ORIGINAL ARTICLE

Impact of Pioglitazone on Anthropometric and Metabolic Parameters in PCOS-Infertile Women

Ayesha Khan[1], Nasim Karim[2], Jahan Ara Ainuddin[3]

ABSTRACT

Objective: To evaluate the effect of pioglitazone on anthropometric and metabolic parameters in infertile women suffering from polycystic ovarian syndrome (PCOS).

Study Design: Randomized controlled trial.

Place and Duration of Study: The study was conducted in the Pharmacology Department of Bahira University Medical and Dental College in collaboration with infertility clinic, Mamji Hospital Karachi from 24th September 2018 to 30th March 2019.

Materials and Methods: Forty infertile women aged 20-40 years using non-probability convenient sampling technique were enrolled as per Rotterdam criteria 2003. They had fasting insulin level > 9µU/mL, the fasting glucose level of 7 mmol/L or ≥126 mg/dl, and cyclical irregularity such as oligomenorrhoea/amenorrhea. They were given tablet pioglitazone 30 mg once daily per orally for three months. All participants were subjected to evaluation of anthropometric (weight, BMI, waist and hip circumference, and waist-hip ratio) and metabolic parameters (1. carbohydrate – fasting serum glucose and insulin, 2. lipids – Total cholesterol, triglycerides, low-density lipoprotein *cholesterol (*LDL-C), very-low-density lipoprotein cholesterol (*VLDL-C*), High-density lipoprotein *cholesterol* (HDL-C), and 3. protein–serum hs-CRP). The Paired T-test was applied for comparison at the end of three months. Data analysis was performed by SPSS version 23.

Results: Thirty-one participants completed the study. We found a mean reduction of 3.17 kg in weight, BMI 1.2 kg/m^2, and W/H ratio 0.018 in anthropometric parameters. Mean reduction of fasting serum glucose 19 mg/dl, insulin 6.61 µIU/ml, HDL- C 3 mg/dl, LDL-C 7 mg/dl, VLDL- C 6 mg/dl, Total cholesterol 14 mg/dl, Triglycerides 32 mg/dl and serum hs-CRP level 1.85 mg/L was found.

Conclusion: Pioglitazone reduces anthropometric parameters and causes a significant reduction in metabolic parameters among polycystic ovarian syndrome infertile women.

Key Words: *Infertility, Insulin Resistance, Pioglitazone, Polycystic Ovarian Syndrome.*

Introduction

Polycystic ovarian syndrome (PCOS) is a hormonal syndrome of females that affects reproductive life, found in 6-10 % of females.[1] Irregular menstruation (oligomenorrhea/ amenorrhea), hyperandrogenism, polycystic ovaries, decreased sensitivity to insulin and persistent oligo-anovulation are its main components.[2] PCOS is diagnosed by the internationally accepted Rotterdam criteria upon having 2 out of 3 characteristics: oligo or anovulation, increased serum androgen level & appearance of multiple cysts in the ovaries on ultrasound scan along with the omission of other reasons for hyperandrogenism, such as the adrenal or pituitary malfunction.[3] More than half of the PCOS patients have increased basal metabolic rate or are obese and thus have an increased risk of concomitant obesity-related diseases.[4] All these abnormal metabolic characteristics lead to infertility that includes insulin resistance, overweight/obesity, type 2 diabetes, dyslipidemia, and a greater chance of developing heart disease.[5] If left untreated PCOS can cause endometrial cancer due to elevated level of estrogen and lower level of progesterone that predispose to endometrial hyperplasia.[6] Pathophysiology of Polycystic ovarian syndrome is complicated and vague, it is said that resistance develops against

[1,2]*Department of Pharmacology*
Bahria University Medical and Dental College, Karachi
[3]*Department of Gynecology*
Dow International Medical College
Dow University of Health Sciences, Karachi

Correspondence:
Dr. Ayesha Khan
Senior Lecturer
Bahria University Medical and Dental College, Karachi
E-mail: dr.ayeshakhan85@gmail.com

