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EFFECTS OF PIOGLITAZONE AND METFORMIN IN IMPROVING INSULIN RESISTANCE AND CLINICAL ANDROGENIC SYMPTOMS IN PATIENTS WITH POLYCYSTIC OVARIAN SYNDROME

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ABSTRACT

Background: polycystic ovary syndrome PCO is a common hormonal disorder that affects women of reproductive age. It is characterized by menstrual disorders, hyperandrogenism, insulin resistance, obesity and infertility, in addition to long-term consequences as cardiovascular diseases such as atherosclerosis and hyperlipidemia, which justifies the importance of diagnosing and treating this syndrome to improve the quality of life and decrease the symptoms of hyperandrogenism. **Objective:** identify the optimal therapy to improve insulin resistance and symptoms of hyperandrogenism in patients with Polycystic Ovary Syndrome. **Methods:** This study included patients with polycystic ovarian syndrome in a randomized clinical trial (RCT) who had visited obstetrics and gynecology department in Tishreen University Hospital, Lattakia according to inclusion criteria. The patients were divided into two groups, the first treated with Pioglitazone and the second treated with Metformin. A Clinical, laboratory and abdominal ultrasound examination were carried out for all the participating patients at the first visit and also after 6 months. **Results:** weight and body mass index BMI decreased in both groups, in Group B, weight decreased by up to 10 % compared to 5% for Pioglitazone with important statistical differences P = 0.00 and body mass index decreased in Group B by 8% compared to 6 % with important statistical differences P = 0.02. Fasting blood Glucose Concentration decreased in both groups without significant statistical differences. The concentration of fasting insulin decreased in both groups, but with clear advantage for Group A with significant statistical differences P= 0.00. The concentration of insulin resistance decreased in both groups with a preference for Group A with significant statistical differences P= 0.19. **Conclusion**: Using Pioglitazone has an advantage over Metformin in improving insulin resistance in patients with Polycystic Ovary Syndrome, in contrast, Metformin has better results in reducing weight and BMl.

KEYWORDS: Polycystic Ovarian Syndrome, insulin resistance, hyperandrogenism, Metformin, Pioglitazone.

INTRODUCTION

Polycystic Ovarian Syndrome (PCO) is considered the most common endocrine adenopathy in women of reproductive age and manifests as menstrual disorders (oligomenorrhea) with signs of hyperandrogenism, infertility and several small cysts in the ovary.

PCO Syndrome is diagnosed if the patient has two of Rotterdam Criteria: anovulatory cycles, hyperandrogenism and multiple follicles on echography.[1]

Hyperandrogenism presents in many clinical manifestations, such as hirsutism, rosacea, baldness, acanthosis nigricans, in addition to the metabolic disorders that accompany this syndrome, such as insulin resistance, fasting hyperglycemia and increased BMI.[1]

The aim of current therapeutic options for polycystic ovarian syndrome is to regulate the menstrual cycle, reducing weight, alleviating symptoms of hyperandrogenism, managing metabolic disorders, as well as increasing fertility.

Metformin: An anti-hyperglycemic drug from the group of Biguanides which is considered as the first line in treating diabetes mellitus type 2 and it is used in the treatment of Polycystic Ovarian Syndrome, where it reduces glucose synthesis in the liver, reduces its absorption from the intestine and increases insulin sensitivity, that leads to reduce blood glucose and has benefits such as weight loss.[2, 3, 4]

Pioglitazone: an anti-hyperglycemic drug that increases insulin sensitivity in the body by activating PPARy and

may be useful in the treatment of polycystic ovarian syndrome. Many recent studies have shown its effect to be the first factor to prevent the development of diabetes, cerebrovascular diseases and heart diseases as complications of diabetes type 2.[5]

Insulin resistance: it is a complex condition where insulin-dependent cells such as skeletal muscle cells and adipocytes respond inappropriately to normal insulin levels, which increases the need for insulin to maintain normal function. Obesity is one of the factors that aggravate insulin resistance, which leads to hyperinsulinemia and the occurrence of diabetes in addition to its association with the risk of cardiovascular diseases, therefore it is better to firstly improve the insulin resistance index HOMA-IR in order to achieve optimal control of clinical symptoms.[6, 7, 8]

Objective

To conduct a statistical study comparing the results between the two groups to determine the optimal treatment for insulin resistance improvement and to relieve androgenic symptoms in patients with Polycystic Ovarian Syndrome (PCO).

