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## Original Research Article

# A prospective study of metformin versus myoinositol plus d-chiroinositol combination therapy in polycystic ovarian syndrome

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### ABSTRACT

**Background:** Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age. Insulin resistance and resultant hyperinsulinemia contribute to hyperandrogenism in these patients. Weight loss or pharmacologic interventions that lower insulin levels reduce androgen levels. This study was planned to evaluate efficacy of metformin versus myoinositol plus d-chiroinositol combination therapy in PCOS patients and its effects on clinical, hormonal and radio diagnostic dimensions.

**Methods:** This was a prospective study for nine months. 50 newly diagnosed PCOS patients from the Department of Obstetrics and Gynaecology, Government Medical College (GMC), Amritsar, were randomly divided into 2 groups. One group was given metformin 500 mg twice daily and another myoinositol plus d-chiroinositol 1000 mg twice daily for 9 months. Follow up was done at 3, 6, 9 months. At each visit, ultrasonography and hormone levels were evaluated. Informed consent was taken. The approval of the Institutional Ethics Committee, GMC, Amritsar was also obtained.

**Results:** The percentage change in free testosterone levels ( $22.46 \pm 6.47$ ) and insulin levels ( $34.24 \pm 15.02$ ) show statistically significant decrease in group 2 ( $p < 0.001$ ). There was statistically significant ( $p < 0.05$ ) fall in AMH levels ( $22.41 \pm 7.78$ ) in group 1. There was no statistically significant difference between the 2 groups in ovarian volume on ultrasonography, random blood glucose levels, luteinizing hormone (LH), follicle-stimulating hormone (FSH) levels, estrogen and progesterone levels.

**Conclusions:** It was observed that both treatments are equally effective in the treatment of polycystic ovarian syndrome with better tolerability in myoinositol and d-chiroinositol group.

**Keywords:** PCOS, Metformin, Myoinositol, d-chiroinositol

### INTRODUCTION

Hormonal disorder common among women of reproductive age is polycystic ovarian syndrome (PCOS) and globally its incidence ranges from 2.2-26%.<sup>1</sup> Hyperandrogenism in these patients is the result of insulin resistance and resultant hyperinsulinemia. Life style modification and pharmacological agents that lower insulin levels improve menstrual cycle regularity by further reducing androgen levels.

Metformin by decreasing insulin resistance improves ovulation in women with PCOS.<sup>2</sup> Myo-inositol a naturally occurring member of the vitamin B group regulates glucose transport and follicle-stimulating hormone signaling in the ovary whereas glycogen and insulin-induced androgen synthesis is mainly controlled through d-chiroinositol.<sup>3,4</sup> Considering the alleviation of insulin excess by both the drugs metformin and myoinositol, the present study has been designed to study

and compare the effects of these two drugs in patients with PCOS.

## METHODS

The present study was prospective randomized parallel design interventional study. The study comprised of 50 newly diagnosed PCOS patients in the age group of 15-45 years in the outpatient department of Department of Obstetrics and Gynaecology at Bebe Nanki Centre for Mother and Child Care, Government Medical College (GMC), Amritsar. This study was conducted from April 2018 to September 2019. An informed consent was taken from all the patients after explaining study drugs, its benefits and side effects. The approval of the Institutional Ethics Committee, GMC, Amritsar was also obtained.

The diagnosis of the syndrome was made according to the Rotterdam's criteria in which at least two out of three criteria (hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology) are needed to diagnose the disorder.<sup>5</sup> Patients with history of hypertension and diabetes mellitus, women who received previous treatment with other drugs within last 6 months and pregnant females were excluded from the study.

### Study design

All the newly diagnosed PCOS patients from Department of Obstetrics and Gynaecology at Bebe Nanki Centre for Mother and Child Care, Amritsar were recruited for the study. Baseline Tests were done at the start of therapy in all these patients. 50 patients meeting the inclusion criteria were selected. Systemic disease, other comorbidities excluded.

Subjects selected were randomly divided by Simple Randomization method into 2 groups such as Group 1 with 25 patients on Metformin 500 mg BD daily and Group 2 with 25 patients on Myoinositol and d-chiroinositol 1000 mg BD daily. Follow up done at 3<sup>rd</sup>, 6<sup>th</sup>, 9<sup>th</sup> month to evaluate the results of the drugs on the hormone levels of the subjects and if any adverse effects encountered. At the end of nine months, data was collected and results were evaluated using appropriate statistical methods.

