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A COMPARATIVE STUDY OF MYO INOSITOL VERSUS METFORMIN ON BIOCHEMICAL PROFILE IN POLYCYSTIC OVARIAN SYNDROME IN WOMEN

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ABSTRACT: Objective: PCOS is a common endocrine disorder in women of reproductive age associated with insulin resistance. Metformin and Myo-inositol being insulin sensitizers improve biochemical parameters. This study was done to compare the effects of these drugs on biochemical profile in PCOS. **Material and Methods:** A prospective, open labeled, randomized, comparative, clinical study was conducted on 60 patients. The patients were randomly divided in two groups of 30 each to receive either of the following two treatments: Group A: Tab Myo-inositol 1g twice daily & Group B: Tab Metformin 500 mg thrice daily for 24 weeks. Biochemical profile was assessed by measuring fasting blood sugar, insulin levels & calculating glucose/insulin ratio and homeostatic model assessment- insulin resistance (HOMA-IR) index at baseline and subsequently at the end of 12 & 24 weeks. Serum Lipid profile was also assessed. **Results:** In both the groups, there was statistically significant improvement in insulin resistance. In group A & group B, the values for glucose/ insulin ratio improved from 6.77±0.99 to 7.87±1.03 and 5.5±0.42 to 6.90±0.47 respectively at the end of 24 weeks. HOMA-IR values decreased from 4.18±0.4 to 2.88±0.27 & 4.38±0.43 to 2.99±0.29 in group A & B respectively over a period of 24 weeks. Lipid profile was also improved in both the groups. However, on comparing both the groups, no statistically significant difference was observed. **Conclusion:** There was a definite improvement in biochemical profile with both metformin and myo-inositol. Thus, myo-inositol can be a new addition in the armamentarium for the treatment of PCOS.

INTRODUCTION: Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, prevalent across different populations around the world. PCOS prevalence worldwide is estimated to be 6-10% or even 15% when the diagnosis is based on Rotterdam criteria. [1] Studies of PCOS in India carried out in convenience samples reported a prevalence of 3.7% to 22.5%, [2, 3] with 9.13% to 36% prevalence in adolescents only. [4, 5]

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This syndrome was first described by Stein and Leventhal in 1931. It is a disorder characterized by excessive secretion of androgens by the ovaries, oligomenorrhoea, anovulation/oligoanovulation and insulin resistance and with variable clinical manifestations that include irregular menstrual cycles, hirsutism, alopecia and acne. [1] PCOS increases woman's risk of infertility, dysfunctional uterine bleeding, endometrial carcinoma, as well as insulin resistance, dyslipidemia and hypertension [all risk factors for cardiovascular disease (CVD)]. The potential increased risk of CVD may be related to the higher incidence of metabolic syndrome in this population. [6]

The pathogenesis of PCOS has not been completely elucidated and is multifactorial, with genetic and environmental factors being implicated.

Insulin resistance is presumed to be caused by defects in the insulin receptor and post receptor components of the insulin signaling pathway. [7, 8]

Elevated insulin levels cause abnormal functioning of hypothalamic-pituitary-ovarian axis that lead to PCOS. Women with PCOS experience an increased frequency of hypothalamic GnRH pulses, which in turn results in an increase in the LH/FSH ratio. [9]

Insulin resistance is main causative factor for all these consequences & morbidity. Failure of the target cells to respond to normal or ordinary levels of insulin is regarded as insulin resistance irrespective of the body mass index (BMI). Hyperinsulinaemia due to insulin resistance occurs in approximately 80% of PCOS Women with central obesity and 30%–40% of lean PCOS women. Hyperinsulinemia is the main causative factor in PCOD women both obese and lean and cause hyperandrogenism. [10] Insulin directly promotes ovarian steroidogenesis, and inhibits liver release of the sex hormone binding globulin (SHBG) and production of insulin-like growth factor binding protein 1 (IGFBP-1). Increased concentrations of IGF-1 additionally promote ovarian release of androgens. [9]

Metformin is a hepato-selective insulin sensitizer. It has beneficial properties of weight loss, lipid reduction and modulator of endothelial function. It also improves ovarian function in insulin-resistant women. It does not cause hyperinsulinaemia or hypoglycaemia.[11]