PATIENTS AND METHODS

Study design: Randomized Controlled Trial (RCT).

This study was conducted in Department of Obstetrics and gynecology at Tishreen University Hospital, Lattakia between 1/8/2021 and 1/8/2022.Informed written consent was taken to participate in the research

Inclusion criteria

- Women are between 18-30 year-old whom first menstrual cycle had been started 8 years ago or more.
- No pregnancy or breastfeeding during the study
- Body mass index (BMI) greater than 25

Exclusion criteria

- Exclusion of any causes of hyperandrogenism
- Previous of chronic diseases
- Previous medications that affect the menstrual cycle or hormones until 6 months before the study.
- Age: younger than 18 or older than 35.

The study involved 65 women who had visited Obstetrics and Gynecology Department at Tishreen University Hospital, in addition taking informed consent to participate in the research after explaining all medical procedures.

All patients' details were documented and randomly divided after performing laboratory analysis for Fasting Blood Glocuse value, calculating insulin resistance and identifying patients with significant insulin resistance.

Finally two homogeneous groups with a 1:1 allocation ratio were obtained:

- The first group consisted of 33 patients treated with Pioglitazone
- The second group consists of 32 patients treated with Metformin

All patients were subjected to Rotterdam criteria and had an abdominal ultrasound, fasting blood Glucose, fasting blood insulin value and determination of insulin resistance. Also height, weight and BMI had been measured. As well as searching for hyperandrogenism symptoms: hirsutism, baldness, acanthosis nigricans and obesity.

All patients were asked to return for a second revision after 6 months from the first one for a clinical, laboratory and ultrasound re-examination.

RESULTS

Demographic data showed that all patients were of Mediterranean white ethnicity, classified by the degree of anesthetic severity ASA I & II. None of them was diagnosed with hepatitis B or C nor CMV and weren't treated from any septic infection before this study.

At the beginning of the study, both groups were homogeneous with no statistical differences in the following: age, weight, height and BMI This had been shown with P-value greater than 0.05 which was important to ensure that no bias influence the results of the experiment as much as possible. Clinical, laboratory and ultrasound re-examination was also carried out 6 months after the first visit.

There were no differences between the two groups in the studied laboratory tests: fasting blood glucose, fasting insulin concentration and insulin resistance. Both are suitable for comparison to look for the difference between the pharmacological effect on the two groups with no need to add a control Group.

Weight and body mass index (BMI) decreased in both groups, in Group B, weight decreased by up to 10 % compared to 5% for Pioglitazone with important statistical differences (P-value = 0.00) and BMI decreased in Group B by 8% compared to 6 % with an important statistical differences (P-value = 0.02). Metformin had an advantage over Pioglitazone in weight loss and BMI reduction.

Table 1: Comparing weight and BMI between first and second visit in patients with PCOs.

	Drug	N	Mean	Std. Deviation	P
Weight at first visit	Pioglitazone	33	74.6106	9.02616	0.624
	Metformin	32	75.6294	7.54791	
Weight after six months	Pioglitazone	33	71.1285	8.78593	0.045
	Metformin	32	65.9762	11.33458	
BMI at first visit	Pioglitazone	33	27.0379	1.78855	0.956
	Metformin	32	27.0603	1.48489	
BMI after six months	Pioglitazone	33	25.3355	1.58764	0.001
	Metformin	32	22.9278	3.54235	

Fasting blood sugar concentration decreased in both groups without significant statistical differences. Metformin and Pioglitazone were equally effective in lowering fasting blood glucose.

The concentration of fasting insulin decreased in both groups, but with a clear advantage for Group A with significant statistical differences P= 0.00.

The concentration of insulin resistance decreased in both groups with a preference for Group A with significant statistical differences P= 0.19.

Pioglitazone had an advantage over Metformin in reducing blood insulin and therefore insulin resistance.

Table 2: Comparing of laboratory values variations between first and second visit.

