

Physiological Effects of Metformin on Hirsutism, Ovarian Volume and Insulin Resistance in Patients With PCOS

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ABSTRACT

Background: Polycystic Ovary Syndrome (PCOS) commonly encountered by gynaecologist, is reflected by menstrual irregularity, infertility, hirsutism, increased androgen levels and insulin resistance. Use of metformin can significantly affect the outcome in these patients.

Objectives: This Study demonstrates the effect of metformin on hirsutism, ovarian volume and insulin resistance in females having PCOS.

Methods: 40 women with PCOS were included. Women with chronic oligomenorrhea or amenorrhea, hirsutism and classic look of polycystic ovaries on ultrasound were labelled PCOS according to ESHRE guidelines. Those taking other medication and not agreed for next visit were excluded and then randomly grouped into two. After history and examination anthropometric measurements and hirsutism assessment was done. Base line Investigations including blood for fasting glucose, insulin levels and pelvic ultrasounds were done. The intervention group and placebo took metformin and placebo tablets respectively for 3 months at the end of which clinical assessment and investigations were done.

Results: Hirsutism dropped from 12.5% to 7.5% in metformin group at post intervention ($p < 0.05$). The mean volume of right ovary reduced significantly in the group taking metformin vs. placebo ($p < 0.05$). The mean insulin levels fell from baseline of 17.1 IU/l to 14.1 IU/l in metformin group. The mean level of glucose in fasting state did not change in the metformin intervention group. On the other hand, the level of glucose in fasting state increased from baseline of 100.6 (mg/dl) to 105.6 (mg/dl) at post intervention in placebo group trending towards statistical significance ($p = 0.06$).

Conclusion: Metformin significantly reduced hirsutism, ovarian volume and insulin resistance in females with polycystic ovary disease.

Keywords: Hirsutism, Insulin resistance, Metformin, Ovarian volume, polycystic ovary disease.

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) constitutes a common gynaecological problem reflected by menstrual irregularity, fertility problems, hirsutism,

increased androgen levels and insulin resistance. It is affecting 8 -13% of women in their reproductive age globally [1]. PCOS highly prevails in Pakistani women (52%) [2]. Obesity is present in 80%, acne in 67.3% , hirsutism in 68% , hyperglycaemia in 63.2%, irregular

menstrual cycle in 71.8% and ovarian cysts in 61% of females with PCOS[3]. If left untreated, PCOS is associated with health risks such as hypertension, diabetes, sleep apnoea, high cholesterol level and low quality of life owing to depression [3].

No single etiologic factor is responsible for the range of aberrations in PCOS. This syndrome is known to start by hyperandrogenism and chronic ovulatory problems and advance to the resistance of insulin in peripheral tissues [4]. At the level of liver, firstly, hyperinsulinemia caused by the resistance of insulin impedes the production of globulin that binds sex hormone and as a result androgen levels are elevated causing hirsutism and secondly it inhibits the secretion of insulin like factor binding proteins causing increased bioactivity of IGF1 and IGF2, the two vital regulators of follicular maturation leading to atretic follicles and follicular arrest which result in multiple cysts formation in ovaries [5].

The infertility in PCOS is largely attributed to the resistance of insulin which if reversed improves ovulation and subsequently infertility. It is possible to reverse insulin resistance by agents that sensitize the actions of insulin like metformin thus reducing the levels of androgen which is the main culprit for all the problems associated with PCOS [6]. Most of the women from rural areas are reluctant to consult gynaecologist, our aim is to get an insight into the clinical picture of PCOS regarding hirsutism, acne, ovarian volume, insulin resistance and if these can be affected by the use of metformin.

MATERIALS AND METHODS

This placebo, randomized trial was accomplished in Hayatabad Medical Complex Peshawar, Pakistan. A total of 40 females aged 18–35 years were recruited. Women with chronic oligomenorrhea or amenorrhea, hirsutism and typical features of PCOS on ultrasound were considered PCOS. Ultrasound scan was diagnostic if it revealed ten or more follicular cysts of 2 - 9 mm diameter or having ≥ 10 cm volume of ovary [7]. Those patients were excluded who were on other medicines or not ready for follow-up visit. A detailed history and physical examination was done followed by anthropometric measurements and hirsutism assessment. Investigations were done including fasting blood glucose, insulin levels and pelvic ultrasound at base levels. Patients were randomly grouped into two. The intervention group was advised metformin 500 mg 3 times per day and the other

group took placebo tab, 3 times a day for a total of three months. Clinical assessment and investigations were again done after intervention. The following formula was used to calculate the volume of each ovary, Ovary volume = $(\pi/6 \times (D1 \times D2 \times D3))$ where D1, D2 and D3 were the maximum diameter in the transverse, antero-posterior and longitudinal axes, respectively. Ferriman and Gallwey score were used for the assessment of hirsutism by the same examiner. Hirsutism was diagnosed if the score was 8 or more [8].

