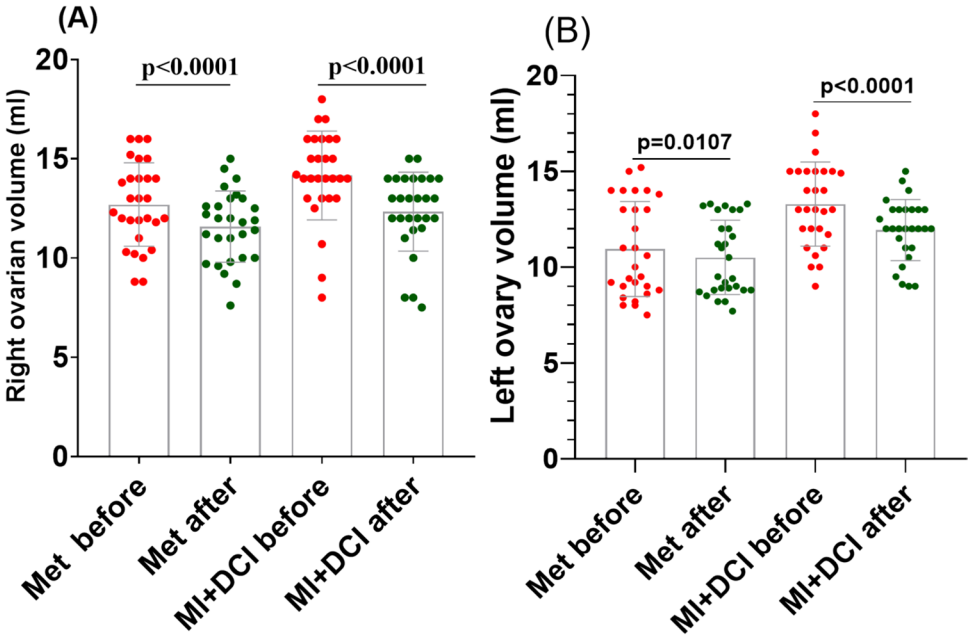

Fig. 2 Comparison of Ovarian Morphology in PCOS with Metformin and MI + DCI. Treatments — **A**: Side-by-side comparison of the right ovarian volume (ROV) for both the MI + DCI and metformin groups before and after treatment; **B**: Side-by-side comparison of the left ovarian volume (LOV) for both treatment groups before and after treatment. Values are represented as mean ± SD

