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Effects Of Metformin And Myo-Inositol In Combination Versus Metformin As Monotherapy On The Metabolic Profile Of Polycystic Ovarian Syndrome Patients With Infertility

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Abstract

Objective: To compare the effects of myo-inositol combined with metformin vs. metformin used alone on the metabolic profile of patients with polycystic ovarian syndrome with infertility.

Methods: A randomised controlled trial that was double-blinded was conducted from September 2022 to February 2023. One hundred fourteen PCOS females with infertility were randomly assigned to 57 people made up Group A, which received oral Metformin in a dose of 500 mg 3 times per day together with oral Myo-inositol 4 g once per day; 57 people made up Group B, which received oral Metformin in a dose of 500 mg 3 times per day only. Following the start of medication, all hormonal and metabolic profile parameters were assessed at baseline, one, three and, six months later. Our main goal was to improve polycystic ovarian syndrome patients' metabolic profiles regarding mean change in serum Triglycerides, serum HDL and mean HOMA-IR index throughout one, three and six months. Comparable demographic, hormonal, and biochemical baseline characteristics were present in both groups.

Results: In comparison to Group B, Group A's mean serum triglycerides improved (p=0.16) although not significant, significant improvement in mean serum HDL in Group A as compared to Group B (p=0.00), additionally a significant improvement in the mean HOMA-IR index in Group A when compared to Group B was observed.

Conclusion: Compared to Metformin administered as a monotherapy, it seems promising to treat PCOS and insulin resistance using a combination of metformin and myo-inositol.

MeSH Keywords: Polycystic Ovary Syndrome, Inositol, Metformin, Infertility.

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1. Introduction

Among the most typical hormonal, genetic, metabolic, and reproductive diseases that impact reproductive-age women is polycystic ovarian syndrome. The estimated prevalence varies depending on the diagnostic criteria utilized.[1] Near 33% of PCOS-afflicted women have metabolic abnormalities,[2] such as dyslipidemia(1), chronic inflammation, vascular and endothelial dysfunction.[3] Which can cause additional serious health diseases like obesity, anxiety, heart issues, type 2 diabetes mellitus, and also increase the chances of endometrial cancer, in addition to being one of the primary reasons for female infertility.

According to Rotterdam criteria, it roughly affects one hundred and sixteen million women globally (3.4 per cent) and can rise to 14.6 per cent.[4] Obesity, glucose intolerance and insulin resistance, which are frequently linked to this condition, seem to exacerbate the symptoms.[5] Numerous patients exhibit abnormal luteinizing hormone (LH) secretion, as evidenced by raised blood levels and more frequent LH pulses and magnitudes.[6] In addition, regardless of body mass index (BMI), it is crucial to recognize the community of lean females with PCOS who are also hyperandrogenic, anovulatory, and may also be the most insulin resistant.[7] The synthesis of androgens by the ovaries appears to be increased by insulin resistance, compensatory hyperinsulinemia, and elevated LH secretion. In addition, elevated insulin levels hinder the liver from producing sex hormone-binding globulin (SHBG)(2).[8] These alterations result in an increased bioavailability of free androgens (hyperandrogenemia) which leads to anovulation, premature ovarian follicle termination, and irregularities in the menstrual cycle.

The Homeostatic Model Assessment of Insulin Resistance, or HOMA-IR, predicts fasting insulin and glucose concentrations under stable settings, making it possible to examine different states of insulin

resistance and pancreatic cell β activity.[9] HOMA-IR = fasting blood glucose (mg/dL) × fasting insulin (mIU/mL)/22.5 is the formula for the HOMA-IR index. If it's less than 1, one is sensitive to insulin. Beyond 1.9, insulin resistance is considered borderline. Nonetheless, HOMA-IR more than 2.5 is the definition of insulin resistance.

Acne is a prevalent immune-mediated ailment that commonly affects adults and adolescents, and it is usually linked to PCOS.[10]

The Global Acne Grading System (GAGS) was created in 1997. The face (forehead, each cheek, nose, and chin), chest, and back are divided into six regions by the GAGS. The severity in each zone is then graded from 0 to 4 (0, no lesions; 1, comedones; 2, papules; 3, pustules; and 4, nodules). After calculating the overall score for all six zones, the severity of acne is categorized as mild (1–18), moderate (19–30), severe (31–38), or very severe (>39).[11]

Combined oral contraceptive pills (COCPs) are used as first-line medical therapy and a great substitute when acne, hirsutism, and irregular menstruation are the primary symptoms and complaints in PCOS patients.[12]

However, in the case of PCOS with obesity and glucose intolerance, the use of long-acting insulin sensitizers, particularly metformin along with or without the lifestyle changes,[13] such as low-calorie diet, weight loss, and increasing exercise, is the subject of an interdisciplinary debate. Metformin is the gold standard insulin sensitizer as it improves glucose tolerance and insulin sensitivity, lowers hyperinsulinemia, and lowers elevated levels of androgen in adolescents with obesity, PCOS, and impaired glucose tolerance. Metformin usage is well-tolerated,[14] but in some patients, it is more likely to cause upset stomach symptoms, such as gas, vomiting, and diarrhoea which may contribute to reduced treatment adherence and efficacy.

