ORIGINAL ARTICLE

Metabolic and Hormonal Effects Of Rosiglitazone In Overweight Women With PCOS

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ABSTRACT

Objective: Polycystic ovary syndrome(PCOS) is the most common hormonal disorder which mostly affects women of childbearing ages. Almost,women with this syndrome, insulin sensitizing drugs can have both beneficial hormonal and biochemical effects. Hence, the objective of this research was to assess and compare the effects of insulin sensitizing drug, rosiglitazone, on hormonal and biochemical profiles in patients with PCOS.

Methods: In this simple randomization study, approximately, one hundred and twenty subjects were enrolled in this study, they were divided into two groups of 60 subjects each. The patients' group were received rosiglitazone treatment for three months (4-5mg/day) and the other 60 were the control group which included apparently healthy volunteers. Hormonal profiles (serum testosterone, serum insulin, HOMA-IR and serum resistin) and biochemical profiles (fasting serum glucose and lipid profile), in addition to body weight, height, body mass index, and even blood pressure were evaluated before and after treatment for both the patient and control groups.

Results: The current study found a that there was a significant increase in the mean of body mass index (BMI), serum levels of glucose, insulin, testosterone, resistin, lipid profile (TC, HDL, LDL, TG) in addition to systolic and diastolic blood pressure in women with PCOS prior to rosiglitazone in comparison to controls. Whereas after drug therapy the patient experienced a significant decrease in all of the studied parameters associated with insulin resistance improvement, as well as a nonsignificant decrease in serum testosterone level.

Conclusion: This study found that treating women with PCOS with rosiglitazone resulted in a decrease in hormonal profiles of serum insulin and serum testosterone, as well as an improvement in metabolic profiles, indicating the potential benefit of this drug in the treatment of PCOS patients.

Keywords: Polycystic ovary syndrome; Rosiglitazone, insulin resistance, serum glucose, ,BMI, testosterone, lipid profile, resistin.

INTRODUCTION

Polycystic ovary syndrome, is a hormonal condition that affects women of with childbearing ages. Women with this disease typically have hormonal and metabolic abnormalities that affect their overall health and general appearance. [1,2] Recently, the diagnosis of PCOS is made on the basis of Rotterdam Sponsored Consensus Workshop Group (ESHRE/ASRM) 2003 criteria by the presence of at least two of the following criteria are present: Rare or no ovulation, clinical and/or laboratory evidence of androgen excess (hirsutism, acne, and/or increased androgen concentrations in serum) or the ultrasound picture of polycystic ovaries. At the same time, other reasons for hyperandrogenism should be excluded.[2] Dyslipidemia and infertility were also linked to PCOS.[3] It is clear that insulin resistance and PCOS causes are not yet well understood,[4,5] a multifactorial syndrome is taken under consideration with several genetic, metabolic, endocrine, and environmental disorders.[6] Hyperinsulinemia plays a critical role in PCOS.[7,8] It can cause abnormal ovarian testosterone and insulin secretion, resulting in dysfunctional ovarian and menstrual activity.[9]

Insulin tolerance, and hence a reduction in insulin concentration and function, is often accomplished in many ways: I through lowering weight by dietary modifications if overweight, or through using the insulin sensitizing drugs and even antiandrogens if obesity is present.[10] Recently, insulin sensitizing agents have been found as the standard treatment. Some studies found that rosiglitazone therapy improved the irregularities in the reproduction in these patients, although others found no pathophysiological or biochemical improvements following rosiglitazone therapy.[11]

Thiazolidinediones, the current medications, support optimal clinical approaches for the treatment of PCOS. These drugs include the insulin sensitizer rosiglitazone, that increases insulin sensitivity without causing hypoglycemia or causing changes in body fat distribution. [12,13, 14]

Treatment for PCOS results in a normal menstrual cycle, the reduction of hyperandrogenism and cardiovascular risk factors, and an increase in responsiveness to ovulation induction therapies in a large percentage of cases.[15,16]

The aim of this research is to assess the hormonal and biochemical changes in women with PCOS after treatment with rosiglitazone.