Funding Source: NIL; Conflict of Interest: NIL
Received: January 11, 2020; Revised: November 17, 2020
Accepted: November 18, 2020

circulating insulin and is associated with hyperinsulinemia that plays a major part in the endocrine and reproductive features of PCOS.[7] Hypothalamus secrets Gonadotropin-releasing hormone in an episodic manner that is often disrupted in PCOS, leading to the excessive release of luteinizing hormone (LH) by the pituitary gland, causing ovulatory dysfunction and increased blood androgen levels.[8] Pathogenesis of PCOS is associated with the modification or alteration of the PPAR-γ gene and thus drugs acting at this level can improve the anthropometric and metabolic characteristics of such women. PPAR-γ agonists reduce the androgen synthesis in the ovaries indirectly and improve resistance against insulin in peripheral tissues.[9] Pioglitazone, a thiazolidinedione effective for type two diabetes, is a highly selective agonist acting on PPAR-γ receptors, located in the liver, fat tissues, skeletal muscle, etc. It is susceptible to insulin. There is a role of PPAR-γ receptor in the expression of gene responsible for insulin release and metabolism of carbohydrates, fat, and proteins.[10]

Documented literature on anthropometric and metabolic parameters in polycystic ovarian syndrome infertile women following the use of pioglitazone is scarce, therefore this study was conducted to evaluate the effect of pioglitazone on anthropometric & metabolic parameters in PCOS induced infertility.

Materials and Methods

This clinical trial was conducted after approval from ERC of Bahria University Medical & Dental College vide (51/2018) for six months from 24th September 2018 till 30th March 2019 at the Pharmacology Department of Bahria University Medical & Dental College in collaboration with the infertility clinic of Mamji Hospital Karachi. The sample size was calculated by using prevalence of PCOS coded by Bozdag and his colleagues[1] via www.Openepi.com taking a 5% margin of error and 95% Confidence Interval. Written informed consent was taken from all patients. The Total sample size was 80 with 40 patients in each group. This manuscript is based on the data of Group A only. Diagnosed PCOS infertile women were enrolled as per Rotterdam criteria 2003.[8] Our patients had classic PCOS phenotype "A". It includes clinical and biochemical hyperandrogenism (clinical hyperandrogenism was evaluated by modified Ferriman-Gallwey (mFG) scoring system for hirsutism (mean value in our patients = 9.07±1.753, cutoff value ≥ 6)[8] and biochemical parameters (serum total testosterone level in our patients = 79.42 ± 17.40 ng/dl, cut off value ≤ 67 ng/dl)[11], Oligo-anovulation (Serum progesterone level in our patients = 1.24 ± 0.50 ng/ml, cut off value of 3 ng/ml)[12], polycystic ovarian morphology (total number of follicles in our patients = 13.06 ± 0.68, cut of value of 10-12 follicles).[13] The inclusion criteria was infertile females, aged 20-40 years with fasting levels of serum Insulin (>9µU/mL)[14], glucose (7 mmol/L or ≥126 mg/dl)[15], and suffering from cyclical irregularity such as oligomenorrhea/ amenorrhea. Women with endocrine disorders such as Cushing's syndrome, hypothyroidism, congenital adrenal hyperplasia, hyperprolactinemia, acromegaly, metabolic (Familial hypercholesterolemia) and organic diseases (diabetes, hepatic or renal insufficiencies), women using oral contraceptives/injectables, and females who had undergone oophorectomy/ovarian ablation therapy[16] were excluded from the study by biochemical tests (Data not mentioned in the present manuscript) and clinical examination by the gynecologist. All patients were advised for 30-60 minutes daily walk, avoidance of oily foods, red meat, and bakery product. They were given tablet pioglitazone 30 mg orally once daily for three months.[17] Anthropometric measurements–weight (kg) was measured by using a weighing scale, Quetelet index formula: BMI=Weight / Height (m^2) was used to calculate BMI, as per Asian criteria; BMI ≥ 25 and waist to hip ratio ≥ 0.80 in women is considered as obesity documented by Hastuti and his team,[18] waist circumference was measured at the minimum circumference between the iliac crest and the rib cage in standing position at the end of normal expiration using a non-elastic tape, hip circumference was measured at the level of greater trochanters using a flexible tape, waist to hip ratio was calculated by dividing waist circumference (WC) to hip circumference (HC) as per the method documented by Chen and his colleagues.[19]

The Blood sample was drawn from the cubital vein after an overnight fast of 12-14 hours for the detection of metabolic parameters – Fasting serum glucose, Insulin, Lipid Profile (HDL-C, LDL-C, VLDL-C,

Total Cholesterol, Triglycerides), and hs-CRP. They were measured by chemiluminescence immunoassay. The Glucose/insulin ratio was calculated by dividing fasting serum glucose value with insulin. VLDL-C was estimated by Friedewald's equation.[20] All parameters were assessed at baseline and at the end of 3 months. SPSS version 23 was used to analyze the data. Data was normally distributed and Paired t-Test was used for comparison at the end of treatment.