Myo-inositol (MI) is a naturally occurring substance produced in the human body that belongs to the vitamin B complex group. MI is One of the nine different types of inositol and can be found naturally in many foods. Of the nine different types of inositol, two have insulin-sensitizing capabilities: MI and d-chiro-inositol. PCOS has been linked to a deficiency in myo-inositol. MI can be synthesized by the body from food, but when we are already deficient, the lack of MI can impact the ability of the body to be sensitive to insulin. Women with PCOS are also known to have a defect in their insulin-signaling pathways, which are heavily dependent upon inositol-containing substances (phosphoglycan mediators). During certain conditions like periconceptional periods in PCOS women, the physiological requirements of MI increases. MI plays an important role as the structural basis for a number of secondary messengers including synthesis of phosphatidyl inositol 3-kinase (PI 3-kinase), a key messenger to improve insulin sensitivity and thereby reducing insulin resistance. Supplying extra MI appears to temporarily correct the impaired insulin pathways and reduce the signs and symptoms of insulin resistance. [12]

Metformin and Myo-inositol being insulin sensitizers correct biochemical parameters i.e. insulin resistance parameters, hormonal parameters and lipid profile, leading in improvement in menstrual irregularities, hyperandrogensim and infertility in PCOS in women. This study was done to compare the effect of myo-inositol versus metformin on biochemical profile in PCOS in women.

MATERIAL AND METHODS: This was a prospective, open label, randomized, comparative clinical study conducted by the Department of Pharmacology and Obstetrics and Gynaecology, Pt. B.D. Sharma PGIMS, Rohtak, India in 60 patients. Study was in accordance with the principles of good clinical practice (ICH-GCP) and declaration of Helsinki. An informed consent was obtained from all patients enrolled for the study. The study was approved by the PG Board of study, Pharmacology and Dean Faculty in Para-clinical sciences, University of Health Sciences, Rohtak.

An adequate number of patients were screened and selected as per the inclusion and exclusion criteria for the study. The eligible patients were randomly divided into two study groups i.e. Group A (myo-inositol) and Group B (metformin) with the help of computer generated random numbers. Each study group had minimally 30 patients who completed the study as per the protocol. During the study, patients were not permitted to take any non-study drugs.

The inclusion criteria were females of reproductive age group (15-45 yrs), diagnosed with PCOS according to AES (Androgen Excess Society)/2006 criteria: Presence of hyperandrogenism (clinical and/or biochemical), Oligo or anovulation, PCOM (Polycystic ovarian morphology)- at least one

ovary with 12 or more follicles (2-9 mm in diameter) or ovarian volume >10 ml and those willing to give a written informed consent. The Exclusion criteria were women suffering from any neoplastic disease, hyperprolactinemia, Cushing's disease, Hypothyroidism / Hyperthyroidism, Pregnancy and nursing, Active liver disease, renal impairment, Established type 1 or type 2 diabetes mellitus, any history of drug intake- Anti diabetic (or) oestrogen and progesterone, history of any treatment taken in last 3 months, Smokers and alcoholic subjects, inability to come for regular follow ups.

Patients who were diagnosed with PCOS according to the AES (Androgen excess society) 2006 criteria were included in the study. The patients were randomly divided in two groups of 30 each to receive either of the following two treatments: Group A: Tab Myo-inositol 1g twice daily. Group B: Tab Metformin 500 mg thrice daily for 6 months. Hormonal parameters like Insulin, FSH, LH, LH/FSH ratio, Serum testosterone and parameters for insulin resistance, HOMA-IR (Homeostatic assessment for insulin resistance) [13] & Glucose/ insulin ratio were assessed at baseline, at the end of 12 and 24 weeks. Serum lipid profile including total cholesterol, triglycerides, VLDL cholesterol, LDL cholesterol, HDL cholesterol was also assessed.

Data was expressed as Mean ± SEM unless specified otherwise. Both intragroup and intergroup statistical analysis was done. Intragroup analysis for repeated measures was done using ANOVA for parametric data and pairwise comparison was done. Intergroup analysis was done using unpaired 't' test for parametric data. A p-value <0.05 was considered as statistically significant.

RESULTS: A total of 79 patients with symptoms of PCOS were screened for this study. Out of this, 8 patients were excluded, as 6 patients did not fulfill the predefined inclusion criteria of the study and 2 were not willing to give informed consent. Rest of the 71 patients, enrolled in the study were randomized with the help of computer generated random numbers and were allocated to either of the two treatment groups. Patients in Group A received Myo-inositol 1gm BD while Group B received Metformin 500 mg TDS for 24 weeks. Of the 71 patients enrolled in the study, 35 were allocated to Group A and 36 allocated to Group B. 5 patients in Group A and 6 patients in Group B were lost to follow-up and were dropped from the study and the remaining 30 patients in either group completed the treatment successfully. The baseline characteristics of the patients are tabulated in **Table 1**.