PATIENTS AND METHODS

One hundred and twenty participants were enrolled in this study. The study include the participation of a sixty newly diagnosed PCOS patients. They were selected from the Al-Batool Maternity and Children Teaching Hospital in Mosul's out-patient clinic. The study protocol was approved by the Mosul Health Administration and the University of Mosul's research ethics committees. Another sixty subjects of apparently healthy volunteers comprised the control group. Each subject in the patient and control groups gave their informed consent. Between December 1st, 2019 and June 1st, 2020, a three-month unrestricted, supervised, comparative clinical trial was conducted.

Patient diagnosis with PCOS is according to the Rotterdam 2003 diagnosis Criteria (Rotterdam Consensus, 2004). According to the ESHRE/ASRM PCOS consensus workshop group in Rotterdam (2004). The presence of every two of the following parameters had been used to diagnose PCOS. The study excluded women who have NIDDM, or patients taking drugs that alter hormonal or biochemical parameters under study. For 3 months, the participants received rosiglitazone 4-5mg daily in two divided doses after meals.

Biochemical and hormonal parameters were assessed in both patients (at the beginning of rosiglitazone therapy and at the end of three months of treatment) and controls which includes: Fasting serum insulin, serum testosterone, fasting serum glucose [FSG]), serum triglyceride (TG), serum total cholesterol(TC), serum high-density lipoprotein (HDL), serum low-density lipoprotein (LDL), and serum resistin . The FSG and lipid profile were evaluated using standard enzymatic methods. Enzyme-linked immunosorbent assays (ELISA) were used to evaluate free testosterone. Serum Insulin level was analyzed by using ELISA technique.[4] The biochemical and hormonal profiles, such as insulin and testosterone in the serum, were assessed again after treatment and compared to their pre-treatment values. A common formula was used to calculate BMI. A mercury sphygmomanometer was used to take each subject's blood pressure from the arm in the sitting position. The calculation was taken after at least five minutes of rest.[5] The HOMA-IR was determined using the standard formula below, which took into account both fasting serum insulin and fasting glucose levels.[6] Insulin resistance is diagnosed when the HOMA value is greater than 2.[7]

In statistical analysis, the unpaired t-test was used to compare the ages of the two groups, as well as the baseline results of the patient and control groups. To compare the results before and after drug treatment, a paired student t-test was used. The statistical results were considered significant if P≥0.05.[7]

RESULTS

Table 1 shows the demographic characteristics of the patients and controls, showing that there was no substantial difference in the age of the patients for both groups under study, although there was a significant increase were found in BMI, systolic, and diastolic blood pressure(P<0.001).

Table 1: Demographic characteristics of patient and controls

Parameters	Patient	Control	P- value
Age (years)	30.45 ± 4.32	29.3 ± 4.9	0.342
BMI (Kg/m^2)	36.78± ± 1.7	21.48 ± 1.9	< 0.001
Systolic blood pressure (mmHg)	129.2 ± 7.1	109.2 ± 7.2	< 0.001
Diastolic blood pressure (mmHg)	82.4 ± 7.3	71.6 ± 7.6	< 0.001

Table 2:Metabolic and hormonal profiles between patients and controls

Parameters	Patient	Control	P- value
Serum Testosterone (ng/dl)	2.6 ± 0.8	0.8 ± 0.5	< 0.001
Fasting serum insulin (mIU/l)	22.3 ± 2.4	4.8 ± 2.4	< 0.001
Fasting serum glucose (mmol/l)	6.2 ± 0.9	4.0 ± 0.6	< 0.001
Total Cholesterol (mg/dl)	170.10 ± 26.30	150.13 ± 20.10	< 0.001
TG (mg/dl)	150.0 ± 44.0	110.12 ± 37.41	< 0.001
LDL (mg/dl)	100.50 ± 19.80	78.78 ± 26.10	< 0.001
HDL (mg/dl)	43.77± 5.75	49.8 ± 4.84	< 0.001
HOMA-IR	3.4±1.4	1.7±0.43	< 0.001
Resistin (ng/dl)	19.83 ± 6.101	9.36 ± 2.17	< 0.001