Results

Out of forty, nine patients failed to return, while 31 completed the study. Anthropometric parameters of weight, BMI, waist circumference, hip circumference, and waist-to-hip ratio showed non-significant reduction as shown in Table-I. Metabolic parameters (carbohydrate, lipid Profile, and protein metabolism) as shown in Table-II. In carbohydrate metabolism, parameters of fasting serum glucose and insulin showed a highly significant reduction. In lipid metabolism, HDL-C also showed a highly significant reduction whereas LDL-C, VLDL-C, cholesterol, and triglycerides showed a significant reduction. Serum hs-CRP representing protein metabolism showed a highly significant reduction.

Table I: Anthropometric Parameters (N=31)

Parameters	Day 0	Day 90	P - value
	Mean ± SD	Mean ± SD	
Weight (kg)	68.90 ± 10.38	65.73 ± 11.46	0.147
BMI (kg/m^2)	27.52 ± 3.71	26.32 ± 4.39	0.173
Waist (cm)	104 ± 49.14	89 ± 10.77	0.076
Hip (cm)	123 ± 52.92	107 ± 8.29	0.091
W / H ratio	0.850 ± 0.049	0.832 ± 0.049	0.056

Note: BMI: Body mass index
W / H ratio: waist to hip ratio
< 0.05 P-value = significant

Table II: Comparison of Metabolic Parameters (N=31)

Parameters	Day 0	Day 90	P - value
	Mean ± SD	Mean ± SD	
Carbohydrate Metabolism			
Fasting Serum Glucose (mg/dl)	101 ± 7.98	82 ± 6.16	< 0.001*
Fasting Serum Insulin (µIU/ml)	14.31 ± 5.87	7.70 ± 3.02	< 0.001*
G / I ratio	7.98 ± 2.41	11.58 ± 2.85	< 0.001*
Lipid Metabolism			
HDL-C (mg/dl)	43 ± 2.13	40 ± 1.15	< 0.001*
LDL-C (mg/dl)	100 ± 24.32	93 ± 18.79	0.027*
VLDL-C (mg/dl)	32 ± 19.50	26 ± 14.48	0.028*
Total Cholesterol (mg/dl)	166 ± 37.80	152 ± 40.33	0.032*
Triglycerides (mg/dl)	145 ± 55.10	113 ± 45.19	0.003*
Protein Metabolism			
Serum hs-CRP (mg/L)	5.24 ± 1.25	3.39 ± 0.81	< 0.001*

HDL-C: High-density lipoprotein cholesterol
LDL-C: Low-density lipoprotein cholesterol
VLDL-C: Very-low-density lipoprotein cholesterol
hs-CRP: High sensitivity C-reactive protein, G/I ration glucose / Insulin ratio
< 0.05 P-value = significant
*= significant

Discussion

Polycystic ovarian syndrome (PCOS) is a prevalent endocrine disorder and affects 6%–18% in reproductive age group females. It is not only in association with reproductive and obstetric problems such as hyperandrogenism (HA), menstrual irregularities, infertility, and pregnancy complications, but also causes long term complications such as dyslipidemia, insulin resistance, elevated risk of type two diabetes and metabolic syndrome.[21] We have found a reduction but non-significant in mean weight and BMI after 3 months of treatment with pioglitazone. This reduction may be due to a combination of lifestyle changes (one hour daily brisk walk) and dietary advice (avoidance of red meat, bakery products, and oily foods) given to all study participants along with the drug treatment. These findings are contradictory to Sohrevardi et al. They have documented that pioglitazone produced weight gain after three months of treatment.[22] This is probably due to fluid retention that leads to weight gain or it might be due to an increase in the mass of adipocytes.[23,24]

Central obesity is more common in PCOS; fat accumulates in the abdomen predominantly and is

related directly to an increase in insulin resistance. This can be measured by waist circumference.[25] In our study, waist circumference (WC) and hip circumference (HC) were exhibited non-significantly reduced in the end and so do the waist-to-hip ratio because Pioglitazone effectively decreases central obesity in polycystic ovarian syndrome (PCOS) and these are similar to the findings reported by Gupta and colleagues.[26] Waist and hip circumference were significantly increased, documented by Tanwar and his team and this is contradictory to our findings. It may be due to a decrease in visceral fat and an increase in subcutaneous fat.[23]