DATA ANALYSIS

Data was analysed using SPSS version 20. Shapiro-wilk test was used to check the Normality of the data. Statistical significance was considered at $P < 0.05$. Data for continuous variable was shown as mean \pm standard deviation. To compare pre- and post-intervention degree of hirsutism, ovarian volume, fasting blood glucose and insulin levels pair t test was used. Independent sample test was used to compare the differences in degree of hirsutism, ovarian volume, fasting blood glucose and insulin levels between the 2 groups. Insulin resistance was calculated by Homeostatic Model Assessment for Insulin Resistance (HOMA- IR) values calculated by $[\text{fasting blood glucose (nmol/L)} \times \text{fasting insulin } (\mu\text{U/mL}) / 22.5]$.

RESULTS

The features of participants in both the groups regarding age, BMI, fasting glucose, ovarian volume, menstrual blood flow, fasting insulin and HOMA –IR values were not statistically different at baseline (table 1).

Hirsutism dropped from 12.5% to 7.5% in metformin group ($p < 0.05$), on the other hand there was no change in the group taking placebo. With respect to metformin group, the mean right ovarian volume was 10.6mm at baseline which reduced to 9.1mm after treatment ($p < 0.05$) while in the placebo it was 10.8 mm and 11.1mm pre and post intervention respectively. No significant change was observed in the level of glucose in fasting state in the metformin intervention group pre and post intervention while placebo group showed a trend towards significant increase at post intervention from 100.6 mg/dl to 105.6 mg/ dl ($p = 0.06$). The levels of insulin reduced from 17.1 IU/l to 14.1 IU/l at post intervention with metformin. HOMA IR value dropped from 4.25 to 3.51 ($p = 0.002$) in metformin group. On the other hand

HOMA IR worsened in the placebo group from 4.60 to 4.85, which can be attributed to greater fasting blood glucose in placebo group (table 2, figure 1 and 2).

Table 1. Baseline Features of Participants in The Metformin and Placebo Group.

| Characteristic | Metformin Intervention Group Mean ± [SD] | Placebo Intervention Group Mean ± [SD] | p - value |
|----------------------------|--|--|-----------|
| Age (years) | 25.85 [6.098] | 27.10 [6.365] | 0.530 |
| Menstrual duration(days) | 5.25 [2.197] | 4.65 [3.117] | 0.486 |
| Height in inches | 62.45 [3.762] | 62.30 [2.515] | 0.883 |
| Weight in Kilograms | 66.80 [14.717] | 74.05 [24.639] | 0.266 |
| Systolic Blood Pressure | 118.00 [9.515] | 121.00 [12.096] | 0.389 |
| Diastolic Blood Pressure | 82.00 [5.231] | 85.00 [8.272] | 0.178 |
| Left Ovarian volume (ml) | 9.830 [3.865] | 10.560 [2.596] | 0.488 |
| Right Ovarian volume (ml) | 10.690 [2.922] | 10.360 [3.827] | 0.761 |

Table 2. Changes in Variables after Taking Metformin.

| Variables | Pre intervention | Post intervention | p |
|-------------------------------|------------------|-------------------|--------|
| Hirsutism | 12.5% | 7.5% | < 0.05 |
| Fasting blood glucose (mg/dl) | 100.2 | 100.8 | > 0.05 |
| Right ovarian volume(mm) | 10.6 | 9.1 | < 0.05 |
| Fasting insulin level (IU/l) | 17.1 | 14.1 | < 0.05 |
| HOMA IR | 4.25 | 3.51 | 0.002 |

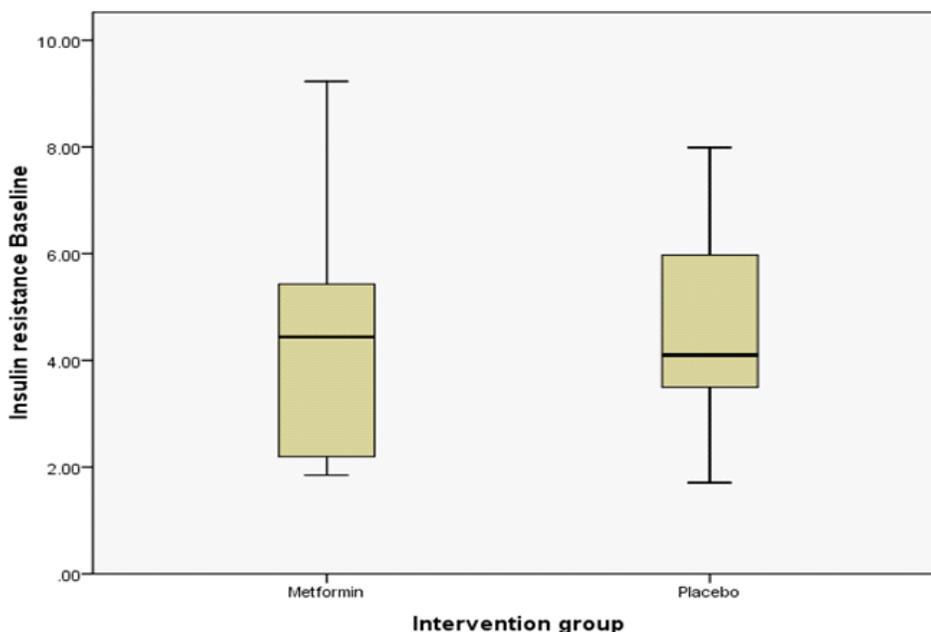


Figure 1. Insulin Resistance in Metformin and Placebo Groups at Baseline.

