Original Article

Efficacy Of Insulin Sensitizers Metformin, Pioglitazone And Combination Myo-Inositol (MI) Plus D-Chiroinositol (DCI) Plus Folic Acid In Women With Polycystic Ovary Syndrome: A RCT

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Abstract

Background

One of the most widespread endocrine disorders in women is Polycystic Ovary Syndrome (PCOS). There are many abnormalities associated with PCOS, such as hyperandrogenism, chronic anovulation, and hyperinsulinemia.

Objective

The aim of the study was to examine the effects of Metformin, Pioglitazone, and the combination of Myo-inositol (MI) (MI) and D-chiroionsitol (DCI) on PCOS-related parameters in female patients.

Methodology

96 PCOS-afflicted women (aged 18–40) were given either Group A: oral Metformin (500 mg, three times daily), Group B: oral Pioglitazone (30 mg), or a Group C combination of Myo-inositol (MI) and D-chiroionsitol (DCI) for three months. The levels of total testosterone, menstrual cycle length, fasting blood glucose, and fasting insulin were assessed both before and after treatment.

Results:

Significant decreases were seen after treatment with all the three groups. However, when all the three groups where compared Combination of Myo-inositol (MI) and D-chiroinositol had statistically significant improvement over the other two groups.

Conclusion:

In PCOS patients, Pioglitazone, Metformin, and the combination of Myoionsitol and D-Chiroionsitol significantly improve symptoms indices. Despite the fact that we were unable to recommend one treatment plan over another, Myoionsitol plus D-Chiroionsitol is a helpful alternative for PCOS patients who are unable to tolerate or respond to Metformin and Pioglitazone.

INTRODUCTION:

Polycystic ovarian syndrome (PCOS) is the most prevalent and heterogeneous endocrinological disorder affecting 4-21% of females of childbearing age worldwide (1, 2). The characteristic features of PCOS are ovarian dysfunction, anovulation, and hyperandrogenism. These characteristics are preceded by metabolic disorders such as insulin resistance, hyperinsulinemia, and obesity. Long-term effects of PCOS on general health include an increased risk of endometriosis, type II diabetes, and cardiovascular issues (3, 4).

The pathogenesis of PCOS may be significantly influenced by insulin resistance and hyperinsulinemia (5). It has been reported that insulin resistance and subsequent hyperinsulinemia play a significant role in hyperandrogenism through direct mechanisms such as initiation of androgen production by theca cells and indirect mechanisms such as increased luteinizing hormone (LH) secretion, decreased insulin-like growth factor (IGF) binding protein, and decreased hepatic synthesis of sex hormone binding globulin (SHBG), and subsequently free androgen level augmentation (6, 7). Because of a gonadotropin secretory disorder, hyperinsulinemia and insulin resistance in PCOS patients seem to mimic or worsen hyperandrogenism (8).

Given that there is a link between PCOS and hyperinsulinemia, it is recommended that drugs that improve insulin sensitivity and ovarian activity be used to treat this syndrome (9). Several randomized trials have concentrated on two types of insulin-sensitizing medications for the treatment of PCOS in women. Metformin and thiazolidinedione (TZD) (troglitazone, rosiglitazone, Pioglitazone) are standard medications for the treatment of type 2 diabetes (10). They work by decreasing insulin resistance, enhancing insulin sensitivity in peripheral tissues, lowering free testosterone levels, and enabling normal regular menstruation and pregnancy (11). Metformin decreases hepatic glucose production and lipogenesis while increasing peripheral glucose uptake and decreasing fatty acid oxidation. As a peroxisome proliferator-activated receptor agonist, Pioglitazone reduces insulin resistance in the liver and peripheral tissue while also having anti-arteriosclerotic and anti-inflammatory properties (12, 13).

Inositols are a current addition to insulin sensitizers, with Myo-inositol (MI) being the one with the most research. It functions as a post-receptor mediator (second messenger) of the insulin signal and lowers hyperinsulinemia through the membrane-associated sodium-dependent inositol co-transporter GLUT4. Myo-inositol (MI) enhances ovulation, reduces the ratio of luteinizing hormone to follicle stimulating hormone (LH/FSH), lowers serum androgens, raises sex hormone binding globulin (SHBG), and lowers total and free testosterone levels in the blood (14).