PCOS causes ovarian hyper-androgenemia due to increased sensitivity to insulin by the ovary as opposed to the resistance of the whole body. It is prevalent in 65-80% of patients. It increases the chances of diabetes mellitus as well as diseases of heart and blood vessels.[27] We have found a significant reduction in mean fasting serum glucose and insulin levels, which is coinciding with the study done by Rokade and colleagues.[28] However, Hwang and colleagues have documented a non-significant reduction in mean fasting serum glucose and insulin levels and this is contradictory to our study.[29] Glucose to insulin ratio was significantly increased which is coinciding with the study conducted by Narsing and his team members.[30] Decreased sensitivity of insulin causes increased shunting of free fatty acids from fat tissues to the liver in adipocytes. Free fatty acids induce hepatic synthesis of VLDL-C resulting in increased levels of triglycerides and decreased level of HDL-C. These derangements in lipid parameters lead to atherogenic dyslipidemia. In our study, we have found significant reduction in LDL-C, VLDL-C, Total cholesterol, and triglycerides levels after three months of treatment with Pioglitazone, which is like the study done by Devi and colleagues.[31]

cholesterol level, low-density lipoprotein cholesterol (VLDL-C), and triglycerides also showed a significant decrease as documented by Dawson and his team which is similar to our finding.[32] Significant reduction is found in the serum high-density lipoprotein cholesterol level which is similar to the study done by Shahebrahimi and colleagues.[17] However, the exact cause of the decrease in HDL-C could not be elucidated, whereas Sangeeta has documented a significant increase in HDL-C which is contradictory to our study. This may be due to the anti-arteriosclerotic properties of pioglitazone and could also be due to a long duration of study that is six months in comparison to our study period of three months.[33] A Non-significant reduction in all lipid parameters is observed by Sohrevardi and his colleagues which is contradictory to our study.[22] It is probably due to the difference in ethnicity of study populations.

C-reactive protein is produced by the liver. It is an acute-phase reactant, indicates chronic inflammation & its level is elevated in PCOS because of subclinical inflammation in PCOS.[34]

We have found a significant reduction in serum hs-CRP which is like the study done by Dawson and his colleagues. This is because Pioglitazone decreases serum hs-CRP level by modulating inflammation through PPAR-γ.[32] Present study was conducted at a single infertility clinic with an individual period of 3 months. Large multicentric studies of longer duration should be conducted to authenticate our result findings and to produce generalize data for implementation.

Conclusion

Pioglitazone produces favorable effects on anthropometric and metabolic parameters in polycystic ovarian syndrome induced infertility. Therefore, it could be used as an effective treatment option to prevent and or to improve immediate and long-term complications associated with polycystic ovarian syndrome related infertility.

REFERENCES

1. Bozdag G, Mumusoglu S, Zengin D, Karabulut E, Yildiz BO. The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta- analysis. Hum Reprod. 2016; 31:2841-55.
2. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. FertilSteril. 2018;110(3):364-79.
3. Hiam D, Moreno-Asso A, Teede HJ, Laven J S.E, Stepto NK, Moran LJ, et al. The Genetics of Polycystic Ovary Syndrome: An Overview of Candidate Gene Systematic Reviews and Genome-Wide Association Studies. J. Clin. Med. 2019; 8:2-17.
4. Kim JY, Tfayli H, Michaliszyn SF. Distinguishing characteristics of metabolically healthy versus metabolically unhealthy obese adolescent girls with polycystic ovarysyndrome. FertilSteril. 2016; 105:1603-11.

