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Original Research Article

Comparison of effects of metformin and inositol on AMH levels in PCOS patients

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ABSTRACT

Background: PCOS is very common problem. Insulin resistance is an integral part of PCOS. AMH level in women with PCOS are 2-3 times higher than in healthy women. In PCOS patients, there is excess amount of AMH and its physiological effect lasts longer than it should in larger follicles, leads to arrest of dominant follicle selection.

Methods: It was a prospective, interventional randomized clinical trial, a single tertiary center study over a period of 8 months. Cases with the documented PCOS were taken into account and divided into 2 groups, group A and group B randomly by alternate assigning of patients. Group A was given metformin and group B was given inositol. Group A was given metformin 850 mg twice daily orally and group B was given myo-inositol 1100 mg +D chiro inositol 27.6 mg plus 100 pg folic acid once daily for 12 weeks.

Results: AMH levels were reassessed after 12 weeks of period and changes in the levels of AMH were compared. In metformin group total number of patients were 86 of which 84 patients (97.7%) showed decrease in AMH levels while 2 patients (2.33%) did not show any changes. In inositol group total number of patients were 87 of which 53 patients (60.91%) showed decrease in AMH levels while 34 patients (39.1%) did not show any changes. There was a significant difference between the groups in terms of distribution of decrease in AMH ($\chi^2=35.454$, $p<0.001$).

Conclusions: As compared to Inositol group there were more patients who had decrease in AMH levels in metformin group. Hence, metformin is better than inositol in decreasing AMH levels in PCOS patients.

Keywords: AMH, Inositol, Metformin, PCOS

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most frequently encountered endocrine disorders affecting women of reproductive age. According to the Rotterdam criteria developed in 2003, PCOS is diagnosed if two out of the three following features are fulfilled: chronic oligo- or anovulation, anatomically polycystic ovaries on ultrasonography, and clinical and/or biochemical hyperandrogenism.¹

It is proposed that insulin resistance and hyperinsulinemia are the main culprits for anovulation and infertility in PCOS patients. Hyperandrogenism, and increase AMH levels are also associated with PCOS. AMH is a dimeric

glycoprotein belonging to the transforming growth factor beta family, expressed by the granulosa cells of the pre-antral and small antral follicles in the ovary.²

AMH is significantly higher in women with PCOS due to an increased number of antral follicles and also higher ratio of AMH per antral follicle (AMH/AF).³ Serum AMH levels correlate with the severity of hyperandrogenism and oligo/an-ovulation. Hence, it has been suggested that serum AMH levels may also be considered to replace these criteria for the diagnosis of PCOS.

Although not included as criteria, insulin resistance and hyperinsulinemia are important etiologic factors associated with the typical clinical signs and hormonal

disorders of PCOS. It has been proposed that hyperinsulinemia could adversely influence ovulatory function in women by acting at both pituitary and ovarian levels, which has been demonstrated by higher insulin level in women with PCOS lowering the probability of spontaneous ovulation.⁴

HOMA-IR (homeostatic model assessment of insulin resistance) is method of assessing β -cell function and insulin resistance from basal fasting glucose or insulin or C-peptide concentrations (we are considering insulin levels). HOMA-IR is calculated by formula: $\text{HOMA-IR} = \text{Fasting insulin} \times \text{Fasting glucose} / 405$.⁴

Metformin is the most commonly used hypoglycemic agent belonging to biguanide class. It improves ovulatory function and hence clinical pregnancy rates in women with PCOS.⁵

A newer insulin sensitizer recently introduced for the treatment of women with PCOS, Inositol (hexahydroxy cyclohexane) belongs to the vitamin B complex group; It is a nutritional supplement. A recent study has shown a deficiency of myoinositol in PCOS patients with increased insulin resistance and the administration of myoinositol reduces serum insulin, decreases serum testosterone, and enhances ovulation.⁶

On extensive search of literature, we could not find many studies which evaluated inositol alone or compared it with Metformin in regard to AMH levels and androgen levels. This lacuna in literature prompted this study

Both of these modalities i.e., metformin and myoinositol, are in use currently but they have not been compared in juxtaposition. In this comprehensive study we have attempted to compile multiple variables like effect of both these drugs in reducing the two notorious factors hyperandrogenism and insulin resistance along with the change in AMH levels. We also have tried to find out reduction in weight i.e. change in BMI, change in serum testosterone levels, and change in HOMA-IR values, which were studied separately in literature.

