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Original Article

Treatment with Metformin Can Improve Insulin Resistance and Lipid Profile in Non-Diabetic Iraqi Women with Polycystic Ovary Syndrome

Ali M. Kadim Al-Tuma[1], Saba Sabeeh Hussain[2], Muhjah Falah Hassan[3]

[1]Department of Internal Medicine, College of Medicine, Karbala University, Karbala, Iraq, [2]Department of Anatomy, Histology and Embryology, College of Medicine, Thiqar University, Thiqar, Iraq, [3]Department of Anatomy, Histology and Embryology, College of Medicine, Karbala University, Karbala, Iraq

Abstract

Background: Women with polycystic ovary syndrome (PCOS) are usually at increased risk of metabolic syndrome and insulin resistance (IR), regardless of their body weight, and the development of type 2 diabetes in those women is not uncommon. Metformin is an oral hypoglycemic drug with a significant role in improving IR and lipid profile in diabetic persons without causing hypoglycemia. **Objectives:** To study the effectiveness of metformin in reducing body weight, IR, and lipid profile in non-diabetic PCOS women. **Materials and Methods:** Two hundred women with PCOS were included in the study. Serum was taken from them, and measurement of insulin level, fasting blood sugar (FBS), glycosylated hemoglobin (HbA1c), and lipid profile were performed as a baseline. Metformin tabs of 500 mg twice daily were given for 3 months, and measurement of the previous parameters was also performed following treatment. The results were compared between pre- and post-treatment. **Results:** The study showed that body mass index was not changed following 3 months of metformin intake, while there was a significant reduction in FBS, serum level of insulin, HbA1c, and Homa-IR following treatment. Together and with the exception of a non-significant mild improvement in serum high-density lipoprotein level, serum levels of cholesterol, triglyceride, and low-density lipoprotein were improved with a significant reduction following metformin treatment. **Conclusion:** Regardless its ability to reduce body weight, metformin can be effectively used for lowering FBS, lipid profile, and improving IR in non-diabetic PCOS women and can be used as an effective intervention to improve the quality of life in women with PCOS.

Keywords: HbA1c and lipid profile, Homa-IR, metformin, PCOS

Introduction

Polycystic ovary syndrome (PCOS) is the most common disorder affecting reproductive-age females with endocrine and metabolic dysfunction, characterized by a collection of signs and symptoms of hyperandrogenism and chronic anovulation with or without polycystic ovarian morphology by trans-vaginal ultrasound, after the exclusion of other causes of androgen excess.[1] It is of unknown etiology, however, genetic and environmental factors may predispose to these multiple hormonal imbalances.[2] The exact mechanism is poorly understood among physicians and reproductive specialists.[3] The syndrome is seen in approximately 18.8% of childbearing-age women and usually varies according to female age, body mass index (BMI), and type of menstrual dysfunction.[4] Excess body weight/obesity is a common association with PCOS, reaching a prevalence of up to 50%, and may exacerbate metabolic dysfunction making the affected women at an increased risk for metabolic syndrome.[5,6] Hyperinsulinemia and insulin resistance (IR) are common features of PCOS, which usually occur as a result of glucose intolerance and affect 35–40% of

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Address for correspondence: Dr. Ali M. Kadim Al-Tuma, Department of Internal Medicine, College of Medicine, Karbala University, Karbala, Iraq.
E-mail: doctor88ali@gmail.com

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PCOS women when they reach 40 years old.[7] Even though, glucose intolerance and type 2 diabetes can be seen in normal-weight women where the risk is reinforced after gaining weight.[8] It has been suggested that women with PCOS have high triglyceride, cholesterol, low-density lipoprotein (LDL), and low high-density lipoprotein (HDL) levels.[9]