## Statistical analysis

Analysis was based on data obtained from patients who have completed nine months of study phase. Data generated from the study was tabulated with respect to all parameters at specific intervals. The results were expressed as mean  $\pm$ SD of each variable. Comparison between the two groups was done by unpaired T-test. All the statistical analysis was done using SPSS software. Significance was expressed as p value of <0.05 for each parameter.

## RESULTS

Among the radiological parameters, ultrasonography (USG) of left and right ovaries was conducted. Table 1 shows that the percentage change in left ovarian volume at 9 months was not statistically significant (p value >0.05) between the two groups.

Table 2 shows that the percentage decrease in right ovarian volume was not statistically significant (p value >0.05) among the two groups.

Figure 1 shows that there was no statistically significant reduction in luteinizing hormone (LH)/follicle-stimulating hormone (FSH) between the 2 groups (p value >0.05).

Figure 2 shows that the percentage change at 9 months from baseline in the two study groups show statistically significant fall in patients on myoinositol and d-chiroinositol group 2 (p value <0.001).

Figure 3 shows that the percentage change of serum free testosterone from baseline among the group 1 and 2 show statistically significant decrease in group 2 (p value <0.001).

Table 3 shows that the percentage change in estrogen levels was statistically non-significant (p value <0.05) among the two groups.

Figure 4 shows that the percentage change at 9 months from baseline was not statistically significant between the two groups (p value <0.05). Table 4 shows that the values were significant statistically in metformin group (p value <0.05).

**Table 1: Left ovarian volume in study groups.**

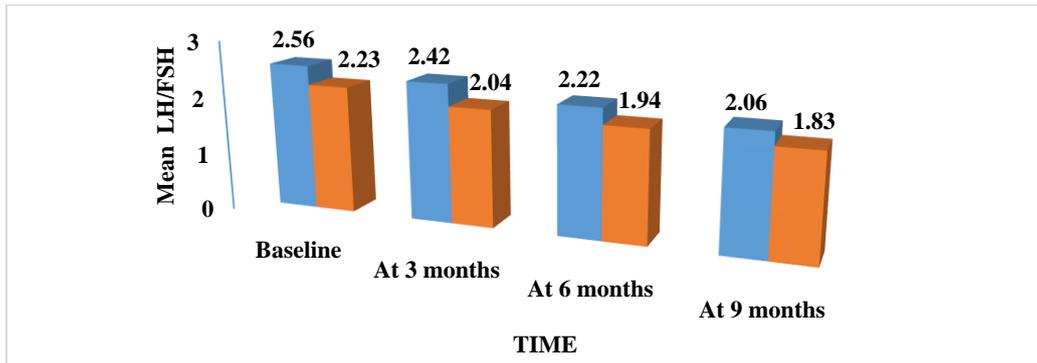
Time	Group 1 (in cm <sup>3</sup> )		Group 2 (in cm <sup>3</sup> )		P value
	Mean	SD	Mean	SD	
Baseline	11.61	2.34	11.46	1.62	0.801
At 3 months	10.42	2.02	10.30	1.56	0.821
At 6 months	8.76	1.55	8.88	1.01	0.731
At 9 months	7.24	1.41	7.53	0.81	0.381
% change at 3 months	9.99	3.53	10.01	6.50	0.990
% change at 6 months	23.79	7.68	21.98	6.05	0.360
% change at 9 months	36.59	10.25	33.48	8.63	0.251

p>0.05; Not significant; \*p<0.05; Significant; \*\*p<0.001; Highly significant.

