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ORIGINAL ARTICLE

Outcomes of Pioglitazone and Metformin on Anthropometric, Metabolic and Endocrine variables in Polycystic Ovary Syndrome

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ABSTRACT

Aim: To evaluate the outcomes of Pioglita zone and Metformin on anthropometric, metabolic and endocrine variables in PCOS.
Methods: This randomized controlled trial was executed at Pharmacology Department of Bahria University Medical and Dental College in collaboration with Mamji Hospital Karachi from September 2018 to March 2019. Eighty PCOS infertile patients as per Rotterdam 2003 criteria,aged 20-40 years were enrolled. They were divided into two groups of 40 patients each by using computer generated numbers. All patients had fasting insulin levels of >9 µU/mL, serum glucose levels ≥126 mg/dl and suffering from oligomenorrhoea or amenorrhoea. Group A received Tablet Pioglitazone 30 mg once daily and group B was given tablet Metformin 500 mg for three months along with lifestyle changes.
Results: Sixty-one participants completed the study. Anthropometric variables included weight, BMI and W/H ratio. Metformin treated group reduced more weight and BMI as compared to Pioglitazone. Metabolic variables included glycaemic indices, lipid profile and hs-CRP estimation. Pioglitazone group improved glycaemic indices more compared to Metformin. Serum progesterone level was significantly increased in Pioglitazone group (5.20±1.18) than Metformin group. Pioglitazone produced more ovulation in comparison to Metformin. Hence it is proved that it is better option in those patients who are unable to tolerate Metformin and cannot continue treatment for infertility.
Conclusion: Pioglitazone group produced highly significant increase in serum progesterone level indicating ovulation and improved insulin resistance than the metformin group.
Keywords: Female infertility, ovulation induction, Metformin, Pioglitazone, polycystic ovarian syndrome

INTRODUCTION

Polycystic ovary syndrome is a metabolic and endocrine disorder in 8-18% of infertile women. Symptoms of this syndrome include menstrual irregularities, clinical or biochemical hyperandrogenism, and polycystic ovaries[1]. An increase in the gonadotropin-releasing hormone, lower level of FSH and insulin resistance is often associated with PCOS. There is increased ratio of luteinizing hormone to follicle-stimulating hormone[2]. PCOS may also result in long-term complications such as high blood pressure, anxiety, depression, heart disease, type-2 diabetes, and endocrine disorders[3].

The Rotterdam (2003) criteria are widely used to diagnose PCOS where 2/3 criteria to be fulfilled: (1) hyperandrogenism (2) ovulation abnormalities (3) twelve or more cysts on one ovary and/or ovarian volume >10 mL[2].

A healthy lifestyle, such as diet and exercise, is the initial treatment for PCOS to reduce weight, improve PCOS features, and prevent mental and metabolic complications[4]. Insulin sensitizers are frequently used. They increase insulin sensitivity and decrease compensatory hyperinsulinemia, a characteristic feature of PCOS. Insulin sensitizers provide both metabolic and gynecological benefits[5]. The Biguanide-class drug Metformin, used in treating PCOS, reduces insulin resistance in the body. The drug Pioglitazone from the class of Thiazolidinediones also improves insulin resistance[6] that ultimately increases the ovulation rate and post-ovulatory hormone progesterone levels.

This research was carried out to evaluate the outcomes of Pioglitazone and Metformin on anthropometric, metabolic, and endocrine variables in polycystic ovarian syndrome.

METHODS

After approval from the ERC, this research was done at Bahria University Medical and Dental College (Ref no ERC51/2018) of Pharmacology Department in association with Mamji Hospital Karachi from September 2018 to March 2019. The sample size

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was calculated by using "Comparing Two Means" method on www.Openepi.com. The mean and standard deviation of BMI in Pioglitazone and Metformin-treated group were taken from the study.[7] It was 34.0±1.2 for the Pioglitazone group and 32.9±1.7 for the Metformin group, with a 5% margin of error and 95% Confidence Interval. The sample size in each group, n1= 29 and n2= 29. Therefore, the total sample size was n= 58. However, we worked on 80 diagnosed PCOS infertile patients as per Rotterdam criteria 2003. They were divided into two groups with 40 patients each by computer generated numbers. Written informed consent was taken from all study participants.