METHODS

It was a prospective, interventional randomized clinical trial, a single tertiary centre study carried in Max Smart Super Specialty Hospital, Mandir Marg, Press Enclave, New Delhi for the period of 8 months (recruitment of patients done from November 2020 to June 2021) after ethical clearance. After taking well-informed consent, Patients visiting Max smart Super Specialty hospital between 18-35 years were investigated for PCOS as per ROTTERDAM criterion 2003. Patients were excluded if they presented with hyperprolactinemia, thyroid disorders, late-onset congenital adrenal hyperplasia, Cushing's syndrome, PCOS patients with AMH<5, PCOS patients

with contraindication to insulin sensitizer such as metformin to prior adverse effects or hypersensitivity to inositol, usage of OCP or any other insulin sensitizer for previous 3 months, pregnancy and those who were not giving consent.

173 confirmed PCOS patients according to ROTTERDAM criterion 2003, visiting Max smart super-specialty hospital OPD were recruited and assessed with the following parameters: weight, BMI, AMH levels, free serum testosterone levels, fasting blood sugar, fasting insulin levels, HOMA-IR.

Two groups were formed group A and group B randomly by alternate assigning of patients. Group A was given metformin and group B was given inositol. 1) Metformin 850 mg/ twice a day orally (n=86). 2) Myoinositol 1100 mg +D chiro inositol 27.6 mg plus 100 pg folic acid daily (n=87).

Same parameters were reassessed after treatment with these drugs for a period of 12 weeks, and comparison was done for all these parameters.

RESULTS

Here Table 1 summarizes the baseline parameters in both groups. Patients were almost equally distributed in both groups. Group A had 86 patients and group B had 87 patients. There was no significant difference between the groups in terms of age distribution ($W=4046.000$, $p=0.353$) and weight distribution ($t=1.888$, $p=0.061$) BMI (Kg/m^2) distribution ($t=1.582$, $p=0.116$).

There was a significant difference between the groups in terms of distribution of decrease in AMH ($\chi^2=35.454$, $p<0.001$). As compared to inositol group, more patients had a decrease in AMH levels in the metformin group, Hence, metformin is better than inositol in decreasing AMH levels in PCOS patients. There was a significant difference in the trend of fall in AMH (ng/ml) over time between the two groups ($p<0.001$).

There was no significant difference in the trend of fall in serum free testosterone in 12 weeks between the two groups ($p=0.238$).

The difference in the initial levels of fasting blood sugar was not significant but the difference in the post treatment levels was statistically significant with metformin being more effective ($p=0.032$).

There was no significant difference in the trend of fall in fasting insulin over time between the two groups ($p=0.056$). There was a significant difference between the groups in terms of distribution of decrease in fasting insulin ($\chi^2=4.124$, $p=0.042$).

Table 1: Baseline characteristics of the study groups.

Characteristics	Metformin (n=86)	Inositol (n=87)	P value
Age (mean)	26.83 years (3.88)	26.24years (4.23)	0.353
Weight (mean)	67.95 (9.35)	65.41 (8.29)	0.061
BMI (mean)	27.20 (3.55)	26.44 (2.68)	0.116
AMH (mean)	7.82 (2.55)	6.77 (2.33)	0.001
Free serum testosterone (mean)	0.86 (0.49)	0.96 (0.54)	0.192
Fasting blood sugar (mean)	101.54 (14.45)	97.26 (12.47)	0.045
Fasting serum insulin	14.06 (6.36)	12.31 (4.87)	0.154
HOMA-IR	3.53 (1.71)	2.94 (1.14)	0.034

n= numbers of women, BMI= body mass index, AMH = Anti Mullerian hormone, HOMA IR= homeostatic model assessment of insulin resistance.