Eating meals with Metformin can help minimize side effects by reducing its amount and rate of absorption and somewhat delaying its absorption.[15-18] Also introducing prebiotic fiber supplements during metformin therapy can reduce GI symptoms. Patients also reported that the gastrointestinal adverse effects of Metformin usually get better with time.[19]

Inositol is a recently added ingredient to insulin sensitizers, of which Myo-inositol is the most fully researched, by serving as a second insulin messenger through the membrane-linked sodium-dependent inositol co-transporter GLUT-4, it lowers serum androgens as well as hyperinsulinemia by increasing insulin sensitivity, improves ovarian function, increases SHBG, improves various hormonal and metabolic parameters including lowering of both total and free testosterone in PCOS patients.[20]

To date, the level of evidence has not been satisfactory for accepting them as standard therapy in the guidelines to use inositol as an adjunct or alternate therapy for the treatment of PCOS but still for the reason that the two insulin sensitizers have different modes of action, they may be utilized as a combination therapy to improve PCOS women's metabolism and hormone levels.[21] Few research has been published to determine whether metformin combined with myo-inositol works better in insulin-resistant PCOS females than metformin alone. The rationale of the study needs to be improvised (already a meta-analysis has been done on the use of inositol as an alternative to Metformin). The goal and novelty of this research was to assess the results of the combination of myo-inositol and metformin against metformin alone based on metabolic markers in females who have PCOS with insulin resistance and infertility in the Pakistani population. Our study will be a helpful tool and instruct clinicians on how to care for their PCOS patients, especially those suffering from insulin resistance.

2. Materials & Methods

A randomized controlled trial with double-blinding was performed in the obstetrics and gynaecology outpatient clinic at the Khyber Teaching Hospital in Peshawar from September 2022 to February 2023. The study was started after being given the go-ahead by the institute's Clinical Research Ethics Committee. 114 PCOS-positive women with infertility were evaluated for the study using Rotterdam criteria.

Adult female PCOS patients with infertility, aged (20–38) years, were included in the study. Those showing signs of PCOD without insulin resistance, androgen-secreting tumours, Cushing's syndrome patients, uncontrolled hypothyroidism or hyperthyroidism and congenital adrenal hyperplasia (ambiguous genitalia) patients were excluded**.**

Each participant received a random assignment to either of two groupings, according to a computer-generated randomization table. After a detailed explanation of the study's objective, duration, and thorough methodology in the patient's native language, their informed written consent was acquired. After a thorough review of the patient's medical history regarding PCOS, a comprehensive physical examination with measurements of the patient's height, weight, BMI

(kg/m2), waist-to-hip ratio(WHR), hirsutism scoring, Global acne assessment score, and secondary sexual features were documented. Baseline tests on the second to fifth day of the female monthly cycle included lipid profile (serum Triglycerides, sr. HDL and sr. Total cholesterol), fasting blood glucose(FBG md/dl)) and Fasting serum insulin(FI pmol/L), HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) as well as hormonal profile including serum Luteinizing hormone, serum total and free testosterone, sr. SHBG and DHEA (dehydroepiandrosterone) (Table I). The prescribed course of action was followed after administering the therapy. Group A (n=57) received tabs of metformin 500 mg TDS and myo-inositol 4 gm once a day in envelopes, while Group B (n=57) received tabs of metformin 500 mg TDS in envelopes for the same period. Patients of both groups were advised to take medication with food to decrease the intensity of gastrointestinal side effects associated with metformin.

Following the first, third, and sixth months of treatment, every patient was checked in. All metabolic and hormonal measurements were repeated after the first, third, and sixth months to evaluate advancement.

All study participants had open lines of communication with the researchers during the 6-month trial period to resolve this problem. To check on their adherence to their meds and any adverse effects, they received a phone SMS once a month. Additionally, they were urged to SMS the researchers at any time during the trial to provide updates on their progress and ask any questions about PCOS or their meds. The frequent interaction probably increased compliance and may have had an impact on the results of both treatments.

Early trial terminations were noted for two members in Group A and three members in Group B. Improvement in mean serum Triglycerides, Serum HDL and HOMA-IR index were primary among primary outcomes.

