The Therapeutic Effect of Oral Insulin Sensitizer Metformin on BMI and Insulin Sensitivity in Women With Polycystic Ovary Syndrome[1]

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ABSTRACT

Objective: Polycystic ovarian syndrome (PCOS) is a common endocrine condition that affects women of reproductive age, its known to be associated with insulin resistance. The study aimed to evaluate the effects of metformin on insulin resistance and body mass index (BMI) in patients affected by PCOS. Materials and method: a total of one hundred women with PCOS were taken, and diagnosed according to standard criteria, patients were divided randomly into two groups, the group that was taken metformin (n=50, the case group), the group that not took metformin (n=50, the control group), blood samples were taken to test insulin level, glucose level, and then we calculate HOMA-IR, and BMI also calculated from the weight and the height of the patient, metformin was taken by the patient in a dose of (500-850mg three times daily), for three to sixth month. Results: Decreased BMI from (BMI=29.23±3.79Kg/m^2)of the control group, (BMI=25.65±2.74kg/m^2) of the case group (p=0.001). Decreased fasting insulin from (19.13±2.47miu/ml) of the control group, (17.02±1.91) of the case group(p value=0.0001). Decreased HOMA-IR from (4.13±0.79)of the control group, to (3.54±0.62) of the case group, (p=0.001), there were no effect on plasma glucose (4.87±0.64) of the control, and (4.65±0.48) of the patient that take metformin. Conclusion: treatment with metformin decreases insulin level, insulin resistance and decrease BMI, there were no effects on FSG.

Keywords: *PCOS; metformin; insulin; insulin sensitivity; HOMA-IR*

INTRODUCTION

The prevalence of polycystic ovarian syndrome (PCOS)is between 5% and 10% worldwide, making it one of the most prevalent metabolic and endocrine illnesses in women[1]. Although Stein and Leventhal initially defined the disease in 1935. The criterion for diagnosing the illness has altered over the years [2,3]

PCOS is present if two of the following three criteria are met, according to a consensus workshop held in 2003 at a conference of the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine. Anovulation or oligo-ovulation, excessive androgen activity in the lab or the clinical setting, or a polycystic ovary ultrasound picture (if other endocrine disorders are excluded)[4,5]

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Numerous studies have demonstrated that insulin plays a significant role in the pathogenesis of this syndrome. It directly affects ovarian steroidogenesis, which in turn stimulates the synthesis of androgens in theca cells, lowers liver steroid hormone binding globulin (SHGC), and raises androgen levels[6]. Women with PCOS frequently experience infertility, which is typically caused by anovulation. These women's fertility may also be affected by other aspects of PCOS, such as poorer egg quality, endometrial development flaws, and irregular implantation [7]. Around 50% of PCOS patients, both fat and lean, have insulin resistance associated with hyperinsulinemia [8–10].

This is brought on by impaired hepatic insulin breakdown and peripheral tissue resistance to insulin. Most likely, abnormalities in tissue insulin receptors are what lead to insulin resistance [11–13].

Pharmacological therapies are advised when IR lasts despite alteration in lifestyle[14]. The pharmacological effects of metformin as insulin-sensitizing have been thoroughly confirmed in women with PCOS[15]. The objective of this study was to find out the effect of metformin on BMI, fasting serum glucose, fasting serum insulin, and HOMA-IR

MATERIALS AND METHODS

Diagnosed cases of PCOS, attending the outpatient clinic and from Alsalam Teaching and Albatool Teaching Hospital from October 2021 to April 2022 were included in the study, the study was a case–control study and the biochemical analysis made in a private laboratory, PCOS was diagnosed by oligomenorrhea, obesity, hirsutism and by us followed Rotterdam criteria[15], A total number of 100women in the reproductive age (the age 18-35years). The scientific committee of the University of Mosul, the College of Pharmacy, and the Nineveh Health Directorate approved the study protocol. Informed consent was obtained from the subjects before the study, the study subjects were randomly assigned into two groups:

Group I: the women that don't take metformin (control group)

Group II: the women that took metformin(case group). The dose of metformin(500-850mg two or three times daily) for 3-6 months. Patient having PCOS with coexisting diseases (Diabetes mellitus, Heart disease), congenital adrenal hyperplasia.

women with pregnancy and getting treatment with clomiphene citrate were not included. Height was measured in centimeters (cm), weight in kilogram (kg) with light clothing and without shoes, and body mass index (BMI) was calculated as weight (kg) divided by the square meter (m^2)[16].