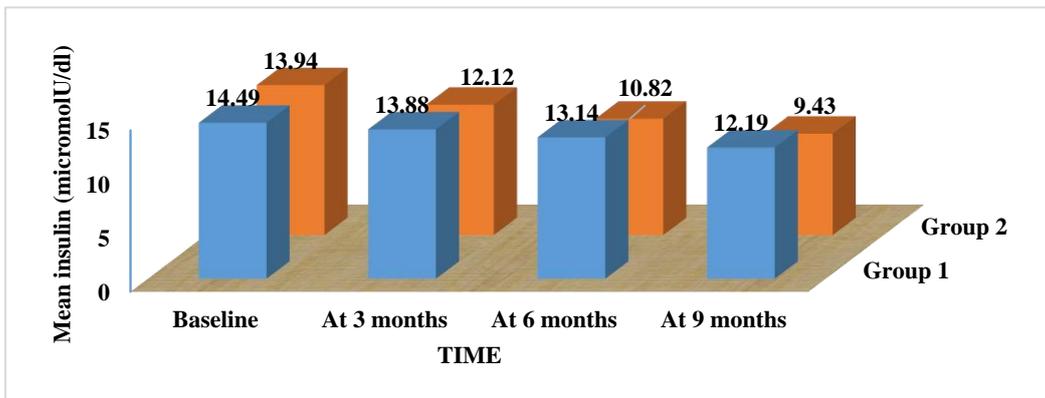
**Table 2: Right ovarian volume in study groups.**

Time	Group 1 (in cm <sup>3</sup> )		Group 2 (in cm <sup>3</sup> )		P value
	Mean	SD	Mean	SD	
Baseline	11.12	2.34	12.58	1.72	0.016
At 3 months	9.90	2.02	11.03	1.73	0.040
At 6 months	8.40	1.48	9.21	1.31	0.044
At 9 months	6.92	1.40	7.40	0.73	0.135
% change at 3 months	10.71	4.35	12.52	3.81	0.124
% change at 6 months	23.54	8.24	26.63	4.82	0.112
% change at 9 months	36.59	11.29	40.46	6.96	0.152

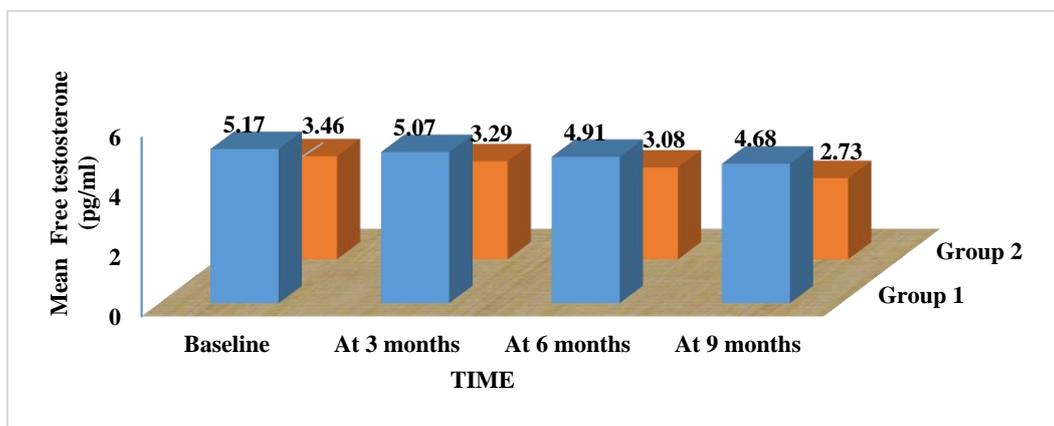
p>0.05; Not significant; \*p<0.05; Significant; \*\*p<0.001; Highly significant.