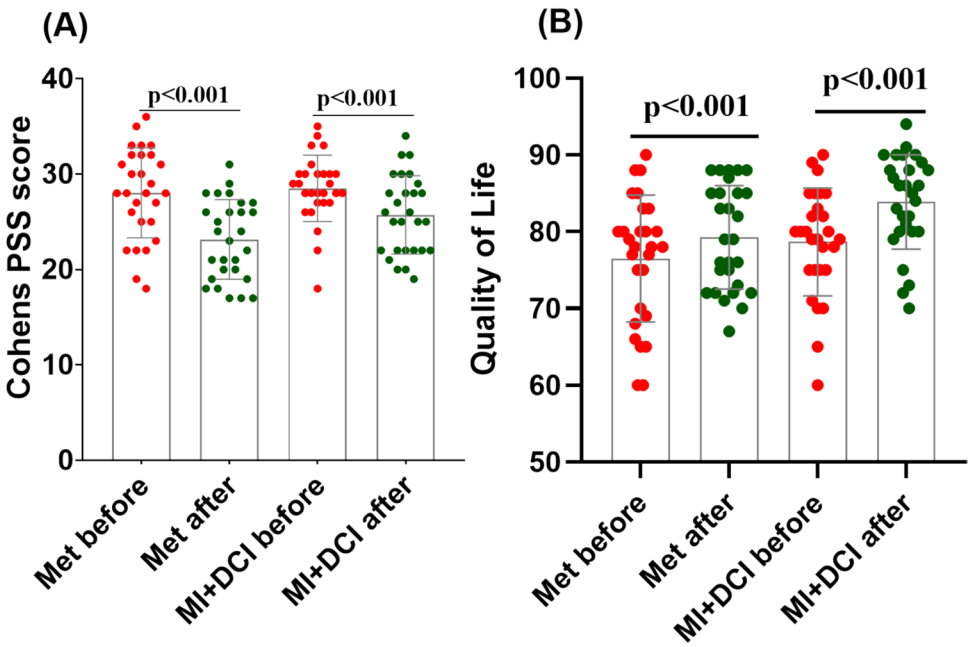

Fig. 3 Comparison of stress and Quality of Life (QOL) outcomes for metformin and MI + DCI Treatments — **A**: Side-by-side comparison of perceived stress scores (PSS) for both treatment groups at baseline and after 3 months of intervention; **B**: Side-by-side comparison of quality of life (QOL) scores for both treatment groups at baseline and after 3 months of intervention. All values are represented as mean ± SD

of treatment, both the MI + DCI and metformin groups showed a significant reduction in perceived stress. In the MI + DCI group, scores decreased to 25.71 ± 4.10, while in the metformin group, similar improvements were observed, with both groups showing $p < 0.001$ for perceived stress reductions.

Before treatment, the quality of life (QOL) for women with PCOS was significantly impaired, with a mean score of 78.68 ± 7.02 as shown in Fig. 3B. After 3 months of intervention, both groups demonstrated statistically significant improvements in QOL. The mean QOL score rose to 83.89 ± 6.15 in the MI + DCI group and showed similar improvement in the metformin group, with $p < 0.001$ for both treatments.

Menstrual cycles of the participants

PCOS-affected women treated with MI + DCI showed significant improvements in menstrual regularity over a three-month period. At baseline, 17 out of 30 women (56.6%) had irregular menstrual cycles, while 13 (43.3%) had regular cycles. By the end of the treatment, all 13 women with

Table 2 Comparison of menstrual cyclicity at baseline and 3 months after intervention in both groups. Values are n (% of total). P for chi-square comparison between menstrual cyclicity at baseline and after 3 months

Menstrual cyclicity before (Met)	N	% within group	Chi-Sq p-value	Menstrual cyclicity before (Comb)	N	% within group	Chi-Sq p-value
Irregular	24	80%		Irregular	17	56.6%	
Regular	6	20%		Regular	13	43.3%	
Menstrual cyclicity after			**< 0.0001**	Menstrual cyclicity after			**0.037**
Irregular	9	33.33%		Irregular	8	28.6%	
Regular	18	66.67%		Regular	20	71.4%	

Table 3 Comparative study count of PCOs phenotypes between treatment groups

Phenotype	Metformin Group (Number of participants)	Metformin Group (%)	MI plus DCI Group (Number of participants)	MI plus DCI Group (%)
A	16	59.26	13	46.43
B	2	7.41	1	3.57
C	5	18.52	8	28.57
D	4	14.81	6	21.43

initially regular cycles-maintained regularity, and 8 of the 17 women with irregular cycles transitioned to regular cycles, reducing the percentage of irregular cycles to 26.6% ($p = 0.002$, chi-square test) as shown in Table 2.

Metformin treatment demonstrated even greater improvements in menstrual regularity. Initially, 24 of the 30 women (80%) had irregular cycles, while only 6 (20%) had regular cycles. After three months of treatment with metformin, the number of women with irregular cycles decreased to 9 (33.33%), while those with regular cycles increased to 18 (66.67%) ($p < 0.0001$, chi-square test) (Table 2). This outcome indicates that metformin was more effective than MI + DCI in normalizing menstrual cycles, resulting in a higher proportion of women achieving regular cycles by the end of the study.

Comparative analysis of PCOS phenotypes across treatment groups

Table 3 shows the distribution of different PCOS phenotypes for each treatment group. In the metformin group, 59.26% of participants were phenotype A, followed by 18.52% on phenotype C, 14.81% on phenotype D, and 7.41% on phenotype B. The MI plus DCI group had 46.43% of participants with phenotype A, 28.57% with phenotype C, 21.43% with phenotype D, and 3.57% with phenotype B.