SPSS version 23 was employed to analyze the data. To ascertain the mean difference in outcome variables, an independent sample *t*-test was conducted. The significance level was accepted when $p<0.05$

3. Results

Based on criterion for inclusion and exclusion, 114 PCOS adult women were chosen for the trial followed by randomization. Metformin and Myo-inositol were given to Group A (n=57), while Metformin was given to Group B (n=57). The research participants' baseline discrepancies in demographic, clinical, hormonal, and metabolic data are shown in Table 1.

Table 1: Baseline discrepancies in the two groups physiology, hormonal profile, and demographics

Features	Group A (n=55)	Group B (n=54)	P-value
Clinical Parameters			
Age	28.94±3.77	28.61± 3.64	(0.64)
BMI(kg/m2)	28.58±2.52	28.65±2.35	(0.88)
WHR	0.880±0.018	0.879±0.018	(0.77)
Menstrual cycle duration	2.36±0.86	2.57±0.59	(0.14)
Bleeding per cycle (days)	13.05±4.5	14.6±4.13	(0.06)
Ferriman Gallawey scale	5.30±1.31	5.25±1.33	(0.84)
Global Acne scale	2.81±1.09	2.66±1.14	(0.59)
Hormonal parameters			
Sr. Free Testosterone(pg/ml)	3.196±0.33	3.199±0.44	(0.96)
Sr. Total Testosterone(ng/dl)	47.4±2.7	47.09±3.25	(0.58)
Sr. LH(mIU/ml)	15.08±2.6	15.03±2.71	(0.92)
Sr. SHBG(nmol/L)	12.8±2.04	12.64±1.99	(0.67)
Sr. DHEA(µg/dl)	199.3±9.8	199.9±12.3	(0.77)
Metabolic profile			
Fasting blood glucose(mg/dl)	99.2±11.1	100.7±11.2	(0.48)
Insulin fasting (pmol/L)	101.30±13.8	101.37±13.35	(0.97)
HOMA-IR index	4.18±0.96	4.2±0.96	(0.99)
Triglycerides(mg/dl)	184.7±26.1	184.79±21.8	(0.98)
HDL(mg/dl)	26.34±7.96	25.66±7.54	(0.64)
Sr. Total Cholesterol	176.4±25.2	175.6±21.9	(0.86)

After the first month of treatment, Group A had lower mean serum triglycerides than Group B, p=0.84 although not significant (Fig. I). After three months of therapy, Group A showed more improvement compared to Group B, p=0.53 although still not significant (Fig. II). After 6 months, improvement was seen in Group A in contrast to Group B p=0.19 (Fig. III) but still not significant.

After 1 month of therapy, Group A showed improvement in mean serum HDL in contrast to Group B with a p value of 0.33 (Fig. I), but significant improvement was noted in Group A after 3 months in contrast to Group B with a p value of 0.02 (Fig. II), similarly after 6 months of therapy significant increased level of mean serum HDL was recorded in Group A vs. Group B with a p value of 0.00 (Fig. III).

In case of mean serum HOMA-IR index (Homeostatic model assessment of insulin resistance) significant improvement was recorded in Group A versus Group B after 1st month of therapy p=0.04 due to improvement in mean FBG level (p= 0.04) as well as mean serum FI (p=

0.50) (Fig. I), after 3 months similar significant results were observed in Group A vs. Group B with a p= 0.00 due to improvement in mean FBG level (p= 0.00) as well as mean serum FI (p= 0.07) (Fig. II), and significant improvement of mean HOMA-IR index was observed in Group A vs. Group B with a p value of 0.00 after 6 months of therapy (Fig. III) due to improvement in mean FBG (p= 0.00) as well as mean serum FI (p= 0.00).

Metabollic Parameters After 1 month			
	Group A n=55	**Group B N=54**	**P-Value**
Sr. Triglycerids	181.91±26.36	182.81±22.05	**(0.84)**
Sr. HDL	28.13±8.10	26.67±7.62	**(0.33)**
FBG	95.09±11.4	98.8±11.3	**(0.04)**
FI	98.1±14.2	99.1±13.7	**(0.50)**
HOMA-IR Index	3.649±0.98	4.029±0.96	**(0.04)**

Figure 1: Metabolic parameters 1 month later
**p <0.05 is statistically significant*

Metabollic Parameters After 3 month			
	Group A n=55	**Group B N=54**	**P-Value**
Sr. Triglycerids	175.87±26.13	178.78±22.05	(0.53)
Sr. HDL	32.12±8.02	28.66±7.5	(0.02)
FBG	88.67±13.1	95.97±11.7	(0.00)
FI	90.96±14.7	95.8±13.6	(0.07)
HOMA-IR Index	3.25±1.07	3.84±0.95	(0.03)