Metformin is an oral hypoglycemic agent belonging to the biguanides class of anti-diabetic drugs.[10] Its hypoglycemic effect is closely due to the inhibition of both hepatic glucose production and intestinal glucose absorption. Metformin also promotes insulin sensitivity and regulates β-cell function.[11] Metformin inhibits both hepatic gluconeogenesis and glycogenolysis and stimulates glycogenesis while it increases both the number and affinity of insulin receptors (tyrosine kinase activity) and the translocation and intrinsic activity of glucose transporter type 4 in the extra-hepatic tissues (adipose tissue and skeletal muscles).[12] Glucose utilization in peripheral tissues can also be regulated by metformin, with the result of lowering food intake and glucose absorption.[13] Metformin does not cause hypoglycemia as it does not stimulate endogenous insulin secretion.[14] Metformin may decrease adiposity and ameliorate obesity and can be used in the treatment of obesity-associated comorbid conditions.[15]

Materials and Methods

Study design and patients

The study is an interventional prospective one in which 200 females diagnosed with PCOS according to the Rotterdam criteria were included. The females were collected from the outpatient clinic at the Gynecology and Obstetrics Teaching Hospital/Karbala—Iraq throughout the period from January 2023 to May 2023. Their age ranged from 18 to 40 (mean age 27.03 ± 6.07) years, and their fasting blood sugar (FBS) was <110 mg/dL.

Baseline serum levels of FBS, insulin, HbA1c (it was measured to exclude sub-clinical diabetes or a pre-diabetic state), and lipid profile (cholesterol, TG, HDL, and LDL) were obtained by collecting a 5 mL of venous blood from the antecubital fossa. All women were given metformin tablets 500 mg orally twice daily for 3 months as standard therapy. After the end of the treatment period, the response to metformin was studied by repeating the measurements of the same parameters. Patient follow-up was through social media during the period of treatment. Only weight and height were measured for them to calculate BMI, and waste circumference was not measured due to lack of privacy and religious issues as it needs a full patient check-up).

Females with endocrine disorders (hypothyroidism in which elevated lipid profile is a common complication and hyperthyroidism in which high blood pressure is a common complication), Cushing's disease (excessive steroid secretion increases blood sugar and may lead to diabetes), androgen-secreting adrenal tumors (a condition that produces similar clinical and hormonal features of PCOS but does not elevate blood sugar and lipid profile), hypertension (systemic disease usually occur in a person with elevated lipid profile), profound diabetes, impaired kidney function (usually have hypercholesterolemia and triglyceridemia, and the use of drugs should be with caution), and taking other hypoglycemic agents (diabetes controlled by medication) or lipid-lowering drugs (persons on those treatments usually have normal glucose levels and lipid profile, respectively) were excluded.

The calculation of BMI was performed by dividing the patient's weight in kilograms by the square of height in meters.[16]

The homeostasis model of IR (HOMA-IR) has been widely used for the best estimation of IR and pancreatic beta cell function.[17] It is calculated according to this equation: (FBS × fasting insulin)/405. All the biochemical tests were conducted using commercial kits and the enzyme-linked immunosorbent assay method.

Statistical analysis

Data were analyzed statistically using Statistical Package for Special Sciences version 24 (IBM Corp., Armonk, NY, USA). All data are continuous, so mean ± standard deviation was calculated for them, and the independent student *t* test was used for the comparison between the data before and after the use of metformin. The variation was considered significant at a *P* value below and equal to 0.05.

Ethical approval

Ethical approval was obtained from the Karbala University/College of Medicine ethical committee. The purpose of the study was explained to the women, and their formal acceptance was obtained from them.

Results

Table 1 exhibits variables including BMI, FBS, insulin level, Homa-IR, and HbA1c measurements before and after metformin intake. There is a significant statistical difference regarding these parameters being lower following metformin intake with the exception of BMI at a *P* value of ≤0.05.

Table 2 illustrates the lipid profile in the form of serum cholesterol, triglyceride, HDL, and LDL before and after metformin intake. It shows an improvement in lipid profile following metformin intake with a significant statistical variation except LDL which exhibits a non-significant improvement at a *P* value of 0.128.

