ORIGINAL ARTICLE OPEN ACCESS

Comparing Myo-Inositol and Folic Acid with and without D-Chiro-Inositol for The Management of Polycystic Ovary Syndrome

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ABSTRACT

Background: Polycystic ovarian syndrome (PCOS) is an endocrinological disease of women of the reproductive age group. The study aimed to compare the efficacy of Myo-inositol and folic acid with and without D-chiro-inositol in the improvement of symptoms of PCOS within 4 months for the evaluation of the most effective therapeutic regimen.

Methods: This Quasi-experimental study was conducted at Gynecology & Obstetrics OPD of two Private Healthcare Hospitals in Sialkot from February 2024-June 2024. The Rotterdam criteria (2003) was used for diagnosis of PCOS in non-pregnant women aged between 18-35 years. A total of 90 PCOS patients (45 in each group) were enrolled using a purposive sampling technique and distributed into two treatment groups. Group A received MI 2000 mg + DCI 50 mg + FA 200 mcg while Group B received MI 2000 mg + FA 200 mcg BD, after meal, for 17-18 weeks. Patients' menstrual cycle history, BMI, transabdominal-ultrasonographic picture, and serum total testosterone levels were evaluated at Day 0, 60, and 120 to compare these measurements before and after initiation of treatment. SPSS was used to analyze the data. Independent samples t-test and Repeated measures ANOVA were used to analyze the data. P-value ≤ 0.05 was considered statistically significant.

Results: After the intervention, body mass index (kg/m²), serum total testosterone levels (ng/dl), and follicular number per ovary decreased, with Group A demonstrating better performance with p-values 0.03, 0.04 and < 0.001 respectively. Both groups exhibited increased follicular size in both ovaries and decreased ovarian volumes. By Day 120, menstrual cycle regularity was more pronounced in Group A than in Group B (1.00 ± 0.00 and 1.13 ± 0.34 respectively, p-value <0.001.

Conclusion: Myo-inositol + D-chiro Inositol + Folic acid and Myo-Inositol + Folic acid showed a change in the studied variables, however, Myo-inositol + D-chiro Inositol + Folic acid demonstrated more efficacy in alleviating PCOS symptoms compared to Myo-Inositol + Folic acid.

Keywords: Myo-Inositol; D-Chiro Inositol; Folic Acid; Testosterone.

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Doi: https://doi.org/10.36283/ziun-pjmd13-4/011

How to cite: Akram R,Jafri SA,Malik S,Nisar S,Irum A Comparing Myo-Inositol and Folic Acid with and without D-Chiro-Inositol for The Management of Polycystic Ovary Syndrome. Pak J Med Dent. 2024;13(4): 85-92. Doi: https://doi.org/10.36283/ziun-pjmd13-4/011

Received: Fri, Aug 30, 2024 **Accepted:** Thu, Sept 26, 2024 **Published:** Thu, Oct 24, 2024

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INTRODUCTION

Polycystic ovarian syndrome (PCOS) is an endocrinological disorder of women of the reproductive age group with a high prevalence rate in young women[1]. Several diagnostic criteria for PCOS have been proposed of which the 2003 Rotterdam Criteria was widely used and practiced, according to which the diagnosis of PCOS could be confirmed if at least two of the following three criteria were present: (1) Evidence of oligo-amenorrhea; (2) Hyperandrogenism; (3) Ultrasonographic picture showing polycystic ovarian morphology (PCOM)[2]. In Pakistan, scanty work was available on this method, and experimental trials were needed.

It had been observed that the longer the symptoms of PCOS the higher the chance of developing metabolic syndrome, and, if left untreated, would increase the risk of development of impaired fasting glucose level, central obesity, dyslipidemia, hypertension, especially in women with waist to hip ratio of >0.87[3-5]. The treatment options for PCOS were often limited especially in Pakistan, although it is a prevalent endocrinological disorder, hence the need for effective therapies. Inositol, particularly Myo-Inositol (MI) and D-chiro Inositol (DCI), have been shown to alleviate symptoms of PCOS, including menstrual irregularity, hyperandrogenism, and insulin sensitivity but limited evidence was available and additional research was required that directed the comparative efficacy of Myo-Inositol (MI) + D-chiro Inositol (DCI) + Folic acid (FA) vs Myo-Inositol (MI) + Folic acid (FA) as a treatment option for PCOS[6-8].

