

DEALING WITH INSULIN RESISTANCE AMONG WOMEN WITH POLYCYSTIC OVARIAN SYNDROME

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Abstract: One of the most prevalent endocrine disorders in females, polycystic ovarian syndrome (PCOS), affects about 7-8% of women of reproductive age. Most females with PCOS also have increased cholesterol levels, insulin resistance, and BMI, leading to obesity. The study aimed to determine the effects of metformin and lifestyle modification (diet & exercise) on insulin resistance secondary to PCOS after 6 months of use. This RCT study was conducted at Arif Memorial Teaching Hospital from October 2022 to March 2023. The study compared the effects of metformin and lifestyle management, including only a diet plan with the use of metformin diet and exercise plan, on insulin resistance in 130 obese females aged between 20-40 years suffering from PCOS and had insulin resistance as diagnosed by HBA1C blood test. The main outcome measure was the reduction in the HBA1C level. The 130 participants were equally divided into two groups. Group A received metformin only, while Group B received metformin and an exercise plan. Baseline treatment included guidance to adopt a healthy diet. The results showed significant improvement in HBA1C level ($P=0.00$), BMI ($P=0.02$), and pregnancy rate. There was an overall improvement in the menstrual pattern but a significant improvement in Group B ($P=0.00$) than Group A ($P=0.06$). With a significant rise in follicle-stimulating hormone (FSH) levels in both groups [$P=0.06$ (A), $P=0.01$ (B)], a statistically significant decrease in luteinizing hormone (LH) [$P=0.02$ (A), $P=0.01$ (B)] was seen. A total drop in free testosterone level was also seen, but it wasn't significant [$P=0.08$ (A), $P=0.06$ (B)]. The study concluded that insulin resistance could be controlled effectively by acquiring a healthy lifestyle, including high protein and low carb, caloric deficient diet, and following an exercise plan and pharmacological treatment. Combining all three treatment options is more effective than using any one option as treatment.

Keywords: Polycystic Ovarian Syndrome, Lifestyle Modification, Metformin, Hyperinsulinemia

Introduction

One of the most common endocrine disorders, polycystic ovarian syndrome (PCOS), is highly frequent in women of childbearing age. (Barry, Azizia, et al. 2014, Goodman, Cobin, et al. 2015). PCOS patients either experience oligomenorrhea or excess male hormones leading to hyperandrogenism. (Ndefo, Eaton, et al. 2013). PCOS is said to have occurred when the ovaries stop releasing a dominant follicle monthly. Rather, numerous immature fluid-filled sacs are developed, known as atretic follicles, which eventually develop into subcapsular cysts (Patil, Singh, et al. 2035).

Polycystic ovarian syndrome (PCOS) affects about 7-8% of women of reproductive age (Azziz, Carmina et

al. 2016). The prevalence of PCOS depends upon the population and the Rotterdam criteria used for its diagnosis, but it is said to vary from 6 percent to 21 percent (Teede, Deeks, et al. 2010, Azziz and Gynecology 2018). The prevalence of PCOS among Pakistani Women is 55.4% which is exceptionally higher than those of the female population in Western Countries (Sidra, Tariq et al. 2019, Zulfiqar, Tahir et al. 2022). Most females with PCOS also have increased cholesterol levels, insulin resistance, and BMI, leading to obesity (Dumesic, Oberfield, et al. 2015, Gunning, Sir Petermann, et al. 2020). Due to the variation in its clinical presentation and underlying etiology is classified as a heterogeneous disorder (Artani, Iftikhar et al. 2018).

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As defined by the Rotterdam consensus criteria, two symptoms are necessary for PCOS diagnosis: Anovulatory or oligo-ovulatory cycles, increased male hormones known as hyperandrogenism, and scan showing polycystic ovaries (Tummon, Gavrilova-Jordan et al. 2005). Patients with PCOS are at increased risk of having Type 2 Diabetes mellitus because of increased insulin resistance and abdominal obesity (Glintborg and Andersen 2010, Dumesic, Abbott, et al. 2020).

Insulin resistance, obesity, hyperlipidemia, and a higher risk of impaired glucose tolerance, which can result in type 2 diabetes mellitus, are the metabolic aspects of this illness (Tsilchorozidou, Overton et al. 2004). It has been determined that obesity does contribute to the pathophysiology and that roughly 50% of the patients are obese females (Cai, Liu et al. 2014). In addition, it has been suggested that PCOS may cause anxiety and sadness (Pastore, Patrie et al. 2011).

Different pharmacological and non-pharmacological methods can treat PCOS. The most common pharmacological treatment includes Metformin 500mg thrice a day (Artani, Ifikhar, et al. 2018), while non-pharmacological treatment includes adopting a healthy lifestyle including high protein and low-fat diet and adding physical activity to the daily routine. Following an exercise plan has also shown significant improvement in insulin resistance secondary to PCOS. A study showed a significant effect of Yoga in reducing Insulin resistance (Farshchi, Rane et al. 2007, Galluzzo, and Amato et al. 2008). Recent research evidence suggests that the use of acupuncture has been proven to be effective in improvising the metabolic markers of the disease (Wang, Xia et al. 2022).