Discussion

The study evaluated the comparative effectiveness of MI + DCI versus metformin in treating PCOS for a 12-week period. Both treatment groups (MI + DCI and metformin) demonstrated significant improvements in stress levels, metabolic and hormonal parameters, weight, BMI, and Ferriman-Gallwey scores, indicating reduced hyperandrogenism. The combination therapy was well-tolerated, with no adverse effects reported, suggesting MI and DCI as a viable comprehensive treatment option alongside metformin for managing PCOS symptoms, including metabolic, hormonal, and ovulatory dysfunctions (Table 1).

Nordio et al. demonstrated that the MI/DCI combination is an effective treatment for PCOS, restoring ovulation and normalizing key parameters (Nordio et al. 2019). Elevated androgen levels in PCOS disrupt hormone balance, increasing GnRH pulse frequency and altering the LH to FSH ratio. This imbalance leads to follicular arrest, dysplasia, hyperinsulinemia, hyperandrogenism, oxidative stress, and irregular menstrual periods, contributing to metabolic syndrome (Bulsara et al. 2021). Similarly, Pizzo et al. reported reductions in serum testosterone and LH levels with myoinositol treatment (Pizzo et al. 2014). Januszweski et al. demonstrated that MI + DCI decreased LH, FSH, and testosterone, while increasing SHBG over six months (Januszewski et al. 2019). In our study, both MI + DCI and metformin treatments showed similar effects with a slight decline in LH and stable FSH levels after three months, which could be attributed to the shorter duration of the trial. Additionally, Kutenaei et al. found MI more effective than metformin in reducing testosterone and DHEA levels in PCOS patients (Azizi Kutenaei et al. 2021); however, in our study, neither group showed a significant change in AMH levels.

Insulin affects SHBG, which regulates testosterone levels in the bloodstream. Lower SHBG levels result in higher free androgen levels, contributing to symptoms such as hirsutism, acne, and alopecia. In our study, both the MI + DCI and metformin groups demonstrated a significant increase in SHBG

levels ($p = 0.021$ for MI + DCI, $p < 0.0001$ for metformin), along with significant reductions in Ferriman-Gallwey (FG) scores ($p < 0.001$ in both groups), indicating improvements in clinical signs of hyperandrogenism (Table 1). These findings are consistent with previous study that links increased SHBG levels with reduced androgenic symptoms in PCOS (Qu and Donnelly 2020).

In terms of ovarian morphology, our study showed that both MI + DCI and metformin treatments resulted in a significant reduction in ovarian volume in women with PCOS. This reduction is illustrated in Fig. 2A and B for the right and left ovarian volumes in both treatment groups, respectively. It indicates that both therapies effectively reduced ovarian size with statistically significant improvements ($p < 0.0001$). These findings are consistent with earlier research, such as Kachhawa et al., reporting a 3.6:1 ratio of MI and DCI significantly reduced ovarian volume and improved menstrual regularity over six months (Kachhawa et al. 2022). Similar results were reported by Papaleo et al. (2007) and Formuso et al., where they demonstrated the normalization of menstrual cycles and hormonal markers with MI + DCI treatment (Formuso et al. 2015; Unfer et al. 2023).

Recent studies indicate that patients with PCOS are at a higher risk for neurodegenerative conditions, e.g., anxiety, depression, and stress (Sadeeqa et al. 2018). Cutler (2019) revealed that supplementation with MI and DCI significantly reduced perceived stress and improved mood in PCOS patients (Cutler, 2019). In our study, both MI + DCI and metformin groups significantly reduced perceived stress scores, as illustrated in Fig. 3A, ($p < 0.001$ for both treatments). This indicates that both treatment options can help alleviate stress in women with PCOS, leading to improved mental health. Concerning quality of life, which is often severely impacted in women with PCOS, both treatment groups in our study demonstrated significant improvements. Initially, the mean QOL score was low, reflecting the substantial burden of PCOS on daily living and well-being. Following 3 months of treatment, the QOL scores in the MI + DCI group improved, and similar improvements were observed in the metformin group, with both showing statistically significant improvements ($p < 0.001$). In a previous study, there is link of MI and DCI supplementation in improvements of mental health in women with PCOS, specifically reducing anxiety and depression and enhancing social functioning (Nestler et al. 2001). Our study's significant improvement in QOL scores in both treatment groups ($p < 0.001$) further supports these findings (Fig. 3B).