Table 3: Metabolic and hormonal profiles before and after Rosiglitazone

Parameters	Before Therapy	After Therapy	P- value
Serum testosterone (ng/dl)	2.6 ± 0.8	1.45 ± 0.70	< 0.001
Fasting serum insulin (µU/ml)	22.3 ± 2.4	12.00 ± 4.22	< 0.001
FSG (mg/dl)	6.2 ± 0.9	76.7 ± 9.25	< 0.001
Total Cholesterol (mg/dl)	170.10 ± 26.30	161.27 ± 29.55	< 0.001
TG (mg/dl)	150.0 ± 44.0	145.68 ± 42.51	< 0.001
LDL (mg/dl)	100.50 ± 19.80	87.50 ± 25.34	< 0.001
HDL (mg/dl)	43.77± 5.75	47.64 ± 3.98	< 0.001
HOMA-IR	3.4±1.4	2.1±0.9	< 0.001
Resistin (ng/dl)	19.83 ± 6.101	12.42 ± 2.23	< 0.001

The present study found that there was a significant increase in the following parameters :serum testosterone, fasting serum insulin, fasting serum glucose, lipid profiles, HOMA-IR and serum resistin (P<0.001)which was observed in women with PCOS in comparison to controls(Table 2). After three months of treatment with rosiglitazone, a significant improvement in all these studied parameters(P<0.001)was observed, this improvement was associated with an improvement in insulin resistance along with a significant decrease in serum testosterone level which were found in PCOS patients as compared to controls(Table 3).In addition,in

considerating correlations significant positive correlation was found between serum insulin and serum testosterone levels,testosterone and HOMA-IR, resistin and BMI, Insulin and Resistin, HOMA-IR, and resistin in all studied groups (P< 0.001)(Table 4).While there was a nonsignificant correlation was found between serum testosterone and BMI and between serum testosterone and serum resistin in all studied groups(Table 4).The serum level of resistin in both patient (before and after treatment with rosiglitazone) and control groups and was found to be significantly affected according to BMI values(P< 0.001) (Table 5).

Table 4: Correlations between Metabolic and hormonal parameters in all studied groups.

Parameter	Correlations	
	r	p-value
Insulin: BMI	0. 456	<0.01
HOMA-IR : BMI	0. 345	<0.01
Testosterone: BMI	0.543	NS
Testosterone: Insulin	0.479	<0.01
Testosterone: HOMA-IR	0.382	<0.01
Resistin: BMI	0.5051	<0.01
Insulin: Resistin	0.6595	<0.01
HOMA-IR: Resistin	0.5908	<0.01
Testosterone: Resistin	0.288	NS
Resistin: FSG	0.5086	<0.01

NS: Non significant

Table 5:Resistin level in patient and control groups according to BMI

Parameter	Patient		Control	
Resistin (ng/dl)	BMI <25kg/m^2 N=15	BMI ≥25 kg/m^2 N=45	BMI <25kg/m^2 N=25	BMI≥25 Kg/m^2 N=35
	13.64±2.01	20.57±5.3	7.9±1.02	11.53±1.76

DISCUSSION

PCOS is a disorder marked by chronic anovulation brought on by a variety of causes, the most common of which tend to be hyperinsulinemia and hyperandrogenism. [17]This is the first study to evaluate the effects of an insulin sensitizer, rosiglitazone, in overweight women with PCOS. Although metabolic abnormalities were already linked to this syndrome, the goal of this work was to see how rosiglitazone influenced testosterone levels, insulin levels, fasting serum glucose, lipid profile, and serum resistin levels in women with PCOS. [18] Another consideration that may trigger menstrual and ovulatory irregularities is overweight. Thus, in the current research, patients who were overweight or normal were randomly assigned to the insulin-sensitizing agents, rosiglitazone, or the control group.[19] Insulin-sensitizing agents have recently been recommended for the treatment of women with polycystic ovary syndrome (PCOS),as insulin resistance and associated hyperinsulinemia are generally accepted as the most prevalent pathologic cusses for this syndrome. [20.21] As a result, the use of insulin sensitizers was recommended in the majority of patients with this condition since these medications were effective not only in lowering serum testosterone levels but also in improving serum glucose and serum insulin levels. serum resistin, and serum lipids.[22,23]