Table 1: Body mass index (BMI) and glycemic index before and after metformin intake

Laboratory Parameters		Mean ± 2SD	Paired t-test p-value
BMI (kg/m2)	PreTretment	28.88±5.45	0.059[NS]
	PostTreatment	28.04±5.29	
FBS (mg/dl)	PreTreatment	94.47±12.13	< 0.001[S]
	PostTreatment	90.56±12.31	
Insulin IU/ml	PreTreatment	19.66±15.16	< 0.020[S]
	PostTreatment	17.56±11.94	
Homa-IR (IU/l)	PreTreatment	4.67±3.89	0.009[S]
	PostTreatment	4.02±2.96	
HbA1c (mmol/mol)	PreTreatment	5.00±0.69	< 0.001[S]
	PostTreatment	4.58±0.66	

[S]: Significant at *p*-value ≤ 0.05, [NS]: Non-significant

Table 2: Lipid profile before and after metformin intake

Laboratory Parameters		Mean ± 2SD	Paired t-test p-value
TG (mg/dl)	PreTreatment	126.9±549.82	< 0.001[S]
	PostTreatment	111.57±37.39	
LDL (mg/dl)	PreTreatment	97.99±70.10	< 0.004[S]
	PostTreatment	84.38±24.60	
HDL (mg/dl)	PreTreatment	45.01±9.68	< 0.054[NS]
	PostTreatment	46.38±8.98	
Cholestrol (mg/dl)	PreTreatment	159.92±45.19	< 0.001[S]
	PostTreatment	144.82±45.61	

[S] : Significant at *p*-value ≤ 0.05, [NS]: Non-significant

Discussion

The novelty of the current study is based on the absence of previous studies in Iraq that had discussed the use of metformin in non-diabetic, reproductive-age PCOS women. Previous Iraqi studies have focused on the usefulness of metformin in diabetic females with or without PCOS or in only obese pre-diabetic women. This study aimed to show the usefulness of metformin in preventing or lowering the risk of diabetes in such females, even in lean ones. Metformin is not a weight-loss drug, but some researchers have found a link between the drug and weight loss due to its role in decreasing appetite and regulating glucose and lipid metabolism.[18]

Although its efficacy for the treatment of obesity has been evaluated in a few clinical trials, metformin still is not FDA approved due to the inconclusive results. The current study exhibited that metformin did not affect body weight when it had been given for 3 months. Similar results were obtained by a meta-analysis in 2020 which includes 21 clinical trials, and it concludes that the reduction in BMI value is not enough (<5% reduction from baseline BMI) to be considered as weight loss according to the clinical practice guidelines for comprehensive medical care of patients with obesity, 2016/American Association of Clinical Endocrinologists and American College of Endocrinology.[19,20] Others showed that metformin had a potent weight reduction effect and can be used effectively as a weight-losing drug in overweight and obese persons.[21-23]

Regarding FBS, a significant reduction after metformin therapy has been shown. This could be explained by the drugs' ability to suppress the hepatic synthesis of glucose, increase the sensitivity of liver and fat cells to insulin, and their role in the decrease of the intestinal absorption of carbohydrates.[18] A study by Cravalho *et al.*[24] was in agreement with this result while a study by Jakubowska *et al.*[25] disagreed and showed a non-significant reduction in FBS. Regarding the glycosylated hemoglobin (HbA1c) level, which usually gives an idea about the average blood glucose levels in the previous 3 months due to its attachment with the red blood cells which have a life span of 120 days or 3 months, the present study showed a significant reduction in HbA1c level following metformin treatment. This outcome was compatible with the results obtained by Scheen,[26] but it was inconsistent with Bredella *et al.*[27]

Regarding lipid profiles, a significant reduction of TG, LDL, and total cholesterol after 3 months of metformin treatment had been seen, which could be due to reduced expression and activity of some products or enzymes involved in lipid synthesis and metabolism mainly acetyl-CoA carboxylase, fatty acid synthase, and HMG-CoA. The same results were reached by several authors worldwide.[28-30] While Jiang *et al.*[31] suggested that despite metformin's ability to reduce serum TG and cholesterol levels, it is not effective in improving LDL levels in drug-induced dyslipidemia. Regarding serum level of HDL, although the present study showed a non-significant mild improvement in LDL, a study by Abrilla *et al.* exhibited a significant improvement in HDL serum level after metformin treatment.[32] Finally, we noticed a rise in blood sugar in a few patients throughout the study period.[33]

Conclusion

Regardless of its ability to reduce body weight, metformin can be effectively used for lowering FBS, lipid profile, and improving IR in non-diabetic PCOS women and can be used as an effective intervention to improve the quality of life in women with PCOS.