**Figure 1: LH/FSH ratio in patients in study groups.**



**Figure 2: Serum insulin levels in micro IU/dl in patients in study groups.**

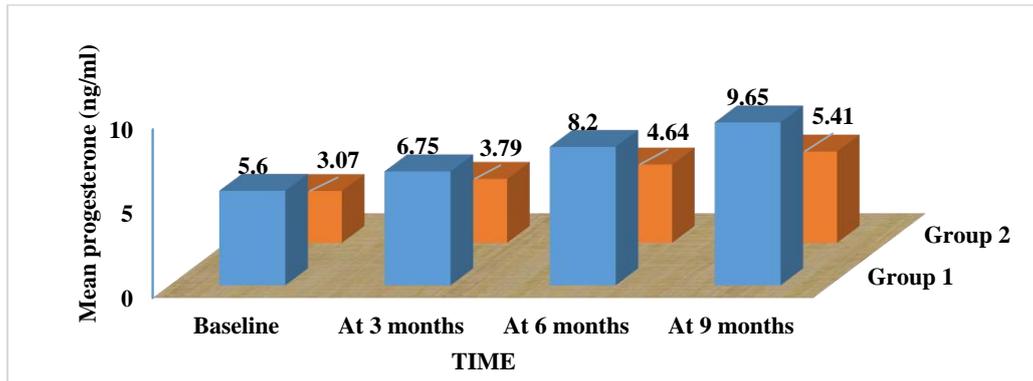


**Figure 3: Serum free testosterone levels in pg/ml in patients in study groups.**

**Table 3: Serum estrogen levels in patients in study groups.**

Time	Group 1 (in pg/ml)		Group 2 (in pg/ml)		P value
	Mean	SD	Mean	SD	
Baseline	61.35	18.96	50.68	13.50	0.026
At 3 months	60.18	18.62	49.46	13.32	0.023
At 6 months	59.08	18.54	49.15	12.76	0.032
At 9 months	57.96	18.19	48.07	12.50	0.030
% change at 3 months	1.89	1.17	2.54	1.52	0.096
% change at 6 months	3.85	1.69	2.74	3.09	0.121
% change at 9 months	5.62	2.30	4.84	4.07	0.406

p>0.05; Not significant; \*p<0.05; Significant; \*\*p<0.001; Highly significant.



**Figure 4: Serum progesterone levels in ng/ml in patients in study groups.**

**Table 4: Serum anti-mullerian hormone levels (AMH) in patients in study groups.**

Time	Group 1 (in ng/ml)		Group 2 (in ng/ml)		P value
	Mean	SD	Mean	SD	
Baseline	9.47	2.15	15.75	3.30	0.000
At 3 months	8.85	2.12	15.26	3.22	0.000
At 6 months	8.11	2.14	14.46	3.22	0.000
At 9 months	7.39	2.06	13.65	3.15	0.000
% change at 3 months	6.68	4.40	3.12	1.86	0.001
% change at 6 months	14.85	7.07	8.38	2.73	0.000
% change at 9 months	22.41	7.78	13.67	3.76	0.000

p>0.05; Not significant; \*p<0.05; Significant; \*\*p<0.001; Highly significant.

**DISCUSSION**

On ultrasonography, it was observed that the mean left ovarian volume at baseline in group 1 was 11.61±2.34 and 11.46±1.62 in group 2. This volume decreased to 7.24±1.41 and 7.53±0.81 after final follow up at 9 months in group 1 and 2 respectively. The percentage change at 9 months from baseline was 36.59±10.25 in metformin group and 33.48±8.63 in myoinositol and d-chiroinositol group. The mean right ovarian volume at baseline was 11.12±2.34 and 12.58±1.72 which decreased to 6.92±1.40 and 7.40±0.73 after final follow up at 9 months in group 1 and 2 respectively. The percentage change at 9 months from baseline was 36.59±11.29 in Metformin group and 40.46±6.96 in combination therapy group. The results were not statistically significant (p value >0.05) between the two groups. Similar results have been reported by

Gharakhani et al and Zeyneloglu et al where decrease in ovarian volume was observed with metformin treatment.<sup>6,7</sup> Our results are not in consonance with the study conducted by Ozay et al where myoinositol administration resulted in significant decrease in ovarian volume.<sup>8</sup>

The mean LH/FSH on day 1 was 2.56±0.49 and 2.23±0.53 which decreased to 2.06±0.47 and 1.83±0.37 after final follow up at 9 months in group 1 and 2 respectively. The percentage change at 9 months from initial value was 20.18±5.87 and 16.89±8.58 amongst the 2 groups. There was no statistically significant reduction in LH/FSH between the 2 groups (p value >0.05). Similar results were reported in the study conducted by Artini et.al. which showed decrease in the levels of LH/FSH ratio with myoinositol and d-chiroinositol whereas Nehra

et.al. has observed more reduction in LH/FSH ratio with metformin group compared to myoinositol.<sup>9,10</sup>

The mean free testosterone at the start of the study was  $5.17 \pm 1.69$  and  $3.46 \pm 1.39$  which decreased to  $4.68 \pm 1.57$  and  $2.73 \pm 1.23$  at 9 months in group 1 and 2 respectively. The percentage change from baseline was  $9.31 \pm 11.99$  and  $22.46 \pm 6.47$  in group 1 and 2 showing statistically significant decrease in group 2 (p value <0.05). The results were consistent with the study conducted by Troisi et al, Ozay et al and Regidor et al presenting reduction in testosterone levels with the administration of myoinositol and d-chiroinositol.<sup>8,11,12</sup> Tiwari et al also observed similar trends in testosterone levels at 6 months in metformin group.<sup>13</sup>