TABLE 1: COMPARISON OF STUDY POPULATION CHARACTERISTICS IN BOTH THE GROUPS

Variables	Group A (n=30)	Group B (n=30)	'p' value
Age in years	23.8± .69	23.26± 1.03	0.669
Weight (Kgs)	63.96± .90	63.58 ± 1.88	0.856
Marital Status	19	22	-
Married	11	8	
Unmarried			
Education			-
Literate	26	28	
Illiterate	4	2	
Age at menarche	11.8±.29	11.1±.21	0.06
History of drug allergy	0	0	-

Age and weight are expressed as Mean±SEM
Group A: MI 1000 mg BD
Group B: Metformin 500 mg TDS

Tables 2 and **3** show the mean blood sugar, insulin, glucose-insulin ratio, HOMA-IR, FSH, LH, LH/FSH ratio and testosterone in myo-inositol and metformin treated patients, respectively, at different time periods in the study. There was statistically significant improvement in insulin resistance as assessed with glucose-insulin ratio and HOMA-IR with both the drugs at the end of 24 weeks as compared to baseline values.

In myo-inositol group, the glucose-insulin ratio increased by 1.10 and HOMA-IR decreased by 1.30, while in metformin group the glucose-insulin ratio increased by 1.40 and HOMA-IR decreased by 1.39 at the end of 24 weeks as compared to baseline values. There was statistically significant improvement in hormonal parameters as assessed by changes in FSH, LH, LH /FSH ratio and testosterone levels with both the drugs over a period of 24 weeks. In myo-inositol group, the LH/FSH ratio and testosterone decreased by 0.48 and 6.46 respectively, while in metformin group the LH/FSH ratio decreased by 0.60 and testosterone by 6.97 at the end of 24 weeks as compared to baseline values.

TABLE 2: ASSESSMENT OF BIOCHEMICAL PARAMETERS IN MYO-INOSITOL TREATED GROUP

Parameter	Baseline	12 weeks	24 weeks	p value (at the end of 24 weeks)
Fasting blood sugar	88.96 ± 2.79	84.66 ± 2.68*	82.00 ± 2.46#	.000
Insulin	18.26 ± 1.52	16.27 ± 1.27*	13.71 ± 1.08#	.000
Glucose/insulin ratio	6.77 ± .99	6.9 ± .92*	7.87 ± 1.03#	.000
HOMA-IR	4.18 ± .41	3.52 ± .32	2.88 ± .27#	.000
FSH	6.80 ± .51	7.13 ± .53*	7.40 ± .53#	.000
LH	12.62±1.62	11.88±1.53*	11.28±1.44#	.000
LH/FSH	2.23±.42	1.99±.38*	1.75±.29#	.000
Testosterone	52.76±3.30	50.06±2.07*	46.30±2.27#	.000

All values are expressed as Mean±SEM
Intragroup Analysis:
* Comparison of values at end of week 12 with baseline values is statistically significant (p<0.05).
# Comparison of values at end of week 24 with baseline values is statistically significant (p<0.05).

TABLE 3: ASSESSMENT OF BIOCHEMICAL PARAMETERS IN METFORMIN TREATED GROUP

Parameter	Baseline	12 weeks	24 weeks	p value (at the end of 24 weeks)
Fasting blood sugar	88.93 ± 2.41	85.16 ± 2.44*	82.76 ± 2.18#	.000
Insulin	18.98 ± 1.48	16.09 ± 1.31*	14.04 ± 1.10#	.000
Glucose/insulin ratio	5.50 ± .42	6.33 ± .48*	6.90 ± .47#	.000
HOMA-IR	4.38 ± .43	3.55 ± .36*	2.99 ± .29#	.000
FSH	6.79 ± .53	7.32 ± .53*	7.50± .53#	.000
LH	12.73±1.64	12.14±1.53*	11.92±1.48#	.001
LH/FSH	2.24±.42	1.72±.20*	1.64±.19#	.004
Testosterone	53.17± 3.74	49.50± 3.57*	46.20±3.12#	.000

All values are expressed as Mean±SEM
Intragroup Analysis:
* Comparison of values at end of week 12 with baseline values is statistically significant (p<0.05).
# Comparison of values at end of week 24 with baseline values is statistically significant (p<0.05).