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Conflicts of interest

There are no conflicts of interest.

References

1. Al-Safi WG, Hassan MF. Pregnancy rate in women with PCOS with high LH/FSH ratio undergoing ICSI. Lat Am J Pharm 2021;40:336-340.
2. Hassan MF, Sengupta P, Dutta S. Assisted reproductive technologies in women with polycystic ovarian syndrome. Biomed Pharmacol J 2021;14:1305-8.
3. Hussain SS, Rustum HM. Evaluation of anti-zona pellucida antibodies in serum and follicular fluid for polycystic ovarian women undergoing intracytoplasmic sperm injection programme. Int J Res Pharm Sci 2018;9:1533-7.
4. Jamal AF, Ismael RA. Ultrasonographic prevalence of polycystic ovarian morphology among women of reproductive age group. Zanco J Med Sci 2019;23:57-65.
5. Hassan MF, Al-Yasiry RZ, Ghaleb RA. Possible predisposing and predictable factors for the development of ovarian hyperstimulation syndrome (OHSS) in women with polycystic ovary syndrome (PCOS) whom undergone intra cytoplasmic sperm injection (ICSI). MJBMB 2020;1:37-40.
6. Hassan MF, Kadim HA, Edan BJ, Dutta S, Sengupta P. Embryo quality and intracytoplasmic sperm injection (ICSI) outcome in Iraqi women with polycystic ovary syndrome (PCOS): A cohort prospective study. Biomed Pharmacol J 2023;16:863-70.
7. Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: A systematic review and meta-analysis. Hum Reprod Update 2010;16:347-63.
8. Peigne M, Dewailly D. Long term complications of polycystic ovary syndrome (PCOS). Ann Endocrinol (Paris) 2014;75:194-9.
9. Wild RA. Dyslipidemia in PCOS. Steroids 2012;77:295-9.
10. Yunoos M, Sankar DG. Stability indicating quantitative RP-HPLC method development and validation for simultaneous determination of metformin hydrochloride and saxagliptin in bulk and combined tablet dosage form. J Chem Pharm Res 2015;7:346-55.
11. Zhou T, Xu X, Du M, Zhao T, Wang J. A preclinical overview of metformin for the treatment of type 2 diabetes. Biomed Pharmacother 2018;106:1227-35.
12. Miceli DD, Vidal PN, Batter MF, Pignataro O, Castillo VA. Metformin reduces insulin resistance and the tendency toward hyperglycaemia and dyslipidaemia in dogs with hyperadrenocorticism. Open Vet J 2018;8:193-9.
13. Rhee SJ, Choi Y, Lee S, Oh J, Kim SJ, Yoon SH, *et al*. Pharmacokinetic and pharmacodynamic interactions between metformin and a novel dipeptidyl peptidase-4 inhibitor, evogliptin, in healthy subjects. Drug Des Devel Ther 2016;10:2525-34.
14. Gong L, Goswami S, Giacomini KM, Altman RB, Klein TE. Metformin pathways: Pharmacokinetics and pharmacodynamics. Pharmacogenet Genomics 2012;22:820-7.
15. Yanovski JA, Krakoff J, Salaita CG, McDuffie JR, Kozlosky M, Sebring NG, *et al*. Effects of metformin on body weight and body composition in obese insulin-resistant children: A randomized clinical trial. Diabetes 2011;60:477-85.
16. Maqbool M, Dar MA, Gani I, Geer MI. Insulin resistance and polycystic ovary syndrome: A review. J Drug Deliv Ther2019;9:433-6.
17. Biswas S, Dey SK. A comparative study for diagnostic evaluation of polycystic ovarian syndrome (PCOS) by estimation of high sensitivity C reactive protein (hsCRP) and insulin resistance. JMSCR 2018;6:69-74.
18. Malin SK, Kashyap SR. Effects of metformin on weight loss: potential mechanisms. Curr Opin Endocrinol Diabetes Obes 2014;21:323-9.