Figure 2: Metabolic parameters 3 months later
**p <0.05 is statistically significant*

	Group A n=55	**Group B n=54**	**p-value**
Sr. Triglycerides	167.24±26.47	173.78±22.05	(0.16)
Sr. HDL	38.13±8.10	31.67±7.62	0.00
FBG	78.50±13.3	89.33±12.2	0.00
FI	78.96±17.1	88.55±14.4	0.00
HOMA-IR index	2.60±0.98	3.32±0.93	0.00

Figure 3: Metabolic parameters 6 months later
**p <0.05 is statistically significant*

4. Discussion

PCOS-affected women's insulin-resistance is independent of BMI, and it is exacerbated by obesity. The greatest reduction in insulin sensitivity is brought about by PCOS and obesity combined. Half of the PCOS-afflicted women who have obesity are insulin resistant. Impaired glucose tolerance is more common by 2.5 times, and the likelihood of developing Type 2 diabetes and other cardiometabolic disorders, such as hypertension, is higher in those with PCOS, according to a systematic review and meta-analysis.[22]

In the US, 70% of patients with PCOS experience dyslipidemia, compared to fewer in other nations where the mean body weight is lower. Hypertriglyceridemia, a rise in small, dense LDL, and a reduction in high-density HDL cholesterol are the three most prevalent atherogenic dyslipidemic features in PCOS. In the current study, 12.87% of the cases had a family history of diabetes mellitus, and 43.3% of cases had a family history of high blood pressure, respectively. For the first time, we compared the effects of myo-inositol, coupled with metformin, against metformin alone on the metabolic profile of patients with PCOS. The present study shows that the insulin sensitivity and HOMA-IR index are favorably impacted by myo-inositol and metformin, which have the ability to significantly lower fasting blood sugar and fasting insulin. In the studies performed by Agrawal A. et al,[21] Thakur et al,[23] and Nagaria T. et al,[24] the groups using combination therapy of myo-inositol and metformin showed significant reduction in HOMA-IR index when compared to groups using metformin alone, with p-values of <0.05, indicating significant improvements in insulin sensitivity. However, Bahadur et al,[25] proposed that although the HOMA-IR index declined in the group receiving a combination therapy of metformin as well as myo-inositol, as compared to group utilizing metformin, but there was no significant difference (p=0.746). In another study performed by Zhao et al,[26] it was concluded that when combined with D-chiro-inositol, myo-inositol was linked to a lower insulin resistance index (HOMA-IR) than metformin alone.

Compared to Group B, in our study, the mean serum HDL, after 1st month in Group A was improved (p=0.32) although not significantly, but after the 3rd month and 6th month it was much better (p<0.05). In terms of serum triglycerides, our study did not show any significant differences after 6 months of therapy, although there was improvement in Group A compared to Group B (0.16). Bahadur et al,[25] retrieved similar outcomes while observing the effects of the Metformin plus Myoinositol plus D-chiro-inositol versus Metformin alone on PCOS patient's serum Triglycerides (p=0.38); however, in case of serum HDL, combination therapy showed significant improvement (p=0.04).

In another study done by Prabhakar et al,[20] there was significant improvement after 3 months in mean serum Triglycerides and serum HDL levels in both Group I (Metformin plus Myoinositol) and Group II (Myoinositol), although the research did not detect any

appreciable variations. Similarly, the study conducted by Agrawal et al,[21] on serum HDL for a period of 3 months showed improvement in both groups, but did not show significant difference (p=0.54). Pourghasem et al,[27] recorded improvement in serum Triglycerides levels, but the difference was not statistically significant among the groups (p=0.53). In another study, JQ Zhang et al,[28] observed that, in terms of decreasing serum triglycerides, myo-inositol is superior to metformin (p=0.0001). Whereas Zhao et al.[26] found that, compared to using metformin alone, treatment with thiazolidiones plus metformin was linked to decreased triglyceride levels. (p=0.00).

Although the study's results are encouraging, its limitations namely, its brief duration and limited sample size are acknowledged by its authors. Additional research with a larger sample size and a longer follow-up period is needed to support these findings.

5. Conclusion

The current study comes to the conclusion that treating insulin resistance in PCOS patients with myo-inositol plus metformin rather than the more popular metformin alone can be effective. Additional randomized controlled trials comparing the two compounds alone and in other combinations are necessary to support or reject the benefits of combinations.

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H.E.K - Conception of study
M.I.A - Experimentation/Study Conduction
T.A.C, M.E.K - Analysis/Interpretation/Discussion
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