By conducting this study, aimed to contribute valuable evidence to the existing body of knowledge regarding the comparative effectiveness of two different treatment modalities (MI + DCI + FA and MI + FA) to alleviate symptoms of PCOS, and to identify whether one treatment was more effective than the other, hence giving a more personalized and targeted treatment strategy and assessing the potential benefits of adding FA to MI or FA to MI + DCI. The most important aim was to give clinically relevant outcomes for better-informed PCOS management in Pakistan.

A study conducted stated that the physiological concentrations of MI and DCI in different tissues differed. In PCOS patients, epimerase activity was reduced due to insulin resistance in most PCOS patients, and it was observed that a 40:1 concentration of MI and DCI was effective in managing PCOS in overweight and obese women, where DCI's role was reduction in peripheral hyperinsulinemia and regulation of ovulation by MI[9].

METHODS

This quasi-experimental research was carried out at Gynecology & Obstetrics OPD of two Private Healthcare Hospitals, in Sialkot, from February 2024-June 2024, with ethical approval dated 2nd February 2024 and ref no: NA. Purposive sampling, a type of non-probability sampling[10]. The total sample size was N=90, where participants were allocated into two groups, 'A' and 'B', each comprising 45 females. Inclusion criteria was non-pregnant women of reproductive age between 18-35 years, as per the 2003 Rotterdam criteria, two out of following three conditions must be met to declared PCOS patients: (a) Evidence of oligomenorrhea or amenorrhea (menstrual cycles of >35 days apart or <8 menses a year), (b) Hyperandrogenism i.e., elevated serum testosterone levels, (c) Ultrasonographic picture of polycystic ovaries, defined as either ≥12 follicles measuring 2-9mm and/or an ovarian volume of ≥10 cm^3 in at least one ovary. Rest were excluded.

Group A received Myo-Inositol 2 grams + D-chiro Inositol 50 mg (at the ratio of 40:1) + Folic acid 200 mcg BD after meal[11-12]. Group B (MI + FA Group): Participants received Myo-Inositol 2 grams + Folic acid 200 mcg BD after meal. Serum total testosterone (TT), using TT kit by Roche Diagnostics13. Trans-abdominal-ultrasonography diagnosed ovarian morphology that showed either ≥12 follicles measuring 2-9 mm and/or an ovarian volume of ≥10 cm3 in at least on ovary14. Body Mass Index was calculated as weight (kg) divided by height (m^2)[15]. Menstrual Cycle History Menses per month or menses per year[16]. These variables were reported at 3 different intervals, i.e., Day 0, Day 60, and Day 120. Data analysis was conducted using SPSS 26.0 software for Windows[17]. Mean ± SD was used to represent quantitative data. Independent t-test and repeated measure ANOVA were applied. P-value ≤ 0.05 was considered statistically significant.

RESULTS

The mean ages of Group-A of 26.44 years ±3.28 SD and Group-B of mean 26.58 years ±3.27 SD were almost identical, with very similar variability and standard deviation suggesting that the age distribution of the two groups was nearly the same as illustrated in Table 1 below.

The average marital status (coded numerically) for Group-A of mean 1.64 ±0.48 SD and Group-B of mean 1.60 ±0.49 SD were also very close, indicating that the marital status distribution was similar across both groups. The small SD suggested that majority of the participants in both groups had similar marital status, indicating similarity between the two groups in respect to marital status.

 DOI: https://doi.org/10.36283/PJMD13-4/011

Table 1 Descriptive Analysis of Demographic Characteristics

Variables	Group-A (Mean ±SD)	Group-B (Mean ±SD)	p-value
Age (Years)	26.44 (3.28)	26.58 (3.27)	0.85
Marital Status	1.64 (0.48)	1.60 (0.49)	0.39

**p-value of <0.05 indicated statistical significance, while p-value of >0.05 indicated non-significance*

Figure 1 below represented a line graph showing the estimated marginal means of BMI over the three days for two different treatment groups (Group-A and Group-B), where the normal range of BMI (kg/m²): 18.5-24.5 kg/m² whereas above normal BMI: ≥ 25 kg/m²18.

