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Original Research Article

A comparative study of combination of Myo-inositol and D-chiro-inositol versus Metformin in the management of polycystic ovary syndrome in obese women with infertility

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a symptom complex associated with increased amounts of circulating androgens in females, increased insulin resistance and obesity. The drugs, Myo-inositol, D-chiro-inositol and Metformin, which are insulin sensitizers, are very helpful in taking care of one of the key components of PCOS that is insulin resistance. This study was done to compare the effects of combination of Myo-inositol and D-chiro-inositol with the use of metformin on clinical and biochemical profile in PCOS.
Methods: A prospective, randomized, comparative study was conducted on 200 patients. The patients were randomly assigned into the two groups of 100 each. Group A receiving Tab. Myoinositol 550mg twice daily and Tab. D-chiro-inositol 13.8mg twice daily and Group B receiving Tab. Metformin 500mg thrice daily. The patients were assessed by menstrual cycle regulation, hirsutism score (Ferriman Gallwey), fasting and post prandial glucose and insulin levels, serum DHEA levels, serum free testosterone levels and fasting day 3 serum LH and FSH ratio.
Results: In both the groups there was significant improvement in all the above mentioned parameters, however the group with Combination of Myo-inositol and D-chiro-inositol had statistically significant improvement over the Metformin group.
Conclusions: Combination of Myo-inositol and D-chiro-inositol and use of metformin, significantly improved insulin sensitivity in PCOS women. But combination of Myo-inositol and D-chiro-inositol was effective in controlling the hormonal profiles (LH/FSH ration and free testosterone) when compared to Metformin.

Keywords: D-chiro-inositol, Hirsutism score, Insulin resistance, Myo-inositol, Polycystic ovary syndrome

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a complex heterogenous reproductive endocrine disorder affecting women throughout their lifetime. PCOS affects about 116 million women worldwide (3.4% of women) and even reaches up to 14.6% according to Rotterdam criteria.[1,2] The prevalence in India is reported between 3.7% and 22.5% with 9.13 to 36% in only adolescents.[3] Infertility is the major concern posed by PCOS, due to oligo/anovulation. Hence this hidden epidemic has become an important public health issue in India, which is not only a reproductive endocrine disorder, but also associated with insulin resistance and associated metabolic disorders and future high risk for cardiovascular events and malignancies.[4] PCOS is primarily a disorder associated with increased amounts of circulating androgens in females, increased insulin

resistance and Obesity. The syndrome was first described by American Gynaecologist Irving F. Stein Sr. and Michael L. Leventhal, in 1931. The Rotterdam definition extended the diagnosis of PCOS to women with oligoovulation and polycystic ovaries (non-hyperandrogenic) as well as to women with hyperandrogenism and polycystic ovaries (ovulatory). Despite its pathophysiology being elusive, the role of Insulin resistance as the main cause in addition to genetic and environmental causes. Insulin resistance is presumed to be caused by defects in the insulin receptor and post receptor components of the insulin signalling pathway.[5,6]

Metformin is a biguanide, an oral diabetic agent used often as first line treatment of diabetes. It improves hyperglycemia primarily through its suppression of hepatic glucose production (hepatic gluconeogenesis) via activation of AMP-activated protein kinase (AMPK), a liver enzyme that plays an important role in insulin signalling, whole body energy balance, and the metabolism of glucose and fats.[7] In addition to suppressing hepatic glucose production, metformin increases insulin sensitivity, enhances peripheral glucose uptake, increases fatty acid oxidation, and decreases absorption of glucose from the gastrointestinal tract. Increased peripheral utilization of glucose may be due to improved insulin binding to insulin receptors. AMPK most likely also plays a role as metformin administration increases AMPK activity in skeletal muscle. AMPK is known to cause glucose transporter GLUT4 deployment to the plasma membrane, resulting in insulin-independent glucose uptake.

Myoinositol (MI) and D-chiro inositol (DCI) are isomeric forms of inositol that were found to have insulin-like properties, acting as second messengers in the insulin intracellular pathway; both of these molecules are involved in the increasing insulin sensitivity of different tissues to improve metabolic and ovulatory functions.[8–10] Myoinositol is the predominant form that can be found in nature and food. It is produced by the human body from D-glucose, but it is present in all living cells as membrane phospholipids and phytic acid. In food it is contained especially in pulses (beans, grains, and nuts) and fruits (in particular citrus fruits).