The findings in Table 3 suggest that metformin was more effective in various parameters as compared to MI + DCI and thus could be effectively used for managing PCOS especially for patients with Phenotype A. Phenotype A is often associated with insulin resistance which may respond well to metformin due to its established role in improving insulin sensitivity. The higher prevalence of Phenotype A within the metformin group attributes to the potential effectiveness of metformin for this specific phenotype. On the other hand, if Phenotypes C or D had been more predominant, it is possible that the MI + DCI treatment would have demonstrated greater effectiveness, as these phenotypes were more prevalent in the MI + DCI group. This distribution suggests that the choice of treatment could be optimized based on individual PCOS phenotypes, emphasizing the need for a tailored approach in clinical practice. Supporting our findings, Pustotina et al. evaluated the effects of a 40:1 ratio of MI + DCI in women with PCOS Phenotype A, characterized as an endocrine-metabolic syndrome (EMS-type 1) under the EGOI criteria (Pustotina et al. 2024). This study included 34 women aged 20–40, with 55.9% of participants classified as overweight or obese and 50% exhibiting insulin resistance. Participants received a daily dose of 2,255 mg of MI + DCI over three months, during which various hormonal and metabolic parameters were measured. Significant improvements were noted, including reductions in BMI, HOMA-IR, fasting insulin, total testosterone, free testosterone, LH, and the free androgen index (FAI). Furthermore, SHBG and estradiol levels increased substantially. These results align closely with the observed improvements in metabolic and hormonal profiles in our study. However, Pustotina et al. highlighted the need for longer treatment durations to assess outcomes such as menstrual cycle restoration and sustained relief in hyperandrogenic symptoms.. Importantly, this study underscores the role of MI + DCI as a targeted therapy for Phenotype A, which is characterized by insulin resistance and hyperandrogenism, further reinforcing the need for phenotype-specific treatment approaches in PCOS management.

A retrospective analysis examined the phenotype specific therapeutic approach to myo-inositol across various PCOS phenotypes (Unfer et al. 2023). This study categorized women with PCOS into two groups: hyperandrogenic phenotypes (A, B, and C, or H-PCOS) and non-hyperandrogenic phenotype D (NH-PCOS). Over a six-month period, participants received myo-inositol therapy, and the results revealed significant improvements in metabolic and endocrine parameters in women with H-PCOS. Specifically, there was an observed increase in endometrial thickness, alongside improvements in hormonal markers. However, women with NH-PCOS (Phenotype D) exhibited minimal therapeutic response, underscoring the limited efficacy of myo-inositol in phenotypes lacking metabolic dysfunctions. This finding aligns with our observation that Phenotype D participants in the MI + DCI group showed suboptimal improvement, potentially diluting the overall treatment effects. Moreover, the study reinforces the importance of classifying PCOS phenotypes accurately when designing treatment regimens, as insulin-sensitizing agents like MI + DCI are most effective

for phenotypes characterized by metabolic and endocrine imbalances.