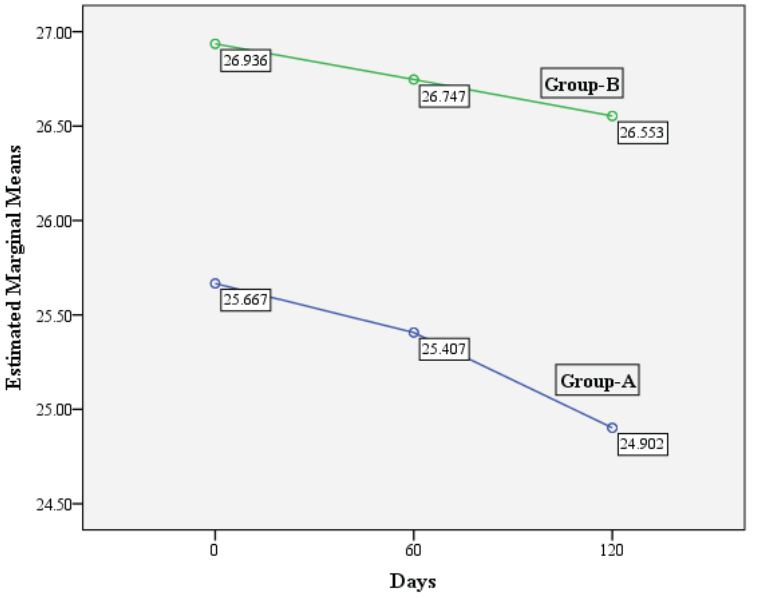

Figure 1: Estimated Marginal Means of Body Mass Index (kg/m²)

Note x-axis: Days (Day 0, Day 60, and Day 120); y-axis: Estimated Marginal Measure of BMI kg/m²

Table 2 and Table 3 provided detailed breakdown of how each variable changed over the course of days in both groups, i.e., Group-A and Group-B

Table 2: Comparison of Outcome Variables at day 0, day 60 and day 120 for Group-A

Outcome Variables	Day 0 (Mean ±SD)	Day 60 (Mean ±SD)	Day 120 (Mean ±SD)	p-value
Body Mass Index (kg/m²)	25.66 ± 3.22	25.41 ± 3.08	24.90 ± 2.93	**<0.001**
Serum Total Testosterone (ng/dL)	81.68 ± 3.89	79.24 ± 3.79	75.33 ± 4.23	**<0.001**
Follicular Number Per Ovary (FNPO)	13.29 ± 2.77	10.13 ± 2.21	5.91 ± 2.40	**<0.001**
Follicular Size in Right Ovary (mm)	7.90 ± 3.39	12.47 ± 3.47	18.24 ± 5.28	**<0.001**
Follicular Size in Left Ovary (mm)	7.70 ± 3.26	13.00 ± 3.95	19.69 ± 4.42	**<0.001**
Ovarian Volume of Right Ovary (ml)	17.56 ± 6.88	13.97 ± 6.26	9.77 ± 4.39	**<0.001**
Ovarian Volume of Left Ovary (ml)	19.80 ± 11.43	14.48 ± 6.20	10.48 ± 3.55	**<0.001**
Menstrual Cycle Regularity	1.73 ± 0.44	1.11 ± 0.31	1.00 ± 0.00	**<0.001**

**p-value of <0.05 indicated statistical significance, while p-value of >0.05 indicated non-significance*

Table 3: Comparison of Outcome Variables at day 0, day 60 and day 120 for Group-B

Outcome Variables	Day 0 (Mean ±SD)	Day 60 (Mean ±SD)	Day 120 (Mean ±SD)	p-value
Body Mass Index (kg/m²)	26.93 ± 2.98	26.74 ±2.90	26.53 ± 2.91	**<0.001**
Serum Total Testosterone (ng/dL)	81.60 ± 5.10	80.44 ± 4.44	79.74 ± 4.42	**<0.001**
Follicular Number Per Ovary (FNPO)	12.87 ± 2.46	11.18 ± 2.37	8.80 ± 2.07	**<0.001**
Follicular Size in Right Ovary (mm)	8.64 ± 4.04	11.87 ± 4.74	18.07 ± 3.11	**<0.001**
Follicular Size in Left Ovary (mm)	7.32 ± 2.96	11.89 ± 4.16	15.86 ± 3.90	**<0.001**
Ovarian Volume of Right Ovary (ml)	16.89 ± 5.83	14.05 ± 5.22	11.99 ± 4.03	**<0.001**
Ovarian Volume of Left Ovary (ml)	17.62 ± 6.16	14.43 ± 5.21	12.60 ± 4.47	**<0.001**
Menstrual Cycle Regularity	1.82 ± 0.38	1.49 ± 0.50	1.13 ± 0.34	**<0.001**

**p-value of <0.05 indicated statistical significance, while p-value of >0.05 indicated non-significance*

Table 4 provided results of comparison all dependent variables of two groups, Group-A and Group-B, with mean values and standard deviation (SD) for each variable, along with corresponding p-values to assess statistical significance.