The current study discovered a significant rise in body mass index (BMI), systolic and diastolic blood pressure, and serum levels of serum glucose, insulin, testosterone, resistin, and lipid profile (TC, HDL, LDL, TG) in women with PCOS prior to rosiglitazone (P<0.001). When compared to controls, the fasting serum glucose to insulin ratio, a measure of insulin tolerance, decreased significantly in patients prior to rosiglitazone therapy. These results contradicted previous research on the positive impact of insulin sensitizers in the treatment of PCOS.[24,25] In the patient group, rosiglitazone therapy resulted in a significant decrease in all the studied parameters associated with insulin resistance improvement, as well as a nonsignificant decrease in serum testosterone levels when compared to the control group. In patients, there was a significant positive correlation (P<0.001) between BMI, serum insulin, serum resistin, lipid profile, and serum testosterone levels as compared to the control group.

In comparison, rosiglitazone treatment resulted in a significant reduction in fasting serum insulin and insulin tolerance (HOMA-IR).[26.27] As a result of these changes, there was even a reduction in both total testosterone and lipid parameters, that attained statistical significance. The values decreased significantly following treatment with rosiglitazone, as previously stated. [28] Insulin resistance in muscle tissues and even adipose tissues increases plasma FFA and insulin levels, promoting VLDL production and secretion in the liver, resulting in hypertriglyceridemia. This, in turn, raises blood levels of postprandial lipoprotein (LDL), which lowers HDL cholesterol. In PCOS, rosiglitazone, an insulin-sensitizing agent, performs a beneficial role in lowering serum testosterone by exerting on serum insulin and increasing insulin sensitivity of tissues.[29]

The most important explanation for rosiglitazone's effect on these parameters is that insulin sensitizing agents may actually act as a selective agonist for the peroxisome proliferator-activated receptor gamma (PPAR) receptor and, by this variable mechanism, might affect the occurrence of various enzymes and proteins involved in metabolic pathways in patient.28 These agents may have pleiotropic therapeutic effects on a variety of metabolic disorders, actually improving insulin sensitivity and glucose

absorption in peripheral tissues, resulting in hypoglycemia as a pharmacological effect. [29] Rosiglitazone and pioglitazone have also been found to improve IR in PCOS patients.[30] Treatment with an insulin sensitizer improves cardiovascular risk factors associated with lower triglyceride and resistin levels in women with PCOS. [31,32] All of the recent studies available today have been small, short-term, and based on ovulation and menstrual regularity change. As a result, it is unclear whether long-term treatment of PCOS patients will avoid the development of type 2 diabetes or boost cardiovascular risk factors. [33] This is due to the fact that all available thiazolidinedione drugs acted by activating nuclear peroxisome proliferator-activated receptors, these receptors that controls the occurence of different genes needed for glycemic control, lipid metabolism,inflammation, vascular tone and arteriosclerosis.[34,35,36] Thiazolidinediones,which inhibit P450c17 and 3-hydroxysteroid dehydrogenase, two primary enzymes in human androgen synthesis, can have androgen-lowering effects.[37,38,39] Our findings are consistent with previous reports on the clinical effects of thiazolidinediones in patients with PCOS. [37,38,39] The present research showed that there was no statistically meaningful variation in age between the treatment and study groups when they were paired, but systolic and diastolic blood pressure in the patient group was slightly higher than in the control group ($P<0.001$). [40, 41, 42]

After 3 months of rosiglitazone therapy, the results showed a substantial decrease in fasting serum insulin and serum testosterone levels ($P<0.001$), which was compatible with the findings of other research and reinforced the hypothesis that an insulin sensitizing drug could exert its effect by encouraging peripheral glucose consumption.[43,44,45,46]

CONCLUSION

According to the results of this study, rosiglitazone therapy appears superior in these patients by improving insulin tolerance and elevated testosterone levels, but it may be particularly effective in promoting the recovery of ovulation and menstrual irregularities in these patients. It also has the additional potential of improving fasting serum glucose and serum resistin levels. In general, since the information currently available is of poor quality, large-scale clinical trials assessing multiple therapies with insulin-sensitive drugs are critically intended to successfully guide the clinical care of women with PCOS.

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Conflicts of interest: No potential conflicts exist. We had full access to all the information in the study and take full responsibility for the integrity of the information and the accuracy of the data analysis.

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