Our study acknowledges the 2012 NIH revision of the ESHRE/ASRM criteria, which classifies PCOS into four main types. Following this classification has been critical for our treatment strategies. However, recent advances like the EGOI-PCOS classification have introduced new distinctions between hyperandrogenic (A, B, C) and normoandrogenic (D) PCOS types. These distinctions are based on metabolic factors and their impact on the syndrome. We recognize the importance of these differences, as they help tailor treatments more effectively based on individual metabolic profiles. Our findings support the need for updated classification systems that reflect these nuances, which can optimize treatment outcomes for different PCOS types. In future updates of our work, we aim to integrate these insights to better address the distinct etiopathogenesis of each PCOS phenotype. Incorporating phenotype-specific analyses into future trials could enable personalized treatment strategies. This will optimize outcomes for the diverse manifestations of PCOS. Additionally, using biomarkers to assess inositol resistance and designing longer-duration trials will help capture sustained therapeutic outcomes and improve treatment strategies. Despite the promising results, resistance to inositol therapy has emerged as a significant consideration in PCOS management. Approximately 30% of women with PCOS may exhibit resistance to inositol therapy, which can limit its effectiveness in improving metabolic and endocrine parameters (Fitz et al. 2024). However, our study did not explicitly assess resistance to inositol, representing a limitation in addressing individual variability in treatment response. Future studies should incorporate specific diagnostic criteria and biomarkers to evaluate inositol resistance systematically, particularly in patients who show suboptimal response to MI + DCI treatment. Another limitation of the study is related to the inclusion of Phenotype D participants in the MI + DCI treatment group along with the absence of clustering by phenotypes in the analysis. Phenotype D participants are non-hyperandrogenic and lack significant metabolic alterations. It may not benefit significantly from MI + DCI therapy, which primarily targets metabolic and androgenic dysregulation. This may partially explain the lack of statistically significant results in some parameters within the MI + DCI group. Previously, research has demonstrated that hyperandrogenic PCOS phenotypes (A, B, and C) respond significantly better to MI + DCI therapy due to the presence of metabolic abnormalities (Pustotina et al. 2024; Unfer et al. 2023). However, Phenotype D, which is characterized by the absence of hyperandrogenism, shows limited therapeutic response. It suggests that MI + DCI may not be effective for all phenotypes. Moreover, the inclusion of diverse PCOS phenotypes without clustering for analysis could have influenced the differential efficacy of treatments for specific phenotypes. Despite these limitations, the study's clinical trial registration adds credibility, and its comprehensive analysis of clinical, metabolic, and stress-related parameters provides a holistic view of the effects of MI + DCI supplementation on PCOS. As we move forward, addressing these limitations will be crucial in refining treatment strategies and enhancing our understanding of how different phenotypes respond to specific therapeutic approaches.

Conclusions

This study demonstrates that both metformin and the combination of Myo-inositol (MI) and D-chiro-inositol (DCI) are effective treatments for managing the symptoms of PCOS. Each treatment offers significant improvements in various clinical, metabolic, and endocrine parameters. Metformin showed a more pronounced effect in reducing insulin levels, HOMA-IR, and specific endocrine markers, such as LH, FSH, and testosterone, along with significant increases in SHBG. These results suggest that metformin may provide superior outcomes in areas related to insulin sensitivity and hyperandrogenism.

Given that metformin is commonly administered to patients with Phenotype A, which is characterized by higher levels of insulin-resistance and hyperandrogenism, we hypothesize that MI + DCI could be more effective in managing other PCOS phenotypes, such as C and D, which present different metabolic and endocrine profiles. The distribution of phenotypes in the study (Table 3) shows a higher representation of Phenotype A in the metformin group, possibly contributing to its observed effectiveness. Future studies focusing on phenotypes C and D could provide further insight into the advantages of MI + DCI for these specific subtypes. These findings underscore the value of a phenotype-specific approach to treatment, enabling more personalized and potentially more effective management of PCOS symptoms for diverse patient profiles.

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Author contributions M.G. and H.K. were involved in the execution of the project. B.R. Co-supervised the study and provided clinical expertise. S.M.S.B. helped in the execution of the project and writing of the manuscript. M.S. supervised, designed, executed the study and wrote the manuscript. F.A.S., F.E.A., and E.E. helped in the revision and editing. M.O.M. helped in organization of data and did the statistical analysis and helped in writing the manuscript. All named authors have read and approved the final version of the manuscript. The authors declare that all data were generated in-house and that no paper mill was used.

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Data availability All source data for this work (or generated in this study) are available upon reasonable request.

Declarations All procedures involving human participants in this study were in accordance with the ethical standards of Khyber Medical University's ethical committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (2013). The study was approved by the institutional board of studies and informed consent was obtained from each participant included in the study.

Competing interests The authors declare no competing interests.

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