DCI and MI have different physiological roles since the former is crucial for glycogen synthesis while the latter increases cellular glucose uptake.[11] Each tissue has its own MI/DCI ratio, which is maintained through the conversion of myoinositol to D-chiro inositol occurring in tissues expressing the specific epimerase. High DCI levels are present in glycogen storage tissues, such as fat, liver, and muscle, whereas very low levels of DCI are typical of tissues with high glucose utilization, such as the brain and heart.[12,13]

Indeed, deficiency or abnormalities in inositol metabolism induce a defect in glucose uptake and have been linked to insulin resistance and long term microvascular complications of diabetes.[14] Depletion of intracellular myoinositol along with lower level of chiro inositol, have been frequently observed in type II diabetic patients and in other conditions associated with insulin resistance, such as polycystic ovary syndrome, gestational diabetes, and metabolic syndrome. In general, certain data suggest that chiro inositol deficiency or imbalance is related more directly to insulin resistance itself, rather than to type II diabetes.

METHODS

The present study was a prospective, randomized, comparative clinical study conducted in the Department of Obstetrics and Gynaecology, Narayana Medical College, Nellore. The study was conducted on 200 patients, from August 2017 to October 2018. An informed consent was obtained from all patients enrolled for the study. An adequate number of patients were screened and selected as per the inclusion and exclusion criteria for the study. 200 eligible patients were alternating, assigned into two study groups i.e. Group A (combination of Myo-inositol and D-chiro-inositol) and Group B (Metformin). Each study group had minimally 100 patients who completed the study as per the protocol.

Inclusion criteria

- Females of reproductive age group (15-45 years), 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 (2-9mm in diameter) or ovarian volume >10ml and those willing to give a written informed consent.

Exclusion criteria

- 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, inability to come for regular follow ups.

All eligible patients were alternatively assigned into two groups of 100 each to receive either of the following two treatments: Group A: Tab Myo-inositol 550mg+D-chiro-inositol 13.8mg twice daily and Group B: Tab Metformin 500mg thrice daily, for 6 months. Hormonal parameters like insulin, LH/FSH ratio, serum free testosterone and parameters for insulin resistance, HOMA-IR (homeostatic assessment for insulin resistance) 13 and glucose/ insulin ratio were assessed at baseline, at the end of 12 and 24 weeks.

Statistical analysis

Data was expressed as Mean±SEM unless specified otherwise. Both intra group and intergroup statistical analysis was done. Intra group analysis for repeated measures was done using Epi-info. Intergroup analysis was done using unpaired 't' test. A p-value <0.05 was considered as statistically significant.

RESULTS

Of the 200 patients enrolled in the study, 100 were allocated to Group A and 100 allocated to Group B and completed the treatment successfully. The baseline characteristics of the patients are tabulated in Table 1.

Table 1: Study population characteristics.

	Group A (n=100)	Group B (n=100)
Age in years	24±4	23±4
Weight in kg	74±7.5	73±5.0
Age at menarche	13±1	13±1
H/o drug allergy	0	0

Tables 2 and 3 show the fasting blood sugar, fasting insulin, glucose-insulin ratio, HOMA-IR, LH/FSH ratio and free testosterone in Myo-inositol + D-chiro-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 in both the groups, at the end of 24 weeks, as compared to baseline values.

In Myo-inositol + D-chiro-inositol group, the glucose-insulin ratio increased by 1.20 and HOMA-IR decreased by 1.32, while in the metformin group, the glucose-insulin ratio increased by 1.03 and HOMA-IR decreased by 1.10, at the end of 24 weeks, as compared to baseline values.

There was statistically significant improvement in hormonal parameters as assessed by changes in DHEA, FSH, LH, LH/FSH ratio and testosterone levels with Myo-inositol and D-chiro-inositol group, over a period of 24 weeks. In Myo-inositol + D-chiro-inositol group, the DHEA level decreased by 76mcg/dl, the LH/FSH ratio and testosterone decreased by 0.82 and 2.90 respectively, while in metformin group, the DHEA level decreased by 30mcg/dl, the LH/FSH ratio decreased by 0.35 and testosterone by 0.840 at the end of 24 weeks as compared to baseline values.