There was statistically significant improvement in lipid profile in both the groups over a period of 24 weeks. In both the groups, reduction in total cholesterol, LDL-cholesterol, VLDL- cholesterol and triglycerides and increase in HDL-cholesterol was observed over a period of 24 weeks. The improvement in the lipid profile observed at the end of 24 weeks was as follows; with myo-inositol, triglycerides decreased by 15.27, total cholesterol by 13.03, LDL-cholesterol by 10.13, VLDL-cholesterol by 6.33 and HDL-cholesterol increased by 3.43 at the end of 24 weeks as compared to baseline values. With metformin, triglycerides decreased by 12.87, total cholesterol by 10.57, LDL-cholesterol by 7.7, VLDL-cholesterol by 4.8 and HDL-cholesterol increased by 1.98 at the end of 24 weeks as compared to baseline values. No significant difference could be found in the number of patients in the two treatment groups at the end of 24 weeks.

TABLE 4: COMPARISON OF LIPID PROFILE IN BOTH THE GROUPS

Parameters	Baseline		12 Weeks		24 Weeks	
Lipid profile	Group A	Group B	Group A	Group B	Group A	Group B
Total cholesterol	183.93±2.73	180.83±6.16	176.26±2.50*	174.53±5.66*	170.90±2.73#	170.26±5.25#
Triglycerides	135.93±6.45	136.30±8.94	126.43±6.40*	128.40±8.24*	120.66±6.10#	123.43±7.68#
HDL-C	47.80±0.93	46.96±1.56	49.63±.67*	47.56±1.42*	51.23±.44#	48.90±1.18#
LDL-C	110.56±2.93	108.13±5.08	104.96±2.70*	103.93±4.85*	100.43±2.73#	100.43±4.54#
VLDL-C	25.56±.94	25.73±1.64	21.66±.84*	23.03±1.26*	19.23±.66#	20.93±.99#

All values are expressed as Mean±SEM
Group A: Myo-inositol 1000 mg BD
Group B: Metformin 500 mg TDS
Intragroup Analysis:
*Comparison of values at end of week 12 with baseline values is statistically significant (p<0.05).
#Comparison of values at end of week 24 with baseline values is statistically significant (p<0.05).
Intergroup Analysis:
Comparison of values between Group A and B isnot statistically significant (p>0.05).

DISCUSSION: PCOS is one of the most common endocrine disorders affecting women, it is the most common cause of female infertility and it is characterized by a combination of hyperandrogenism, chronic anovulation and irregular menstrual cycle. [14, 15] In about 50% of patients with PCOS, insulin receptor phosphorylation is impaired. Several trials showed that insulin sensitizer agents, such as metformin and MI, are the first-line treatment to restore normal menstrual cycles in women suffering from PCOS [16-18] suggesting that an endocellular defect of the precursor of IPG such as MI and/or DCI might trigger the compensatory hyperinsulinemia in most PCOS subjects.

Insulin resistance is main causative factor responsible for clinical features in PCOS. Failure of the target cells to respond to normal or ordinary levels of insulin is regarded as insulin resistance irrespective of the BMI. Hyperinsulinemia due to insulin resistance occurs in approximately 80% of obese PCOS women and 30-40% of lean PCOS women.[19] However recent studies suggest that some abnormal action of insulin might be dependent upon inositol phosphoglycan (IPG) mediators of insulin action and suggest that a deficiency in inositol can lead to insulin resistance.[7] Insulin resistance can be assessed by calculating glucose-insulin ratio and HOMA-IR index.

In a study done by Awalekar et al, in which 102 patients were randomized into three groups i.e. metformin (500 mg TDS), myo-inositol (2 gm BD) plus folic acid (5 mg OD) and life style modification group for a period of 12 weeks. HOMA-IR index decreased by 10.64 with metformin ($p < 0.05$), while there was no change with myo-inositol and lifestyle modification. LH/ FSH ratio decreased by 0.86 with metformin, 0.22 with myo-inositol at the end of 12 weeks. [20] The findings of our study are quite similar to above mentioned study as similar reduction in LH/ FSH ratio was seen with myo-inositol in both the studies at the end of 12 weeks.