As per Rotterdam criteria 2003, two out of three specified characteristics are to befulfilled to attain the diagnosis of PCOS.1) Oligo-/anovulation (>35 days of menstrual cycle and amenorrhea of at least six menstrual cycles). 2) Clinical or biochemical hyperandrogenism (Ferriman-Gallwey score ≥8 or Total testosterone ≥ 50ng/dL). 3) Polycystic ovaries on ultrasound ≥12 antral follicles measuring 2-9 mm in diameter or ovarian volume >10 mL in at least 1 ovary by trans-abdominal ultrasound[8].

Inclusion criteria are 20-40 years of infertile women with fasting insulin levels of >9µU/mL[8] serum glucose levels ≥126mg/dl[9] and suffering from oligomenorrhoea or amenorrhoea Patients having Cushing's syndrome, congenital adrenal hyperplasia, use of oral contraceptives within the last six months or hormonal drugs, and other metabolic, diabetes, hepatic, cardiovascular and renal diseases were excluded[10].

All patients were advised to walk 30 to 60 minutes a day and refrain from eating fatty foods, red meat and baked goods. Group A received, Pioglitazone 30 once daily, while Group B received Metformin 500 mg thrice daily for 12 weeks[11].

The weight (kg) of the patients was measured through a weighing machine. Body mass index was calculated by BMI = Weight / Height (m^2). The obesity criteria, BMI >25 kg/m^2 of body weight based on World Health Organization Asia Pacific Guidelines. The cut-off points to define central obesity; waist circumference ≥80cm and waist to hipratio >0.80 in women is

considered high. The waist and hip circumferences were determined to calculate the waist to hip ratio (WHR)[12]. Waist circumference (WC) is the narrowest circumference between the lower costal margins and the iliac crest. Hip circumference (HC) is the maximum circumference at the level of the femoral trochanters. The waist-hip-ratio was measured by dividing the waist to hip circumference[10].

After an overnight fast for 12 to 14 hours, we drew the venous blood sample for laboratory investigations of the metabolic and endocrine parameters. An Alinity C analyzer (Abbott Laboratories, Park, IL, USA) was used to measure the blood glucose level. An automated immunoassay analyzer Architect i1000SR (Abbott®, Abbott Park, IL, USA) & the Roche Cobas c 311 analyzer were used to evaluate the serum insulin and lipid profile. Friedewald's equation estimated very low-density lipoprotein (VLDL).[13]Clinical hyperandrogenism was evaluated by modified Ferriman-Gallwey (mFG) score which indicates terminal hairs on nine body areas; upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, arms and thigh, ≥8 is considered hirsutism[8]. All the variables were evaluated before and after three months. Data analysis was performed by SPSS version 23 and paired t-test was used for comparison before and after treatment. Data was normally distributed.

RESULTS

Sixty-one out of eighty patients completed the study. There were thirty-one patients in group A and thirty in group B. Four patients from group A and two from group B conceived during three months of study. Five patients from the Pioglitazone group and eight from the Metformin group were lost during follow-up on day 45.The patients in both groups were equally matched as evident from the non-significant P-values of all the parameters. In metabolic variables, p-value of serum glucose in group A and B was 0.175. The p-value of serum insulin in group A and B was 0.110. The p-value in G/I ratio of group A and B was 0.323. In lipid variables, p-values of serum HDL, LDL, VLDL, Cholesterol, Triglycerides were 0.345, 0.226, 0.967, 0.619 and 0.512 respectively. The p-value of serum hs-CRP was 0.074. The endocrine variables and imaging-transvaginal ultrasoundexhibited a non-significant reduction presented in Table 1. Anthropometric variables also showed a non-significant reduction in both groups as shown in Table 2. Metabolic variables also showed a non-significant reduction whereas endocrine parameters were highly significant in group A as presented in Table 3.