Recent findings on PCOS patients found that Myo-inositol (MI) and D-chiro-inositol (DCI), another stereoisomeric form of inositol, reduced androgen levels while improving ovulation and metabolic changes (15). It was emphasized that very promising results were obtained when Myo-inositol (MI) and D-chiroinsitol were administered at their physiological range in plasma (i.e., 40 : 1) to help assure better clinical outcomes in PCOS therapy (15).

Thus far, few research has been done on the treatment of PCOS with Metformin and Pioglitazone, as well as studies comparing Metformin alone with a combination of Myo-inositol (MI) and D-chiro-inositol (16, 17).

The current research sought to compare the PCOS symptoms after treatment with Metformin and Pioglitazone. The specific goal was to determine whether the combination of Myo-inositol (MI) and D-chiro-inositol would be more effective than either drug alone in improving menstrual regularity, hyperandrogenemia, and hyperinsulinemia.

MATERIAL AND METHODS:

Between March 2022 and October 2022, 96 women with PCOS, aged 18-40 years old, with irregular menstruation and/or clinical signs of hyperandrogenism (hirsutism and acne) were recruited from the Department of Gynecology at a Tertiary hospital in Karachi. All participants provided written informed consent. The Ethics Committee approved the research protocol.

All patients experienced sudden puberty and normal sexual development and did not use oral contraceptives or anti-androgens. Furthermore, none of the patients had taken any drugs that affected their hormonal profile, lipoprotein or glucose metabolism, or appetite for at least three months prior to the start of the study.

According to the 2003 Rotterdam Consensus Conference, the diagnosis of PCOS was based on at least two of the three following abnormalities: 1) Oligomenorrhoea or amenorrhea; Oligomenorrhea was defined as a 35-day menstrual cycle. Secondary amenorrhea was defined as a six-month absence of menstruation. 2) Hyperandrogenism manifestations such as hirsutism (Ferriman-Gallwey Score 8), acne, and/or serum total testosterone greater than 70 ng/dL, 3) Ultrasonography confirms polycystic ovaries; presence of 12 or more subcapsular follicles measuring 2-9 mm in diameter at least in one ovary or increased ovarian volume (>10 cm3)(18).

Before and after three months of treatment, venous blood samples were collected after a 10-12h overnight fast to measure fasting insulin, fasting blood glucose and total testosterone in the early follicular phase (day 3-5) of spontaneous bleeding or progestin-induced withdrawal bleeding.

Study Design:

During three months, 96 PCOS women were randomly assigned to one of the following groups: Group A consisted of 32 patients who received 500 mg Metformin (t.i.d) with meals, Group B of 32 patients who received 30 mg Pioglitazone (daily), and Group C of 32 patients who received a combination of Sachet Myo-inositol (MI) 1100mg + D-chiroinositol 300mg + Folic acid 300mcg twice daily.

Prior to the start of the study, all patients were randomly assigned to one of three groups using a computer program that generates random numbers. All subjects were given a sealed envelope with the number A or B or C on it, which represented Metformin, Pioglitazone, and combination therapy, respectively. Because commercially available pills were used in our study, there was no blinding after randomization, so both the investigator and the subjects were aware of the actual treatment.

All subjects followed the normal diet and were informed not to alter their physical activity levels during the study period. Throughout the study, all patients had monthly follow-up visits to assess menstrual status, drug side effects, and patient compliance. A self-filled menstrual calendar was used to assess menstrual period length and cyclicity.

Statistical Analysis

All variables were represented as mean standard deviation. The Wilk-Shapiro test was used in this study to determine the normality of the variable distribution. Paired t-test was used to compare mean variables at baseline to mean values after treatment. To compare means between three groups, one-way ANOVA and Post-hoc Tukey’s were used.

RESULTS:

In the Metformin Group A: three subjects withdrew from the study because of severe gastrointestinal side effects. One woman was lost to follow up, and two became pregnant.

In the Pioglitazone Group B: four women became pregnant

In the combination Group C: none women lost to follow up and six became pregnant.

Of the 96 patients who participated in the study, 32 were assigned to Group A, 32 to Group B, and 32 to Group C. **Table I** summarizes the patients' baseline characteristics.