After the selection of the subjects an appointment was given and advised to come on the appointed day in fasting condition, fasting blood samples for each subject were collected, for measuring insulin level and then calculate HOMA-IR (homeostatic Model Assessment of Insulin Resistance)[17], for this purpose 5ml of the blood sample was drawn from the patient, blood sample is allowed to clot and centrifuged for 10 minutes at rate of3000 rpm and kept frozen at -20°C to be measure. for analysis of fasting insulin, the serum insulin was analyzed using an enzyme-linked immunosorbent assay (ELISA) Kit supplied by DRG Instrument, (Memmert, Germany), insulin sensitivity was calculated from (HOMA-IR) which is calculated from fasting serum glucose (FSG) and fasting serum insulin (FI) using the following formula :

HOMA-IR =FI (miu/ml)×FG (mmol/l)/22.5. The fasting glucose concentration is analysed by the glucose oxidase method supplied by Biolabo glucose kit (Biolabo, France). The data obtained in the current study were analyzed using Micro soft Excel to evaluate data for all mathematical and statistical studies, all values are expressed as (mean±SD) for comparison of the parameter between the cases and the control, unpaired t-test was utilized the differences were considered significant statistically if $p<0.05$, and Pearsons' (r-factor) correlation is used to show the correlation between the parameters of the cases and control group.

RESULTS

A total of one hundred women were included in the study, fifty patients with PCOS that don't use metformin as a control group were included, fifty patients with PCOS that use metformin (the case group) were also included, the dose of metformin were 500 tid or 850 bid for three to sixth month.

The result shows a significant difference in BMI (p value=.0001) and shows a non-significant difference in FSG (p value=0.05). The result shows a significant difference in fasting insulin (p value=0.0001) and also shows a significant difference in HOMA-IR (p value=0.001), see Table 1 and Table 2.

Table1. The effect of metformin on glycemic control and body mass index

Variables	Control (mean± SD)	Case (mean± SD)	P value*
BMI(kg/m2)	29.23±3.79	25.65±2.74	0.0001
FSG(m mole/l)	4.87±0.64	4.65±0.48	0.05
For t-test the result is significant at p<0.05			

Table 2. The effect of metformin on insulinemic state and insulin resistance (HOMA-IR)

Parameter	Control (mean±SD)	Cases (mean ±SD)	P value
Fasting insulin (MIU/ml)	19.13±2.47	17.02±1.91	0.001
HOMA-IR	4.13±0.79	3..54±0.62	0.001

There is a significant positive correlation between BMI and Fasting insulin and there is a significant positive correlation between BMI and HOMA-IR (Table 3)

Table 3. Correlations between parameters

parameters	R	p-value
Fasting insulin:BMI	0.752**	0.0001
HOMA: BMI	0.539**	0.0001
**.Correlation is significant at the the0.01 level (2-tailed)		

DISCUSSION

Insulin resistance (IR) is the term used to describe the inability of the target cells to respond to normal or typical levels of insulin [18]. Yet, the presence of IR results in a compensatory enhanced pancreatic beta cells' production of insulin, which ultimately fails to manage the hyperglycemia and results in T2DM.Hyperinsulinaemia in PCOS has been linked to an increase in hyperandrogenaemia through a central mechanism[19] or by lowering sex hormone-binding globulin levels in the blood. In PCOS, IR is not regarded as a diagnostic factor [20]. Nonetheless, it is well-acknowledged as a characteristic of PCOS that is widespread and unrelated to obesity[21]. The first Insulin sensitized drug to be employed in PCOS to examine the role of insulin resistance in the pathophysiology of the condition was metformin[22]. Nowadays, metformin is the medicine used most frequently around the globe to treat type 2 diabetes. Its principal activity appears to be a suppression of hepatic glucose production and an enhancement in peripheral insulin sensitivity. In non-DM women with PCOS, the advantages of metformin on insulin sensitivity have been shown[23]. The use of metformin is linked to improved menstrual cyclicity, better ovulation, and a reduction in circulating androgen levels[24]. Metabolic benefits are increased when weight loss occurs, and metformin use alone may increase weight loss[25]. Nowadays, biguanide metformin (1,1-dimethylbuguanide

hydrochloride) is utilized as an oral antihyperglycemic medication. Although it also reduces intestinal glucose absorption and boosts insulin sensitivity in peripheral tissues, its main therapeutic effect is to block hepatic glucose synthesis, Metformin contains antilipolytic properties that lower circulating levels of free fatty acids, which ultimately help to decrease gluconeogenesis[26].

As shown in this study there is a significant decrease in BMI, and this is consistent with the study done by Harborne and colleagues that reported a significant decrease in BMI in obese and morbidly obese women independent of lifestyle modification [27], also there is a non-significant difference in FSG level in this study support the idea that metformin has little effect on serum glucose, and this agreement with many studies done [28,29]. Also in this study, there is a significant improvement in fasting insulin and HOMA-IR and this is consistent with studies were done by Goldenberg et al. and Susanne et al[30,31]

CONCLUSION

Hyperinsulinemia and hyperandrogenism increase the risk of diabetes in PCOS patients. Women with anovulation, hyperandrogenism and hyperinsulinemia are more exposed to the risk of diabetes mellitus independent from insulin. Different studies have shown that continuous anovulation made the patients three times more susceptible to endometrial hyperplasia, Metformin increases insulin sensitivity, decreases fasting insulin and HOMA-IR, which decreases the risk of diabetes mellitus, also decreases (BMI)so decreases the risk of obesity, and other complication of PCOS.

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