Table 1: Baseline characterics of metabolic, endocrine variables & ımaging-transvaginal ultrasound **(**n= 61)

Parameters	Group A Mean ± SD	Group B Mean ± SD	p - value
Carbohydrate metabolism			
Fasting Serum Glucose(mg/dl)	101± 7.98	99 ± 8.5	0.175
Fasting Serum Insulin(µIU/ml)	14.31 ± 5.87	12.30±3.48	0.110
G / I ratio	7.98 ± 2.41	8.55 ± 2.03	0.323
Lipid metabolism			
HDL (mg/dl)	43 ± 2.13	42 ± 2.22	0.345
LDL (mg/dl)	100 ± 24.31	108± 24.69	0.226
VLDL (mg/dl)	32 ± 19.50	32 ± 17.97	0.967
Cholesterol (mg/dl)	166 ± 37.80	170± 38.74	0.619
Triglyceride (mg/dl)	145 ± 55.10	155± 60.01	0.512
Protein metabolism			
Serum hs-CRP (mg/ L)	5.24 ± 1.25	6.12 ± 2.38	0.074
Endocrine variables			
Serum FSH (mIU/ml)	5.07 ± 2.19	4.84±2.18	0.678
Serum LH (mIU/ml)	10.17±4.36	9.39 ± 3.66	0.456
LH / FSH ratio	2.91± 0.20	2.90 ± 0.23	0.885
Serum Testosterone (ng/dl)	79.42±17.40	79.90±15.39	0.909
Serum Prolactin (ng/ml)	16.61±9.17	17.82±8.36	0.592
Serum Progesterone (ng/ml)	1.24± 0.50	1.29±0.49	0.675
Serum TSH (µIU/ml)	2.19±1.11	1.77±0.84	0.095
Imaging- Transvaginal Ultrasound			
Size – Right Ovary (cm)	39.32± 25.28	43.97±23.98	0.465
Size – Left Ovary (cm)	39.32± 25.28	43.97±23.98	0.465
Total No. Follicles	13.06±0.68	13.33±0.48	0.064

Group A: Pioglitazone group Group B: Metformin group
G / I ratio: Glucose to insulin ratio Test applied: Unpaired t-test / Independent t-test

Table 2: Anthropometric Variables: A vs B at baseline and 12 weeks (n=61)

Groups	Baseline Mean ± SD	12 weeks Mean ± SD	Mean Difference	p -value
Weight (kg)				
A	68.90 ± 10.38	65.73 ± 11.46	3.18±11.89	0.403
B	76 ± 9.82	70 ± 9.39	5.80±12.43	
BMI (kg/m²)				
A	27.52 ± 3.71	26.32±4.39	1.20±4.79	0.404
B	29.60 ± 4.00	27.37 ± 3.56	2.24±4.84	
W / H ratio				
A	0.850 ± 0.049	0.832 ± 0.049	0.02±0.05	0.275
B	0.824± 0.046	0.817± 0.045	0.01±0.06	

Table 3: Metabolic & Endocrine Variables of Group A versus B at baseline and 12 weeks (n=61)

Parameters	Groups	Baseline (Mean ± SD)	12 weeks (Mean ± SD)	Mean Difference	p -value
Carbohydrate Metabolism					
Serum Fasting Glucose (mg/dl)	A	101 ± 7.98	82 ± 6.16	19.84 ± 10.93	0.072
	B	99 ± 8.55	83 ± 6.77	15.07 ± 9.28	
Carbohydrate Metabolism					
Serum Fasting Insulin (µIU/ml)	A	14.31 ± 5.87	7.70 ± 3.02	6.61 ± 4.47	0.162
	B	12.30 ± 3.48	7.12 ± 1.22	5.18 ± 3.33	
G/I ratio	A	7.98 ± 2.41	11.58 ± 2.85	3.60 ± 2.50	0.967
	B	8.55 ± 2.03	12.12 ± 2.40	3.57 ± 2.46	
Lipid Metabolism					
HDL (mg/dl)	A	43.06 ± 2.13	40 ± 1.15	2.48 ± 2.47	0.132
	B	42.53 ± 2.22	41 ± 1.08	1.60 ± 2.04	
LDL (mg/dl)	A	100 ± 24.32	93 ± 18.79	7.32 ± 17.54	0.942
	B	108 ± 24.69	100 ± 22.05	7.67 ± 18.98	
VLDL (mg/dl)	A	32.03 ± 19.50	26 ± 14.48	6.23 ± 15.01	0.305
	B	32.23 ± 17.97	22 ± 11.65	10.03 ± 13.65	
Cholesterol (mg/dl)	A	166 ± 37.80	152 ± 40.33	13.55 ± 33.59	0.729
	B	170 ± 38.74	154 ± 35.01	16.73 ± 37.55	
Triglyceride (mg/dl)	A	145 ± 55.10	113 ± 45.19	32.03 ± 55.40	0.581
	B	155 ± 60.01	115 ± 43.06	40.00 ± 56.60	
Protein Metabolism					
hs-CRP (mg/L)	A	5.24 ± 1.25	3.39 ± 0.81	1.84 ± 1.30	0.115
	B	6.12 ± 2.38	3.47 ± 1.22	2.64 ± 2.45	
Endocrine variable					
Progesterone (ng/ml)	A	1.24 ± 0.50	6.44 ± 1.02	5.20 ± 1.18	<0.001*
	B	1.29 ± 0.49	4.56 ± 1.52	3.26 ± 1.54	