Table I: Baseline Characteristic of women with PCOS

Drug Treatment	Metformin	Pioglitazone	Combination (Myo-inositol (MI) + D-chiroinositol + Folic acid)	p-value
Mean age	27.2 ± 4.6	24.1 ± 5.3	28.2 ± 4.3	0.17
Weight	73.4 ± 8.2	71.2 ± 10.4	72.8 ± 11.1	0.89

Table II shows the menstrual cycle length, fasting blood sugar, fasting insulin, and total testosterone levels in patients treated with Metformin, Pioglitazone, and Myo-inositol (MI) + D-chiro-inositol, respectively. After 12 weeks of intervention, all three groups reported a significant reduction in all parameters. When the parameters were compared at 12 weeks between the groups using ANOVA, a significant difference was found.

Table II: Post – treatment Characteristics of women after 12 weeks of intervention

Drug Treatment	Metformin	Pioglitazone	Combination (Myo-inositol (MI) + D-chiroinositol + Folic acid)	p-value
Menstrual cycle length				
At 0 week	2.30 ± 0.7	2.27 ± 0.9	2.02 ± 1.0	0.45
At 12 week	1.44 ± 0.2	1.58 ± 0.3	1.03 ± 0.2	0.03
p-value	0.04	0.03	0.01	
Fasting insulin				
At 0 week	15.1 ± 3.7	17.4 ± 4.8	16.0 ± 3.9	0.08
At 12 week	13.3 ± 3.3	14.5 ± 3.9	11.3 ± 2.7	0.001
p-value	<0.001	<0.001	<0.001	
Fasting glucose				
At 0 week	82.8 ± 9.7	83.9 ± 7.3	79.6 ± 12.1	0.19
At 12 week	77.5 ± 10.4	78.4 ± 6.3	69.7 ± 10.4	<0.001
p-value				
Total Testosterone				
At 0 week	71.3 ± 14.5	72.2 ± 12.9	70.3 ± 12.3	0.89
At 12 week	67.3 ± 11.5	68.2 ± 9.9	60.3 ± 9.2	0.004
p-value	0.001	0.001	<0.001	

In **Table III,** the parameter for the Metformin and Pioglitazone groups did not differ significantly. However, a significant difference in the parameters was seen when the Myo-inositol (MI) + D-chiroinositol + Folic acid group was compared to the Metformin and Pioglitazone group alone**.**

Table III: Post hoc Tukey's Comparison among Characteristics of women after 12 weeks of intervention

Drug Treatment	**Metformin**	**Pioglitazone**	**p-value**
Menstrual cycle length At 12 week	**1.44 ± 0.2**	**1.58 ± 0.3**	**0.531**
Fasting insulin At 12 week	**13.3 ± 3.3**	**14.5 ± 3.9**	**0.375**
Fasting glucose At 12 week	**77.5 ± 10.4**	**78.4 ± 6.3**	**0.925**
Total Testosterone At 12 week	**67.3 ± 11.5**	**68.2 ± 9.9**	**0.941**
Drug Treatment	**Metformin**	**Combination (Myo-inositol (MI) + D-chiroinositol + Folic acid)**	**p-value**
Menstrual cycle length At 12 week	**1.44 ± 0.2**	**1.03 ± 0.2**	**0.042**
Fasting insulin At 12 week	**13.3 ± 3.3**	**11.3 ± 2.7**	**0.049**
Fasting glucose At 12 week	**77.5 ± 10.4**	**69.7 ± 10.4**	**0.003**
Total Testosterone At 12 week	**67.3 ± 11.5**	**60.3 ± 9.2**	**0.019**
Drug Treatment	**Pioglitazone**	**Combination (Myo-inositol (MI) + D-chiroinositol + Folic acid)**	**p-value**
Menstrual cycle length			

At 12 week	**1.58 ± 0.3**	**1.03 ± 0.2**	**0.035**
Fasting insulin			
At 12 week	**14.5 ± 3.9**	**11.3 ± 2.7**	**0.001**
Fasting glucose			
At 12 week	**78.4 ± 6.3**	**69.7 ± 10.4**	**0.001**
Total Testosterone			
At 12 week	**68.2 ± 9.9**	**60.3 ± 9.2**	**0.007**

DISCUSSION

There are several symptomatic treatment options for Polycystic Ovary Syndrome that work through different metabolic pathways (19). Several studies have been already been conducted to compare Metformin and Pioglitazone in polycystic ovarian syndrome. However, to the best of our knowledge, this is the first study in Pakistan that has compared the efficacy of three different insulin sensitizing agents.

Metformin and Pioglitazone were given in this study at doses of 500 mg three times per day and 30 mg per day, respectively. Multiple studies used a range of dosages. The intervals between intervention and follow-up have also varied, varying from 12 weeks to 12 months (20-22).