19. Zhu H, Wang L. Interpretation of 2016 American association of clinical endocrinologists (AACE) and American College of Endocrinology (ACE) clinical practice guidelines for comprehensive medical care of patients with obesity. Chin J Diabetes 2017;25:10-13.
20. Pu R, Shi D, Gan T, Ren X, Ba Y, Huo Y, *et al*. Effects of metformin in obesity treatment in different populations: a meta-analysis. Ther Adv Endocrinol Metab 2020;11:2042018820926000.
21. McDonagh MS, Selph S, Ozpinar A, Foley C. Systematic review of the benefits and risks of metformin in treating obesity in children aged 18 years and younger. JAMA Pediatr 2014;168:178-84.
22. O'Connor EA, Evans CV, Burda BU, Walsh ES, Eder M, Lozano P. Screening for obesity and intervention for weight management in children and adolescents: evidence report and systematic review for the US preventive services task force. JAMA 2017;317:2427-44.
23. Graff SK, Mario FM, Ziegelmann P, Spritzer PM. Effects of orlistat vs. metformin on weight loss-related clinical variables in women with PCOS: Systematic review and meta-analysis. Int J Clin Pract 2016;70:450-61.
24. Cravalho CK, Meyers AG, Mabundo LS, Courville A, Yang S, Cai H, *et al*. Metformin improves blood glucose by increasing incretins independent of changes in gluconeogenesis in youth with type 2 diabetes. Diabetologia 2020;63:2194-204.
25. Jakubowska J, Bohdanowicz-Pawlak A, Milewicz A, Szymczak J, Bednarek-Tupikowska G, Demissie M. Plasma cytokines in obese women with polycystic ovary syndrome, before and after metformin treatment. Gynecol Endocrinol 2008;24:378-84.
26. Scheen AJ. Reduction in HbA1c with SGLT2 inhibitors vs. DPP-4 inhibitors as add-ons to metformin monotherapy according to baseline HbA1c: A systematic review of randomized controlled trials. Diabetes Metab 2020;46:186-96.
27. Bredella MA, McManus S, Misra M. Impact of metformin monotherapy versus metformin with oestrogen-progesterone on lipids in adolescent girls with polycystic ovarian syndrome. Clin Endocrinol (Oxf) 2013;79:199-203.
28. Sohrevardi SM, Heydari B, Azarpazhooh MR, Teymourzadeh M, Simental-Mendía LE, Atkin SL, *et al*. Therapeutic effect of curcumin in women with polycystic ovary syndrome receiving metformin: A randomized controlled trial. In: Pharmacological Properties of Plant-Derived Natural Products and Implications for Human Health. New York, USA: Springer Publishing Co.; 2021. p. 109-17.
29. Kocer D, Bayram F, Diri H. The effects of metformin on endothelial dysfunction, lipid metabolism and oxidative stress in women with polycystic ovary syndrome. Gynecol Endocrinol 2014;30:367-71.
30. Rasheed SMH, Eidan AJ, Al-Dujaili AH, Abada LH, Al-Charrakh AH. Different cytokines and lipid profile in suicidal and non-suicidal adults with major depression. Ann Trop Med Public Health 2019;22:S282.
31. Jiang WL, Cai DB, Yin F, Zhang L, Zhao XW, He J, *et al*. Adjunctive metformin for antipsychotic-induced dyslipidemia: A meta-analysis of randomized, double-blind, placebo-controlled trials. Transl Psychiatry 2020;10:1-9.
32. Abrilla AA, Pajes AN, Jimeno CA. Metformin extended-release versus metformin immediate-release for adults with type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials. Diabetes Res Clin Pract 2021;178:108824.
33. Mohammed AG, Al-Kafajy M. AACE2021-A-1021: COVID-19 could trigger diabetes in healthy individuals and worsen symptoms in pre-diagnosed diabetes mellitus patients. Endocr Pract 2021;27:S26-7.