Table 2: Effects of metformin and inositol on AMH levels and on free serum testosterone.

	Metformin (n=86)		Inositol (n=87)		P value
	Baseline	12 weeks	Baseline	12 weeks	
AMH	7.82 (2.55)	5.06 (2.37)	6.77 (2.33)	6.21 (2.45)	<0.001
Free serum testosterone	0.86 (0.49)	0.69 (0.33)	0.96 (0.54)	0.74 (0.30)	0.238

Table 3: Effects of metformin and inositol on fasting blood sugar, fasting serum insulin and HOMA-IR.

	Metformin (n=86)		Inositol (n=87)		P value
	Baseline	12 weeks	Baseline	12 weeks	
FBS	101.54 (14.45)	94.29 (9.25)	97.26 (12.47)	93.73 (8.13)	0.032
Fasting Insulin	14.06 (6.36)	9.21 (2.43)	12.31 (4.87)	9.01 (2.80)	0.056
HOMA-IR	3.53 (1.71)	2.14 (0.66)	2.94 (1.14)	2.07 (0.64)	0.009

Table 4: Effects of metformin and inositol on weight and BMI in PCOS patients.

	Metformin (n=86)		Inositol (n=87)		P value
	Baseline	12 weeks	Baseline	12 weeks	
Weight	67.95 (9.35)	65.68 (9.01)	65.41 (8.29)	63.29 (8.22)	0.430
BMI	27.20 (3.55)	26.35(3.37)	26.44 (2.68)	25.56 (2.70)	0.819

Metformin group had the larger proportion of patients with decrease in fasting insulin rather than patients in the Inositol group. There was a significant difference in the trend of HOMA-IR in 12 weeks between the groups ($p=0.009$) metformin being more effective. After treatment here according to number of participants with decrease in HOMA-IR were statistically significant in each group and there was no significant difference seen between the groups. But in terms of overall change in HOMA-IR there was a significant difference between the groups. Metformin group showed better changes in HOMA-IR in spite it was given in patients with higher HOMA-IR as compared to inositol group.

There was no significant difference in the trend of change in weight over time between the two groups ($p=0.430$). In inositol group total number of patients were 87, of which 85 (97.70%) patients showed decrease in weight while in 2 (2.29%) patients there was no weight reduction. There

was no significant difference between the groups in weight reduction (kg) ($\chi^2=0.218$, $p=0.682$).

There was no significant difference in the trend of change in BMI in 12 weeks between the two groups ($p=0.819$).

DISCUSSION

Insulin-sensitizers such as metformin and inositol have been shown to improve the endocrine and metabolic aspects of PCOS. In this study we have compared their effects on the clinical and metabolic features of women with PCOS.

In our study, we had 86 patients in the metformin group and 87 patients in the Inositol group, hence the distribution was equal. As far as the age distribution was concerned both groups indicated similarity (group A- 26.83 years and Group B- 26.24 years, $p=0.353$)

The decrease in weight in both the groups was statistically significant after 12 weeks of treatment but the difference between the two groups was not statistically significant ($p=0.430$). In study undertaken by Tagliaferri et al did not result in significant changes.⁷

After treatment for 12 weeks 80 (93%) patients in the Metformin group and 84 (96.6%) patients in Inositol group had a reduction in BMI ($\chi^2=1.092$, $p=0.329$). The change in BMI in both the groups was statistically significant ($p<0.001$) without any significant difference between the groups ($p=0.819$). Similar results were obtained in study done by Fruzzetti et al and by Nehra et al and by Riju Angik et al.⁸⁻¹⁰ In study by Grigoryan et al there was a decrease in BMI but they did not compare the effects with Inositol.¹¹

In our study after treatment the mean AMH levels came down and this fall in AMH levels between the two groups was statistically significant with metformin having an advantage ($p<0.001$). In the study Grigoryan et al there was no effect of metformin on AMH levels even after giving it for longer duration.¹¹ However, in a study done by Ahmed et al, Valeria Tagliaferri et al AMH levels were significantly decreased after treatment with metformin.^{7,12}

While in study by Nascimento et al treatment with metformin (1500 mg/day) for a shorter duration of 8 weeks had not shown any changes on AMH levels.¹³ In contrast a study by Foroozanfar et al had shown decrease in AMH with metformin even in the shorter duration of 8 weeks with lesser dose (1500 mg/day) but only in patients with higher BMI (>30 kg/m²).¹⁴

In our study free serum testosterone levels decreased in both the groups. it was not statistically significant when both the groups were compared with each other ($p=0.238$).