Tables 4 and 5 show the Clinical paramaters, that is Menstrual cycle Length, regularity of menstrual cycle and hirsutism score in Myo-inositol + D-chiro-inositol and metformin treated patients, respectively, at different time periods in the study. There was statistically significant improvement in Myo-inositol + D-chiro-inositol group, over a period of 24 weeks, when compared to Metformin group. In Myo-inositol + D-chiro-inositol group, the menstrual cycle length decreased by 7 days, percentage of women with regular menstrual cycles increased by 20% and hirsutism score decreased by 6 points respectively, while in metformin group, the menstrual cycle length decreased by 7 days, percentage of women with regular menstrual cycles increased by 12% and hirsutism score decreased by 1 point, respectively, at the end of 24 weeks, as compared to baseline values.

Table 2: Biochemical parameters in Myo-inositol + D-chiro-inositol group.

	Baseline	12 weeks	24 weeks	p value
Fasting blood sugar in mg	96±8	86±5	80±4	<0.05
Fasting insulin	19.12±1.2	16.84±1.4	12.86±1.1	<0.05
Glucose/insulin ratio	5.02±0.66	5.10±0.35	6.22±0.36	<0.05
HOMA-IR	3.96±0.23	3.24±0.28	2.64±0.21	<0.05
DHEA in mcg/dl	140±60	100±47	64±33	<0.05
LH/FSH	2.85±0.41	2.47±0.25	1.83±0.11	<0.05
Free Testosterone in pg/ml	6.4±1.3	4.8±1.4	3.5±0.8	<0.05

Table 3: Biochemical parameters in Metformin group.

	Baseline	12 weeks	24 weeks	p value
Fasting blood sugar in mg	94±7	87±6	82±4	<0.05
Fasting insulin	19.03±1.3	17.24±0.7	14.46±0.4	<0.05
Glucose/insulin ratio	4.94±0.19	5.26±0.15	5.97±0.36	<0.05
HOMA-IR	3.93±0.36	3.35±0.46	2.83±0.31	<0.05
DHEA in mcg/dl	133±54	120±51	103±49	>0.05
LH/FSH	2.87±0.28	2.68±0.37	2.52±0.11	>0.05
Free Testosterone in pg/ml	6.2±1.5	5.7±1.1	5.4±0.9	>0.05

Table 4: Clinical parameters in Myo-inositol + D-chiro-inositol group.

	Baseline	12 weeks	24 weeks	p value
Menstrual cycle length	42±5	36±5	31±3	<0.05
% of women with regular menstrual cycles	36%	42%	56%	>0.05
Hirsutism score (FG)	18±4	16±2	12±3	<0.05

Table 5: Clinical parameters in Metformin group.

	Baseline	12 weeks	24 weeks	p value
Menstrual cycle length	43±5	39±2	36±3	>0.05
% of women with regular menstrual cycles	38%	43%	46%	>0.05
Hirsutism score	18±4	18±3	17±1	>0.05

Intergroup analysis

Comparison of values between Group A and B, in relation to the hormonal profiles, is 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] In about 50% of patients with PCOS, insulin receptor phosphorylation is impaired. Several trials showed that insulin sensitizer agents, such as metformin and Myo-inositol, are the first-line treatment to restore normal menstrual cycles in women suffering from PCOS 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.[15,16] D-chiro inositol accelerated glucose disposal and activated glycogen synthase in muscle biopsies beyond that of maximal insulin stimulation.[17]

Insulin resistance is the 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.[18] 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. Insulin resistance can be assessed by calculating glucose-insulin ratio and HOMA-IR index.

In a study done by Pintadi B et al, in which they concluded that Myo-inositol and D-chiro-inositol are very effective in Control of insulin resistance.[19]

Various studies have been conducted comparing Myo-inositol with Metformin in obese women with infertility. In a study done by Awalekar et al, in which 102 patients were randomized into three groups i.e. Metformin (500mg TDS), Myo-inositol (2g BD) plus Folic acid (5mg 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]

Present study was directed towards comparing the use of Myo-inositol and D-chiro-inositol compared to Metformin alone where in, both the drugs led to statistically significant improvement in insulin resistance, over the period of 24 weeks, but the hormone profile (LH/FSH ratio and free testosterone) was well controlled in the Myo-inositol and D-chiro-inositol group. As 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

Combination of Myo-inositol and D-chiro-inositol and use of metformin, significantly improved insulin sensitivity in PCOS women. It was associated with improvement in insulin sensitivity in HOMA-IR defined insulin resistant patients. But combination of Myo-inositol and D-chiro-inositol was effective in controlling the hormonal profiles (LH/FSH ratio and free testosterone) when compared to Metformin.

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

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