Numerous studies have been carried out to examine the outcomes of the use of metformin and a healthy lifestyle in PCOS in reducing insulin resistance. This study compares the effect of the combination of metformin with a healthy diet versus the use of metformin & diet combined with exercise on Insulin resistance secondary to PCOS.

Methodology

This Randomized Control Trial (RCT) was conducted over 6 months at Arif Memorial Teaching Hospital, affiliated with Rashid Latif Khan University. For this purpose, 130 non-lactating females of the age of 20-40 years, diagnosed with PCOS based on Rotterdam consensus criteria, with no history of conception in the past year and no history of use of hormonal treatment and having BMI ≥ 25 were recruited in the study while those the lactating females who had a

history of pregnancy in the past year, had any other hormonal or eating disorder were excluded from the study.

The participants were then divided into equal groups, each having 65 candidates. This grouping was done by the lottery method. As a baseline treatment, a diet plan was designed specifically for all the candidates under the dietician's supervision, and an overall reduction of ≥ 450 calories was made in each diet plan. Candidates of Group A received only pharmacological treatment, i.e., Metformin 500mg thrice a day, along with a diet plan. In comparison, those of Group B received pharmacological treatment, i.e., Metformin 500mg thrice a day along with a diet plan by the dietician & exercise plan made by the physiotherapist. Physical therapists created a supervised exercise programme to increase the type (endurance, aerobic, and weight training depending on each subject's preferences) and level of physical activity according to the individual's capacity, objectives, and interests.

The participants were screened at the start of the study (baseline) and after completion of 6 months course. Meanwhile, monthly checkups were done to monitor the overall progress and adherence to the respective groups' diet and exercise plans. The participants were screened for weight, height, BMI, and caloric intake. The FSH, LH, Testosterone, and HBA1C were examined from blood samples before the study.

SPSS version 22 was used for statistical analysis. All the data were presented as mean and standard deviation at 95% CI. The significance among pretest and post-test results were compared using the student's T-test for parametric data while the chi-square test and Wilcoxon's sign rank test for non-parametric data, and P-value <0.05 was considered to be significant.

Results

Table 1 below shows the anthropometric and metabolic measures taken at the start of the study. The anthropometric measures included age, weight in kg, height in cm, and BMI, which were calculated from them. The mean age of the participants of Group A was 27.58 ± 5.64 years, and of Group B was 28.31 ± 6.02 years the minimum age of Group A participants was 20 years, while the maximum age was 40 years in both groups. The mean weight of Group A participants was 82.0 ± 15.0 kg, while Group B's was 86.0 ± 14.0 kg. The average height of Group A individuals was 164.0 ± 4.0 cm, and of Group B was 165.0 ± 4.0 cm. The Average BMI, as Calculated from the data, was found to be 29.43 ± 4.14 in Group A and 30.95 ± 4.15 in Group B.

Metabolic measurements included serum levels of HBA1C, Glucose, and some hormonal levels such as FSH, LH, Free Testosterone, and average caloric intake. The results showed that at baseline, the average HBA1C level was 6.7 ± 2.5 and 6.3 ± 1.5 in groups A and B, respectively, while serum glucose level assessed at fasting was 86 ± 9 mg/dl in Group A and 90 ± 4.5 mg/dl in Group B. the levels of FSH was reduced in both groups and the mean level was 5.2 ± 1.5 and 5.5 ± 2.0 in group A and B respectively. LH and free testosterone levels were raised in both groups before treatment. The mean levels were 9.3 ± 4.5 and 5.5 ± 2.0 for LH and testosterone, 13.4 ± 5.6 and 14.5 ± 6.0 in both groups, respectively. The mean caloric intake of individuals of both groups before treatment was $2,200 \pm 399$ and $2,140 \pm 350$, respectively.

Table 2 shows the measurements taken after 6 months treatment plan as assigned to both groups. All the results obtained were significant in both groups. The

average BMI was reduced in both groups with no significant difference ($P=0.00$). Serum levels of HBA1C were also reduced in both groups, but there was no significant difference because the p-value was 0.002 in both groups. Overall, Glucose levels were reduced in both groups, but there was no significant difference observed ($P=0.56$)

FSH levels were increased in both groups, but there was a significant difference in both groups as the p-value of group B was 0.01, but in group A it was 0.06. The serum levels of LH were reduced in both groups with no significant difference ($P=0.02$, $P=0.01$, respectively). Both groups had an overall reduction in free testosterone levels; no significant difference was observed ($P=0.08$, $P=0.06$, respectively). There was an overall improvement in the menstrual pattern but a significant improvement in Group B ($P=0.00$) than Group A ($P=0.06$). About 10.8% of females from Group A and 15.4% of females from Group B got pregnant at the end of their treatment.