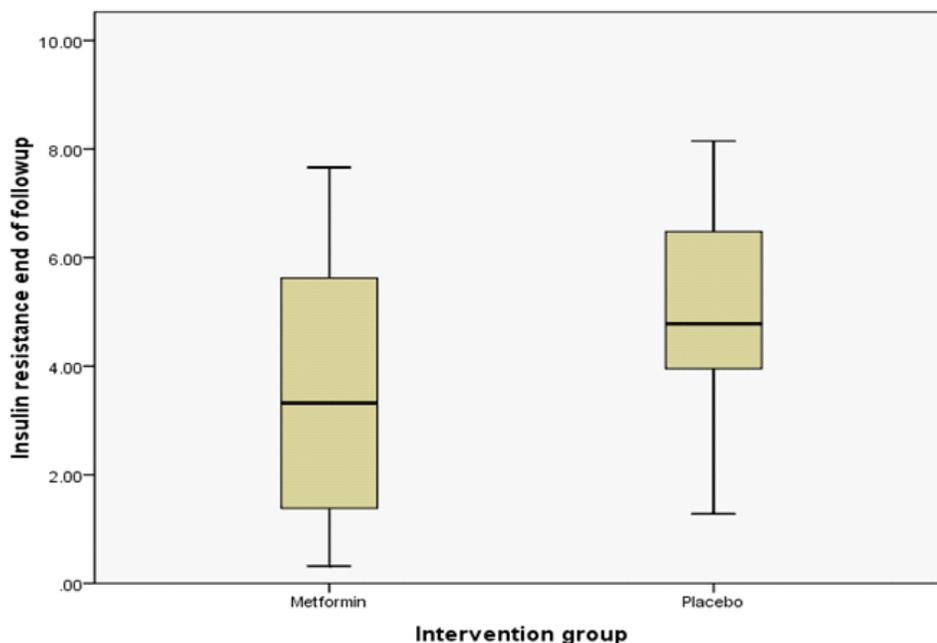


Figure 2. Insulin Resistance in Metformin and Placebo Groups after Follow up.

DISCUSSION

The aim of the current work was to assess the effects of metformin on hirsutism, ovarian volume and insulin resistance which are the main pathologies in patients with PCOS. The main results supported our hypothesis. Metformin significantly reduced hirsutism, ovarian volume and insulin resistance in patients with polycystic ovary disease.

Literature supports our findings regarding effect of metformin on hirsutism [9, 10]. Metformin has been given for different duration to demonstrate its effect on hair growth such as 14 months of metformin therapy by Kelly *et al.*, 2002 [9]. Another study by Pasqual *et al.*, 2000 demonstrated reduction in hair growth after six months of therapy with metformin [10]. However the current study has shown positive effect after three months of taking metformin. Moreover one study failed to show any effect of metformin on hirsutism [11].

Acne affects 63 % patients with PCOS [3]. It is a well-established fact that six months of therapy with metformin reduces acne in patients with PC but surprisingly the current study demonstrated an improvement even after three months [12].

Ovarian volume may be increased owing to greater mass of androgen producing tissue in the ovaries of patients with PCOS but fortunately it can be reduced

by use of metformin [13]. The current study clearly demonstrated that three months of therapy with metformin significantly reduced ovarian volume similarly to a study by Sanoee *et al.*, 2011 [13]. Low insulin levels by metformin increase the production of binding proteins for androgen, IGF1 and IGF2 leading to low androgen levels and as a result ovarian tissue mass reduces.

Metformin exerts its potential effects on glucose metabolism through a number of mechanisms. Firstly gluconeogenesis is inhibited in the liver thus reducing the level of glucose in blood. It also increases the transport of glucose into peripheral tissues. While there was no significant change in the fasting glucose levels in the group taking Metformin; the Placebo showed a deterioration of glucose levels in fasting state. Insulin Resistance has a crucial role in the pathogenesis of PCOS, which has been delineated by several studies both in vitro and in vivo [14]). In our country the frequency of insulin resistance in PCOS is 75% [15]. Fortunately it can be reduced by the use of metformin as documented by prospective longitudinal studies [16, 17]. However, the current study using a placebo controlled design provides stronger evidence in support of the positive effects of metformin on insulin resistance in patients with PCOS. Reduced levels of fasting insulin levels rather than fasting blood

glucose level in the current study contributes to improvement in insulin resistance.

CONCLUSION

Our data supports the finding that Metformin improves the clinical problems encountered by patients with after three months of therapy.

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