Table 4 Comparison of Outcome Between Two Groups

Outcome Variable	Group-A (Mean ±SD)	Group-B (Mean ±SD)	p-value
Body Mass Index (kg/m²)	24.90 ± 2.93	26.53 ± 2.91	**0.03**
Serum Total Testosterone (ng/dL)	75.33 ±4.23	79.74 ± 4.42	**0.04**
Follicular Number Per Ovary (FNPO)	5.91 ± 2.40	8.80 ± 2.07	**<0.001**
Follicular Size in Right Ovary (mm)	18.24 ± 5.28	18.07 ± 3.11	0.99
Follicular Size in Left Ovary (mm)	19.69 ±4.42	15.86 ± 3.90	**<0.001**
Ovarian Volume of Right Ovary (ml)	9.77 ± 4.39	11.99 ± 4.03	0.59
Ovarian Volume of Left Ovary (ml)	10.48 ± 3.55	12.60 ± 4.47	0.96
Menstrual Cycle Regularity	1.00 ± 0.00	1.13 ± 0.34	**<0.001**

**p-value of <0.05 indicated statistical significance, while p-value of >0.05 indicated non-significance*

DISCUSSION

The two groups were comparable and balanced in the demographic aspects, which was important for ensuring that any observed effects were not due to dissimilarity in these variables[19]. Married women were those who were married 6 months to 1 year before the start of the study. These women visited the hospital and became a part of the study mainly due to complaints of having no issues/subfertility. Unmarried women with PCOS were mainly those who presented with complaints of menstrual irregularity.

Both groups experienced a decrease in BMI over the three days, with Group-B starting and ending with higher values compared to Group-A. These findings were consistent with a study in 2020 where they conducted a 12-week retrospective study on PCOS women and observed that obese women experienced a meaningful reduction in body weight[20].

Table 2 and Table 3 outlined the changes in variables for Group-A and Group-B over three-point times: Day-0, Day-60, and Day-120. It was observed that both groups experienced significant changes in their mean values for each variable over the course of the day observed, with p-value 0.00 for each variable of both groups. These results were recognized by a study in 2020 where MI 550 mg + DCI 13.8 mg intervention (40:1) for 6 months in PCOS patients with an average age of 26 was effective in increasing follicular size, maturation of follicles, and ovulation in obese PCOS patients[21].

Table 4 above illustrated a comparison of the means and SD of each variable outcome between the two groups i.e., Group-A and Group-B. Group-A had a mean BMI of 24.90 (±2.93 SD), while Group-B had a higher mean BMI of 26.53 (±2.91 SD). The difference

was statistically significant with a p-value of 0.03, suggesting that Group-A had a lower BMI by the end of the study compared to Group-B. These results correlate with a study in 2024 where participants observed meaningful reduction in BMI, aged 17 – 19 years, who received 2000mg Myo-Inositol + 200mcg Folic acid + a-lactalbumin BD for 3 months[22].

The mean serum TT of Group-A was 75.33 ng/dl with ±4.23 SD compared to 79.7 ng/dl with ±4.42 SD of Group-B which presented that Group-A had lower mean serum TT by the end of the study compared to Group-B. These results aligned with a study in 2024 where PCOS patients aged 20-40 years received 1100mg MI + 27.5 mg DCI + 400mcg Folic acid (40:1) once a day for 3 months, without any diet or lifestyle intervention, and showed a meaningful decrease in serum total testosterone levels[23].

The findings of FNPO were consistent with a study in 2022 where studied subjects received 2000mg MI + 400mcg FA once a day for six months and showed ($p<0.05$) improvement in the ultrasonographic picture[24].