In the current study, menstrual cycle significantly improved in all three groups; however, the combined group of MI plus DCI supplementation demonstrated predominant result. However, it is unclear whether the improvement in menstrual cyclicity equates to the resumption of ovulation because no progestin levels were measured during the study. In about half of PCOS patients, insulin receptor phosphorylation is compromised. Several research studies have shown that insulin sensitizers such as Metformin, Pioglitazone and Myo-inositol (MI) are the first-line treatment for restoring normal menstrual bleeding in women with PCOS, signifying that an endocellular defect of the precursor of IPG, such as MI and/or DCI, may cause compensatory hyperinsulinemia in the majority of PCOS patients (23, 24). In contrast to the outcomes, Angik et al. conducted a study in which Metformin and MI were compared to see how they affected menstrual cycle regularity. After 24 weeks of treatment, 37.73% attained regular cycles, 28.57% with MI, and 48% with Metformin, which could be attributed to differences in Metformin dosage as well as the use of combination of MI and DCI in our study.

Insulin resistance is the most common cause of clinical manifestations in PCOS. Insulin resistance is defined as the inability of target cells to react to normal or ordinary levels of insulin, regardless of BMI. Insulin resistance causes hyperinsulinemia in approximately 80% of obese PCOS women and 30-40% of lean PCOS women (25). In our study, we discovered that fasting insulin was significantly reduced in all three groups; however, the combination of MI and DCI showed a remarkable reduction in fasting insulin. Pintadi B et al. conducted a research study in which they conclusively proved that Myo-inositol (MI) and D-chiro-inositol are very beneficial in the management of insulin resistance (26). Moreover, the study by Sohrevardi et al. demonstrated that insulin-sensitizing drugs had numerous potential benefits on PCOS women. Further research revealed that Pioglitazone and Metformin administration for three months improved insulin resistance and hyperinsulinemia in PCOS women (27).

Fasting blood glucose and fasting insulin levels significantly dropped in the Metformin and Pioglitazone groups after intervention. Correspondingly, Shahebrahimi et al. observed a significant reduction in both the Metformin and Pioglitazone group (17). In the study by Glueck et al., participants who failed to respond to Metformin alone experienced a reduction in insulin resistance and Fasting blood glucose when given combination of Metformin and

Pioglitazone (28). Januszewski et al. in Poland observed only one treatment option on different PCOS parameters and discovered that serum glucose levels during OGTT reduced after 6 months of combined MI and DCI treatment (29).

PCOS patients are predisposed to a variety of metabolic complications, including hormonal imbalances and inflammation. We discovered that giving Myo-inositol (MI) plus d-chiroionsitol combination to PCOS patients for 12 weeks resulted in significant declines in serum total testosterone. Similarly, Sujana Thalmati discovered a significant decrease in DHEA and free testosterone levels in patients taking MI plus DCI than Metformin (30). Few studies have examined the effects of Myo-inositol (MI) intake on clinical symptoms and metabolic profiles in PCOS subjects, and there are few data on the comparison of Myo-inositol (MI) and Metformin on clinical and metabolic parameters in PCOS women. It has been demonstrated that follicles with high-quality oocytes have higher Myo-inositol (MI) levels in the follicular fluid (31). Artini et al. have also demonstrated improved ovarian function (32). Additionally, after taking Myo-inositol (MI), subjects with PCOS showed improvements in insulin sensitivity, decreased testosterone levels, and less severe acne and hirsutism (33). Romualdi et al. reported the opposite result, stating that Pioglitazone treatment had no effects on free and total testosterone levels; even so, clinical signs of high levels of testosterone, such as acne and hirsutism, were obviously improved (34).

It was an interventional study with a small sample size. Nonetheless, the current research found that Myo-Inositol and D-chiroinositol combined treatment is very efficient in alleviating major symptoms in PCOS women in a clinical setting.

CONCLUSION

Clinical and hormonal disturbances in PCOS patients were improved by the all the three insulin sensitizer agents: Metformin, Pioglitazone, and myoinositol plus d-chiroinositol. In comparison to Metformin and Pioglitazone, myoinositol plus d-chiroinositol supplementation demonstrated higher tolerability and led to statistically significant reductions in total testosterone and insulin levels. More research is needed to determine the effects of combining myoinositol and d-chiroinositol therapy for an efficient treatment of PCOS because the current study was conducted for a brief period of time and on a small number of women.

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