In both the studies, reduction in LH/ FSH ratio was observed with metformi Ghalat VS n; however reduction was less in our study as compared to above mentioned study (0.52 vs 0.86) at the end of 12 weeks. [20]

In another study done by Leo et al, 60 insulin resistant PCOS patients were randomly assigned into three groups. All groups were treated for 6 months with either myo-inositol (1500 mg BD) and monacolin k (3000 mg BD), inositol only (1500 mg BD) or metformin only (850 mg BD).in which metformin and myo-inositol were compared to observe their effects on HOMA-IR index. The HOMA-IR index significantly reduced by 1.1 and 0.8 with inositol and metformin respectively at the end of 24 weeks.[21] The findings of our study are similar to above quoted study in the sense that both the drugs led to reduction in HOMA-IR index at the end of 24weeks. But in contrary to the above mentioned study decrease was more with metformin in the present study.

In a study done by Angik et al, in which metformin and myo-inositol were compared to observe their effects on FBS, 100 patients were randomly allocated to treatment with either myo-inositol or metformin. Myo-inositol group received 1 g twice daily while Metformin group received 500 mg twice daily for 6 months, in which metformin and myo-inositol were compared to observe their effects on FBS. The fasting blood glucose levels reduced by 0.46 mg/dl in myo-inositol group whereas by 0.10 mg/dl with metformin at the end of 24 weeks.[22]

In a study done by Ali et al, 95 patients were randomly allocated to treatment with three types of treatment i.e. metformin (850 mg BD), choline & inositol (500/500 BD) plus metformin and life style modification and diet control for a period of 6 months. The value of HOMA-IR reduced by 2.98 in metformin group whereas by 2.78 with choline & inositol plus metformin and by 1.98 with life style modification at the end of 24 weeks.23 The findings of our study are similar to above quoted study in the sense that both the drugs led to reduction in HOMA-IR index at the end of 24 weeks.

In study done by Genazzani et al, in 20 PCOS patients, who were randomly assigned to receive either myo-inositol 2000 mg plus folic acid 200 µg daily or folic acid 200 µg daily for a period 12 weeks changes in HOMA-IR were observed. HOMA-IR decreased by 1.4 with myo-inositol group ($p<0.01$) and by 0.1 with folic acid. [24]

The findings of our study are quite similar to this study as there was decrease in HOMA-IR index in both the studies with myo-inositol. However the decrease in our study was less as compared to above mentioned study i.e. 0.66 vs 1.4 at the end of 12 weeks. The reason could be due to the fact that small sample size was taken in study done by Genazzani et al.

In a study done by Costantino et al, in which 42 women with PCOS were treated in a double blind trial with myo-inositol (4 gm) plus folic acid (400 µg) or folic acid (400 µg) alone as placebo for 12 weeks. The fasting blood glucose levels were reduced by 6 mg/dl at the end of 6-8 week in myo-inositol group whereas there was no effect in the placebo group. The triglycerides levels were reduced by 100 mg/dl (52%) and total cholesterol was also reduced significantly by 39 mg/dl at the end of 12 weeks in myo-inositol group whereas there was not much effect in the placebo group.[25] The findings of our study are similar to the above mentioned study as there is reduction in fasting blood glucose, total cholesterol and triglycerides levels with myo-inositol in both the studies. However the reduction was more in above mentioned study. The reason could be due to the fact that double dose of drug was used in above study.

In a study done by Papaleo et al, twenty-five PCOS women were given myo-inositol combined with folic acid 2 gm twice a day for a period of 6 months. It was observed that testosterone levels reduced by 50.4 at the end of six months. [26] The findings of our study are similar to above quoted study due to the fact that testosterone levels were reduced in both the studies. However decrease in the level of testosterone is much more in above study as compared to present study (50.4 vs 6.46). This could be due to the fact that dose of myo-inositol prescribed in above study is double of that used in our study.

Both the drugs led to improvement in biochemical profile over the period of 24 weeks. As the difference in all these parameters after 6 months of respective treatment in both the groups was found to be statistically non-significant, thus, myo-inositol may be considered comparably effective to metformin in treatment of PCOS. Though the sample size and study duration was small in this study, further research with larger groups and longer study periods is required to support these findings.

CONCLUSION: Metformin and myo-inositol significantly improved insulin sensitivity in PCOS women. It was associated with improvement in insulin sensitivity in HOMA-IR defined insulin resistant patients. Metformin did very well in all aspects we studied, so it can be used as first line therapy in PCOS. Both the treatment groups i.e. MI and metformin were found to be almost equally effective in improving biochemical profile.

Hence, Myo-inositol can be a new addition in the armamentarium for the treatment of PCOS with comparable efficacy.

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CONFLICT OF INTEREST: All the authors declare that there is no conflict of interest.

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