Table 1 Anthropometric and metabolic measures at baseline

	GROUP A (n=65) Metformin + diet plan	GROUP B (n=65) Metformin + diet plan+ physical activity
Age	27.58 \pm 5.64	28.31 \pm 6.02
Weight kg	82.0 \pm 15.0	86.0 \pm 14.0
Height cm	164.0 \pm 4.0	165.0 \pm 4.0
BMI	29.43 \pm 4.14	30.95 \pm 4.15
HBA1C	6.7 \pm 2.5	6.3 \pm 1.5
Glucose mg/dl	86 \pm 9	90 \pm 4.5
FSH U/L	5.2 \pm 1.5	5.5 \pm 2.0
LH U/L	9.3 \pm 4.5	8.7 \pm 3.5
fT, pg/ml	13.4 \pm 5.6	14.5 \pm 6.0
Caloric intake/24 h	2,200 \pm 399	2,140 \pm 350

*BMI= body mass Index, FSH = follicle Stimulating Hormone, LH = Luteinizing Hormone, fT= Free Testosterone

Table 2 Metabolic measures After 6 Months

	GROUP A (n=65) Metformin + diet plan	P-value	GROUP B (n=65) Metformin + diet plan+ physical activity	P-value
BMI	27 \pm 2.5	0.00	26 \pm 3.7	0.00
HBA1C	5.3 \pm 1.5	0.02	5.4 \pm 1.7	0.02
Glucose mg/dl	82 \pm 5.6	0.56*	85 \pm 5	0.56*
FSH U/L	6.0 \pm 2.8	0.06*	7.0 \pm 2.7	0.01
LH U/L	7.3 \pm 4.5	0.02	6.9 \pm 4.0	0.00
fT, pg/ml	4 \pm 2.5	0.08*	5.6 \pm 2.5	0.06*
Caloric intake/24 h	1600 \pm 250	0.01	1500 \pm 220	0.02
Improvement in menstrual pattern=	Yes: 50 (77%) No: 15 (23%)	0.06*	Yes: 61 (93.8%) No: 04 (6.2%)	0.000
Pregnancy reported	Yes: 7 (10.8%) No: 58 (88.2%)		Yes: 10 (15.4%) No: 55 (84.6%)	

* Statistically Non-significant

Discussion

Polycystic ovarian syndrome may begin before puberty and is linked to a number of etiological factors, such as obesity, insulin resistance, and hereditary factors. The current study included females at an early age (20-40 years) having symptoms of PCOS as weight gain (95%), irregular menstruation (90%), hirsutism (85%), and acne vulgaris (88%). The current study demonstrates that insulin resistance encountered in these patients can be effectively managed by using metformin 500mg 3/day and following a supervised exercise programme and a low-calorie diet plan. But more promising results were obtained in individuals who were given metformin plus diet plan and exercise plan than those who only received metformin with diet plan.

Several studies have been done to check the effect of metformin in reducing PCOS-related insulin resistance. A study conducted by Aruna et al. in 2004 showed similar results to the current study, i.e., a decrease in BMI, improved menstruation and pregnancy rate while an overall significant decrease in LH and testosterone and an increase in FSH was observed (Aruna, Mittal, et al. 2004).

The current study's results align with the RCT conducted by Nybacka et al. in 2011, in which they assessed the effect of diet and exercise on metabolic markers of PCOS. They concluded that symptoms significantly improved in all three groups, i.e., diet only, exercise only, diet and exercise both. But in the current study, we compared the effects of metformin and the exercise and diet plans used in both. The results are consistent with the previous study as significant improvement was seen in the group who received metformin, diet, and exercise plan (Nybacka, Carlström et al. 2011).

Farshchi et al. in 2007 studied the dietary management of PCOS along with the exercise plan and concluded that caloric deficient diet and an exercise plan play a major role in improving symptoms of PCOS. A high protein and low carb diet with approximately 2000-2200 kcal effectively improves overall metabolic markers of disease and glucose tolerance. The results are consistent with the current study, where similar results were obtained (Farshchi, Rane, et al. 2007).

Victorin et al. in 2016 evaluated the effect of electro-acupuncture on improving levels of HBA1C and androgen in females with PCOS. A 5-week session of electro-acupuncture with a frequency of 3 times/week showed significant improvement in HBA1C and androgen levels by 9.4% ($p=0.004$) and 22% ($p=0.0007$), respectively (Stener-Victorin, Maliqueo et al. 2016). The following results were also supported by Chen Hui et al. in 2019, who also studied the effect

of acupuncture on PCOS (Chen and Lim, 2019). While the current study evaluated the effect of metformin, physical exercise, and diet plans in controlling insulin resistance. Despite different intervention programmes, similar results were obtained in the current study, where HBA1C and testosterone levels were reduced in both groups.

Conclusion

From the results of the current study, it can be concluded that insulin resistance can be controlled effectively by adopting a healthy lifestyle, including a high protein and low carb caloric deficient diet and following an exercise plan along with pharmacological treatment in the form of metformin. This combination has shown promising results in females suffering from PCOS rather than only following pharmacological treatment combined with a low-calorie diet. Hence the study emphasizes adherence to the combination of diet, exercise, and metformin to treat PCOS-associated insulin resistance.

Conflict of interest

The authors declared an absence of conflict of interest.

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