The mean random blood glucose at baseline was  $108.84 \pm 11.08$  and  $87.07 \pm 4.48$  which decreased to  $100.64 \pm 7.73$  and  $82.57 \pm 2.26$  after final follow up at 9 months in group 1 and 2 respectively. The percentage change at 9 months from baseline was  $7.14 \pm 5.90$  and  $5.00 \pm 4.01$  which was not statistically significant among the two groups (p value >0.05). Similar variation in the mean random blood glucose was observed with metformin in a study conducted by Pradas et al.<sup>14</sup> In contrast to our study, Shokrpour et al in his study reported significant reduction in blood glucose levels with myoinositol supplementation.<sup>15</sup>

The mean insulin on day 1 was  $14.49 \pm 5.48$  and  $13.94 \pm 3.95$  in group 1 and 2 respectively. The levels showed marked decrease in values measured as  $12.19 \pm 4.85$  and  $9.43 \pm 4.36$  after final follow up at 9 months. The percentage change at 9 months from baseline was  $16.26 \pm 7.99$  and  $34.24 \pm 15.02$  in the two study groups showing statistically significant fall in patients on myoinositol and d-chiroinositol (p value <0.05). Our results are in consistence with the study conducted by Fruzzetti et al, where both metformin and myoinositol group presented with decrease in insulin levels after treatment.<sup>16</sup> Similar results have been reported with the use of metformin and myoinositol on insulin levels by Pradas et al and Artini et al, respectively.<sup>10,14</sup> The results of the study conducted by Shokrpour et al are in consonance with our results showing significant reduction in serum insulin levels with myoinositol supplementation.<sup>15</sup>

The mean AMH on the day of enrollment was  $9.47 \pm 2.15$  and  $15.75 \pm 3.30$  in group 1 and 2 which decreased to  $7.39 \pm 2.06$  and  $13.65 \pm 3.15$  after final follow up at 9 months. The percentage change at 9 months from baseline was  $22.41 \pm 7.78$  and  $13.67 \pm 3.76$  in group 1 and 2 respectively. The values were significant statistically in metformin group (p value <0.05). These results are in consonance with studies conducted by Madsen et al where AMH levels significantly decreased during metformin treatment.<sup>17</sup> Another study by Tagliaferri et al showed significant decrease in AMH levels with metformin treatment compared to myoinositol.<sup>18</sup>

The mean estrogen at the beginning of the study was  $61.35 \pm 18.96$  and  $50.68 \pm 13.50$  and these decreased to  $57.96 \pm 18.19$  and  $48.07 \pm 12.50$  at 9 months in group 1 and 2 respectively. The percentage change at the end of the study from baseline levels was  $5.62 \pm 2.30$  and  $4.84 \pm 4.07$  in the two groups. The change was statistically non-significant (p value <0.05) among the two groups. The mean progesterone rose to  $9.65 \pm 3.90$  and  $5.41 \pm 1.38$  in the two groups from the baseline values on day 1 ( $5.60 \pm 1.76$  and  $3.07 \pm 1.54$ ). The percentage change at 9 months from baseline was  $73.83 \pm 45.71$  and  $98.89 \pm 62.27$  which was not statistically significant between the two groups (p value <0.05). Similar results were seen in a study conducted by Ozay et al where myoinositol led to reduction in estrogen levels and increase in progesterone levels.<sup>8</sup> Even Regidor et al demonstrated the increase in progesterone levels with myoinositol supplementation.<sup>12</sup>

Treatment in both the groups was found to be safe. Most patients receiving metformin complained of dyspepsia and few complained of nausea, loss of appetite and diarrhea during the treatment. In contrast, no gastrointestinal side effects were reported in the myoinositol group and d-chiroinositol group, except for one who reported of diarrhea, confirming the high tolerability of myoinositol plus d-chiroinositol combination.

## CONCLUSION

Metformin and myoinositol plus d-chiroinositol combination resulted in improvement of both clinical and hormonal disturbances in PCOS patients. Myoinositol and d-chiroinositol supplementation confirmed higher tolerability and also resulted in statistically significant reduction in free testosterone and insulin levels than metformin. Since the present study was carried out for a short duration and on a small number of patients, more studies are required to establish the effects of myoinositol and d-chiroinositol combination therapy for effective treatment of PCOS.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

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