In contrast to our results a study by Sukhmani Jaura et al elicited a significant decrease in free serum testosterone levels with Inositol (1000 mg twice daily) however they used lesser dose of metformin (500 mg twice daily).¹⁵

In our study fasting blood sugar levels decreased in both the groups with metformin being more effective ($p=0.032$). This difference was statistically significant.

In study by Shokrpour et al PCOS patients were randomly assigned to receive either metformin 500 mg three times a day or inositol 2 gm twice daily for a period of 12 weeks.¹⁶ Fasting plasma glucose were significantly decreased with inositol. This is in contrast to our study because we used higher doses of metformin (1700 mg versus 1500 mg) and they used higher dose of Inositol (1 gm versus 4 gm) as compared to our study.

In recent study by Bahadur et al no significant difference was seen between two groups in terms of Fasting blood glucose level.¹⁷

In our study in terms of fasting insulin levels more participants (89.5%) in metformin group showed fall in fasting insulin level, as compared to inositol group (78.2%). This difference was statistically significant being the metformin more effective ($p=0.042$).

In a study done by Angik et al fasting insulin levels were decreased only on treatment with inositol.¹⁰ As compared to our study they have given Inositol on same doses for longer duration (6 months). In this study metformin group was given lesser dose (500 mg twice daily) than our study.

In a study done by Nehra et al on comparing metformin and inositol there was a significant improvement in fasting insulin levels.⁹ A different study done by Bahadur et al no significant difference was seen between two groups in terms of Fasting insulin levels.¹⁷

In our study, in metformin group 79 (91.9%) patients and in Inositol group 75 (86.2%) patients showed improvement in HOMA-IR. However, the quantitative fall in HOMA-IR was better in the metformin group. There was a significant difference in the trend of HOMA-IR improvement between the two groups ($p=0.009$).

Similar results were seen in a study done by Fruzzetti et al and Nehra et al but their study covered 6 months.^{8,9} In a study done by Angik et al and Zeng et al results showed improvement in HOMA IR with Inositol.^{10,18}

In a study done by Shokrpour et al inositol supplementation significantly reduced HOMA IR compared with metformin.¹⁶ They used higher dose of Inositol (1 gm versus 4 gm) as compared to our study.

Owing to the short period for our study we could not comment over responses on hyperandrogenic features like acne, hirsutism and acanthosis as well as DHEA-S levels because these parameters take time to resolve.

CONCLUSION

Patients in the both groups were adequately matched with respect to the age at presentation, weight and symptoms. Both groups showed significant decrement in weight, BMI and Free serum testosterone individually after the treatment but there was no significant difference between these two groups. Both groups showed fall in AMH level after 12 weeks but this fall in AMH levels between the two groups was statistically significant with metformin having an advantage.

As far as menstrual outcome concerns metformin group showed better menstrual outcome in comparison to inositol. In terms of reduction in fasting blood glucose and fasting insulin levels both groups showed significant reduction but metformin lowered the levels in larger participants in comparison to inositol group. Both the drugs were effective in reducing HOMA IR but metformin was more potent in improving HOMA IR values.

Metformin believed to cause improvement in signs related to hyperandrogenism like hirsutism, acne and acanthosis in many studies, however in our study we could not justify improvement in some signs like hirsutism and acanthosis due to sparsity of time duration.

The results of present study indicate that both metformin and myoinositol led to improvement in anthropometric parameters over the period of 12 weeks. As the difference in all these parameters found to be statistically non-significant when compared, hence myoinositol can be considered comparable to Metformin in the treatment of PCOS. Though the sample size and study duration were small in this study, further research with larger groups and longer study period is required to support these findings.

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

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