DISCUSSION

In this reserach, we evaluated the outcomes of Pioglitazone and Metformin on weight, BMI, carbohydrates, lipid, protein and progesterone levels in polycystic ovarian syndrome. We selected diagnosed cases of infertile PCOS exhibitingoligo anovulation and evaluated them by serum progesterone level (cut-off value 3 ng/ml)[14]. Clinical hyperandrogenism was calculated by mFG score.

The mean valuein the research was 9.07±1.7. A score of ≥8 is considered hirsutism, coinciding with the study by Hussein et al. The cut-off of total Testosterone = ≤57.7 ng/dl. In group A, the total Testosterone was 79.42±17.40 and in the group, B was 79.90±15.39[8]. Total follicles in group A,=13.06±0.68 and in group B=13.33± 0.48, cut-off value = ≥12 and coinciding the study done by Wongwananuruk et al[15].

Weight gain and obesity may contribute to the development of PCOS because they promote insulin resistance and cause metabolic dysfunction. In PCOS 30-88% of women are overweight or obese[16]. In our study Metformin produced more weight loss and caused a reduction in BMI compared to pioglitazone, coinciding study done by Shahebrahimi et al[17]. Pioglitazone treated group also caused a decrease in mean weight and BMI at the end of the study. This might have occured due to modified eating habits, routine brisk walking for one hour and by avoiding the bakery items, red meat, and fatty foods from the diet. However the study by Aroda et al. have found that Pioglitazone increased weight and BMI after six months, which is contradictory to our findings[18].

The metformin-treated patients showed a reduction in the W/H ratio, which contradicts the findings of Morin-Papunen et al., in which waist to hip ratio remained the same after treatment[19] and similar results occurred in the Pioglitazone-treated group reported by Asadipooya and colleagues[20].

Seventy percent of lean women with PCOS are resistant to insulin compared to slim women who do not have PCOS. In addition, internal insulin resistance exacerbates extrinsic insulin resistance, such as obesity. Dysfunctional insulin response in skeletal muscle and adipose tissue may cause intrinsic insulin resistance in PCOS. Skeletal muscles are responsible for 70-80% of insulin-stimulated glucose absorption defects. Therefore, they can profoundly affect the body's overall insulin sensitivity.[21] In our study, we found Pioglitazone to be more effective in improving fasting glucose and insulin level than Metformin, which is similar to the results of Sohrevardi et al[11]. Fasting glucose divided by fasting insulin to obtain the G/I ratio (cut-off<4.5) is a useful screening test of insulin resistance[22].

Approximately seventy per cent of women with PCOS have dyslipidemia. It is considered a biochemical marker.[23] In both groups, low-density lipoprotein cholesterol and total cholesterol were reduced. In addition, high-density lipoprotein cholesterol was decreased in group B, coinciding with Shahebrahimi et al.,group A also obtained similar results[15]. However, we could not find any reason for reduction in HDL-C level in both groups. Triglycerides levels were reduced in both groups but more in the Metformin-treated group, similar to the findings of Ortega-Gonzalez et al[24].

Serum hs-CRP level was reduced more in group B than in group A because metformin also has a direct anti-inflammatory effect. In addition, it has a potent impact on the hs-CRP because it inhibits nuclear factor κB via adenosine monophosphate-activated protein kinase-dependent and independent pathway[25].

We have observed increased serum progesterone levels in Pioglitazone treated group compared to Metformin treated group. Hence, Pioglitazone promoted more ovulation induction than Metformin, similar to Syed SZ et al. They have found that Pioglitazone is more effective than Metformin for ovulation induction because it reduced andogen level and improves insulin resistance[26].

CONCLUSION

This study had a short duration of three months. Accordingly, further multicentric clinical trial should be conducted to authenticate use of pioglitazone as an alternative choice to Metformin and or its use in Metformin resistant infertile PCOS women.

Conflict of interest: Nil

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