The follicular size in the right ovary and both ovarian volumes were very similar between the groups, with p-value of 0.99 for right follicular size, 0.59 for right ovarian volume and 0.96 for left ovarian volume, suggesting similarity between the two groups for these two variables. These findings were inconsistent with a study in 2017, where they found out that 40:1 MI + DCI was better in restoring follicular size, ovarian volumes and ovarian functions, with desirable outcomes, compared to MI and DCI alone[25]. The inconsistency in results was probably due to genetic, environmental, or local health factors. A study conducted in 2019 investigated seven different ratios of two different stereoisomers of Inositol, where 24 PCOS women received 2 grams of MI in powder form and 26 received MI + DCI combination with dosage MI 550 mg and DCI 13.8 mg in soft-gel capsule form for 6 months[26]. Post-treatment, it was concluded that 40:1 of MI and DCI was the most effective combination at normalizing observed parameters in overweight patients of PCOS after three months of treatment.

The left ovarian follicular size of Group-A was 19.69 mm with SD ±4.42 compared to 15.86 mm with SD ±3.90 in Group-B. It indicated that Group A had larger left ovarian follicular size by the end of the study compared to Group-B. These findings were consistent with a study in 2023 where they stated that MI and DCI were effective in improving the metabolic and hormonal profile of PCOS women and improving ovarian functions[27].

Changes in menstrual cycle regularity over time were also observed. Dissimilarity (p=0.00) in menstrual cycle regularity in the two groups was noted, with Group A showing more regularity than Group B by Day 120. These findings were supported by a study in 2022, where 550 mg MI + 150 mg DCI was enough to restore spontaneous menstrual cycle in PCOS women aged 20-45 years[28].

As with any study, this research had certain limitations. The study duration of 17-18 weeks might not be enough to observe the long-term effects of these treatments in alleviating PCOS symptoms, especially considering that hormonal and metabolic changes often require more extended periods to manifest fully, but this study was an M.Phil. thesis research and time available was four months which is a minimum allowed period of their research study.

The fact that 7 to 8 patients did not return for follow-up visits posed limitation. The dropout rate reduced the sample size, diminishing the study's statistical power and potentially skewing the results. As discussed by a study in 2022, dropout is a common occurrence varying between 12 to 47 %, and if the dropouts were not random (e.g., related to adverse effects or lack of perceived efficacy), it could introduce bias into the study, affecting the validity of the findings[29].

Recommendations for future research were that since this was a self-sponsored study, efforts should be made to get financial support from some agency to carry out detailed study. Future studies should also focus on long-term safety and adherence to the treatments, particularly if the interventions are intended for extended use.

CONCLUSION

In conclusion, 2000 mg MI + 50 mg DCI + 200 mcg FA demonstrated superior efficacy compared to 2000 mg MI + 200 mcg FA in improving the studied outcomes, and should be the preferred therapeutic option for non-pregnant women of reproductive age group with PCOS, which would aim to restore spontaneous menstrual cycle, ovarian function, and reduce BMI serum total testosterone levels.

LIST OF ABBREVIATIONS

Notation	Description
ANOVA	Analysis of Variance
BD	Twice a Day
BMI	Body Mass Index
CI	Confidence Interval
cm^3	Cubic centimeters
DCI	D-chiro Inositol
FA	Folic Acid
FSH	Follicular Stimulating Hormone
FNPO	Follicular Number per Ovary
kg	Kilogram

kg/m²	Kilograms per square meter
LH	Luteinizing Hormone
mcg	Micrograms
mg	Milligrams
mm	Millimeters
MI	Myo-Inositol
N	Total sample size
ng/dl	Nanograms per deciliter
PCOS	Polycystic Ovarian Syndrome
SD	Standard Deviation
Serum TT	Serum Total Testosterone Level
SPSS	Statistical Package for Social Sciences
USG	Ultrasonography or Ultrasound

DECLARATION

I declare that the main content of this research accounts for my work and has not previously been submitted to any journal before. The materials taken from other sources have been properly acknowledged.

ACKNOWLEDGEMENT

The researcher would like to acknowledge all authors for their contribution in the study.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

ETHICS APPROVAL

The Ethical Review Committee (ERC) of Nur international University, Lahore, had approved this study (Dated: 2/2/24, Ref. no.: NA)

FUNDING

Self-funded by the author. No external funding was received for this study.

PATIENT CONSENT

Patients' consent was taken prior to data collection for their contribution in this study.

AUTHORS' CONTRIBUTION

This work was carried out in collaboration between all authors. Author RA was responsible for conceptualization, design, data collection, statistical analysis, and manuscript writing of this study. Author SAJ provided supervision and guidance throughout the research process. Author SM and SN facilitated the study by providing necessary samples. Author AI and MA provided valuable insight during the manuscript preparation phase. All authors read and approved the final manuscript.

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