	Drug	N	Mean	Std. Deviation	P
Glucose value at first visit	Pioglitazone	33	85.4242	4.82934	0.581
	Metformin	32	84.8219	3.85325	
Insulin value at first visit	Pioglitazone	33	17.8367	1.91837	0.829
	Metformin	32	17.7381	1.73534	
Insulin resistance at first visit	Pioglitazone	33	3.7482	.30487	0.584
	Metformin	32	3.7063	.30924	
Glocuse value after six months	Pioglitazone	33	77.4242	3.82721	0.112
	Metformin	32	78.8844	3.45086	
Insulin value after six months	Pioglitazone	33	11.2594	1.58305	0.000
	Metformin	32	13.5759	1.52040	
Insulin resistance after six months	Pioglitazone	33	2.1457	0.27097	0.000
	Metformin	32	2.6394	0.27469	

DISCUSSION

An Indian study (2012) aimed to compare the effect of treatment of Polycystic Ovarian Syndrome with Metformin and Pioglitazone, the study included patients between 18-30 year-old who visited Gandhi Hospital, India. The study reported that both drugs maintain menstrual cycle normal, achieve a better ovulation rate and improve clinical symptoms of hyperandrogenism, in addition, Pioglitazone was more effective in improving insulin resistance than Metformin.[9]

After studying the effect of Pioglitazone or Metformin treatment on BMI in patients with PCOs the results showed that Pioglitazone was significantly less effective than Metformin in reducing BMI among PCOS patients.[10, 11, 12, 13, 14]

The results of the meta-analysis for the efficacy of Pioglitazone or Metformin treatment on fasting glucose in patients with PCOs [10, 11, 12] revealed a similar effect of Pioglitazone and Metformin on fasting glucose levels in PCOs.

Six studies compared the effects of Pioglitazone and metformin on the insulin level during fasting:
141 patients were treated with Pioglitazone and 137 patients with Metformin. A meta-analysis showed that Pioglitazone was more effective than Metformin in decreasing Insulin fasting levels in patients with PCOS. The difference in the standardized mean (SMD) was -0.37 (95% CI [-0.61, -0.13]). Heterogeneity Test between the studies was insignificant (P = 0.621, I2 = 0.0%).[10, 11, 12, 13, 14, 15]

There was a significant decrease at Insulin levels in Pioglitazone group compared to the Metformin group.

Five studies compared the effects of Pioglitazone and Metformin on the HOMA-IR index:
127 patients were treated with Pioglitazone and 122 patients with Metformin. A meta-analysis showed that Pioglitazone was more effective than Metformin in reducing the HOMA-IR index in patients with PCOs.

The difference in the standardized mean (SMD) was -0.32 (95% CI [-0.57, -0.06]). Heterogeneity Test

between the studies was insignificant (P = 0.221, I2 = 30.0%).

The results of the meta-analysis demonstrate the effect of Pioglitazone and Metformin on the HOMA-IR index. There was a marked decrease in the HOMA-IR index in Pioglitazone group compared to Metformin group. These studies have shown that Pioglitazone is more effective than Metformin in reducing Insulin resistance in patients with PCOs.[10, 11, 13, 15]

The results were consistent with included studies:
In line with our study, Shigiyama et al, showed a decrease in Insulin resistance {which was assessed by the balanced model of Insulin resistance (HOMA-IR)} significantly in both Metformin and Dapagliflozin groups in patients diagnosed with early-stage type 2 Diabetes Mellitus (T2DM), accounting for more than 90% of diabetic patients. While the improvement in insulin sensitivity was comparable between the two groups.[16]

Patients with T2DM receiving stable basal insulin therapy, their HOMA-IR was improved by additional therapy in combination with Pioglitazone and Metformin other than Metformin only.[17]

Many previous studies proved that Pioglitazone-Metformin combination therapy is associated with a significant decrease in HOMA-IR levels in comparison with Metformin monotherapy in patients with DM type 2.[18, 19]

In contrast, HOMA-IR did not change stably with Dapagliflozin or Metformin treatment in a group of over-weighted women with gestational diabetes GDM.[20]

Pioglitazone is a powerful insulin sensitizer as it directly improves insulin sensitivity by activating insulin signals on muscle cells.[21]

CONCLUSION

The results of the current study show that Pioglitazone has an advantage over Metformin in reducing blood insulin and therefore insulin resistance in patients with PCOs, in contrast Metformin has an advantage in reducing weight and BMI.

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REFERENCES

1. Smet ME, McLennan A. Rotterdam criteria, the end. Australas J Ultrasound Med., 2018; 21(2): 59-60.
2. Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev., 2012; (5): Cd003053.
3. Moll E, van der Veen F, van Wely M. The role of metformin in polycystic ovary syndrome: a systematic review. Hum Reprod Update, 2007; 13(6): 527-37.
4. Costello MF, Eden JA. A systematic review of the reproductive system effects of metformin in patients with polycystic ovary syndrome. Fertil Steril, 2003; 79(1): 1-13.
5. Fonseca V. Effect of thiazolidinediones on body weight in patients with diabetes mellitus. Am J Med., 2003; 115 Suppl 8A: 42s-8s.
6. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia, 1985; 28(7): 412-9.
7. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, et al. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. Diabetes Care, 2000; 23(1): 57-63.
8. Mather KJ, Hunt AE, Steinberg HO, Paradisi G, Hook G, Katz A, et al. Repeatability characteristics of simple indices of insulin resistance: implications for research applications. J Clin Endocrinol Metab., 2001; 86(11): 5457-64.
9. Sangeeta S. Metformin and pioglitazone in polycystic ovarian syndrome: a comparative study. J Obstet Gynaecol India, 2012; 62(5): 551-6.
10. Ortega-González C, Luna S, Hernández L, Crespo G, Aguayo P, Arteaga-Troncoso G, et al. Responses of serum androgen and insulin resistance to metformin and pioglitazone in obese, insulin-resistant women with polycystic ovary syndrome. J Clin Endocrinol Metab., 2005; 90(3): 1360-5.
11. Ortega-González C, Cardoza L, Coutiño B, Hidalgo R, Arteaga-Troncoso G, Parra A. Insulin sensitizing drugs increase the endogenous dopaminergic tone in obese insulin-resistant women with polycystic ovary syndrome. J Endocrinol, 2005; 184(1): 233-9.
12. Naka KK, Kalantaridou SN, Kravariti M, Bechlioulis A, Kazakos N, Calis KA, et al. Effect of the insulin sensitizers metformin and pioglitazone on endothelial function in young women with polycystic ovary syndrome: a prospective randomized study. Fertil Steril., 2011; 95(1): 203-9.
13. Cho LW, Kilpatrick ES, Keevil BG, Coady AM, Atkin SL. Effect of metformin, orlistat and pioglitazone treatment on mean insulin resistance and its biological variability in polycystic ovary

syndrome. Clin Endocrinol (Oxf)., 2009; 70(2): 233-7.
14. Shahebrahimi K, Jalilian N, Bazgir N, Rezaei M. Comparison clinical and metabolic effects of metformin and pioglitazone in polycystic ovary syndrome. Indian J Endocrinol Metab., 2016; 20(6): 805-9.
15. Du Q, Wang YJ, Yang S, Wu B, Han P, Zhao YY. A systematic review and meta-analysis of randomized controlled trials comparing pioglitazone versus metformin in the treatment of polycystic ovary syndrome. Curr Med Res Opin., 2012; 28(5): 723-30.
16. Shigiyama F, Kumashiro N, Miyagi M, Ikehara K, Kanda E, Uchino H, et al. Effectiveness of dapagliflozin on vascular endothelial function and glycemic control in patients with early-stage type 2 diabetes mellitus: DEFENCE study. Cardiovasc Diabetol., 2017; 16(1): 84.
17. Hanefeld M, Pfützner A, Forst T, Kleine I, Fuchs W. Double-blind, randomized, multicentre, and active comparator controlled investigation of the effect of pioglitazone, metformin, and the combination of both on cardiovascular risk in patients with type 2 diabetes receiving stable basal insulin therapy: the PIOCOMB study. Cardiovasc Diabetol., 2011; 10: 65.
18. Perez A, Zhao Z, Jacks R, Spanheimer R. Efficacy and safety of pioglitazone/metformin fixed-dose combination therapy compared with pioglitazone and metformin monotherapy in treating patients with T2DM. Curr Med Res Opin., 2009; 25(12): 2915-23.
19. Kaku K. Efficacy and safety of therapy with metformin plus pioglitazone in the treatment of patients with type 2 diabetes: a double-blind, placebo-controlled, clinical trial. Curr Med Res Opin., 2009; 25(5): 1111-9.
20. Elkind-Hirsch KE, Seidemann E, Harris R. A randomized trial of dapagliflozin and metformin, alone and combined, in overweight women after gestational diabetes mellitus. Am J Obstet Gynecol MFM, 2020; 2(3): 100139.
21. DeFronzo RA, Inzucchi S, Abdul-Ghani M, Nissen SE. Pioglitazone: The forgotten, cost-effective cardioprotective drug for type 2 diabetes. Diab Vasc Dis Res., 2019; 16(2): 133-43.