5. Zeng X, Xie YJ, Liu YT, Long SL, Mo ZC. Polycystic ovarian syndrome: Correlation between hyperandrogenism, insulin resistance and obesity. ClinChimActa. 2019; (19)32118-7.
6. Srivastava N, Singh SP, Shukla A, Gupta KL. Polycystic ovarian syndrome: a curse to young women. Pharmaceutical and biological evaluations. 2018;5(2):14-26.
7. Cassar S, Misso ML, Hopkins WG, Shaw CS, Teede HJ, Stepto NK. Insulin resistance in polycystic ovary syndrome: a systematic review and meta-analysis of euglycaemic-hyperinsulinaemic clamp studies.Hum Reprod. 2016;31(11):2619-31.
8. Azziz, R. Reproductive Endocrinology and Infertility: Clinical Expert Series Polycystic Ovary Syndrome. Obstet Gynecol. 2018;132(2):321-36.
9. Xu Y, Wu Y, Huang Q. Comparison of the effect between pioglitazone and metformin in treating patients with PCOS: a meta-analysis. Arch Gynecol. 2017;296(4):661-77.
10. Vitek W, Alur S, Hoeger KM. Off-label drug use in the treatment of polycystic ovary syndrome. FertilSteril. 2015;103(3):605-11.
11. Song DK, Oh JY, Lee H, Sung YA. Differentiation between polycystic ovary syndrome and polycystic ovarian morphology by means of an anti-Müllerian hormone cutoff value. Korean J Intern Med. 2017;32(4):690-8.
12. Prior JC, Naess M, Langhammer A, Forsmo S. Ovulation prevalence in women with spontaneous normal-length menstrual cycles–a population-based cohort from HUNT3, Norway. PLoS One. 2015;10(8): e0134473.
13. Ali HI, Elsadawy ME, Khater NH. Ultrasound assessment of polycystic ovaries: Ovarian volume and morphology; which is more accurate in making the diagnosis? The Egyptian Journal of Radiology and Nuclear Medicine. 2016;47(1):347-350.
14. Chen YH, Lee YC, Tsao YC, Lu MC, Chuang HH, Yeh WC, et al. Association between high-fasting insulin levels and metabolic syndrome in non-diabetic middle-aged and elderly populations: a community-based study in Taiwan. BMJ. 2018;8(5): e016554.
15. Cefalu WT, Berg EG, Saraco M, Petersen MP, Uelmen S, Robinson S. Classification, and diagnosis of diabetes: standards of medical care in diabetes-2019. Diabetes Care. 2019;42: S13-28.
16. Kabel AM. Polycystic Ovarian Syndrome: Insights into Pathogenesis, Diagnosis, Prognosis, Pharmacological and Non-Pharmacological Treatment. Pharm. Bioprocess. 2016;4(1):7-12.
17. Shahebrahimi K, Jalilian N, Bazgir N, Rezaei M. Comparison clinical and metabolic effects of metformin and pioglitazone in polycystic ovary syndrome. Indian J EndocrinolMetab. 2016;20(6):805-09.
18. Hastuti J, Kagawa M, Byrne NM, Hills AP. Determination of new anthropometric cut-off values for obesity screening in Indonesian adults.Asia Pac J ClinNutr. 2017;26(4):650- 56.
19. Chen S, Guo X, Yu S, Zhou Y, Li Z, Sun Y. Anthropometric Indices in Adults: Which Is the Best Indicator to Identify Alanine Aminotransferase Levels? Int J Environ Res Public Health. 2016; 13(2), 1-12.
20. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the Concentration of Low- Density Lipoprotein Cholesterol in Plasma, Without Use of the Preparative Ultracentrifuge. Clin Chem.1972; 18(6):499-502.
21. Li A, Zhang L, Jiang J, Yang N, Liu Y, Cai L, et al. Follicular hyperandrogenism and insulin resistance in polycystic ovary syndrome patients with normal circulating testosterone levels. J Biomed Res. 2018;32(3):208-14.
22. Sohrevardi SM, Nosouhi F, Khalilzade SH,Kafaie P, Karimi-Zarchi M, Halvaei I, et al. Evaluating the effect of insulin sensitizers metformin and pioglitazone alone and in combination on women with polycystic ovary syndrome: An RCT. Int J Reprod Biomed (Yazd). 2016;14(12):743-54.
23. Tanwar S, Khilnani GD. A clinical comparative study on the effects of metformin and pioglitazone on clinical symptoms in cases of polycystic ovarian syndrome. Int J Basic ClinPharmacol. 2016;5(1):98-104.
24. Filipova E, Uzunova K, Kalinov K, Vekov T. Effects of pioglitazone therapy on blood parameters, weight, and BMI: a meta-analysis.DiabetolMetabSyndr. 2017; 9:90.
25. Çakıroğlu Y, Vural F, Vural, B. The inflammatory markers in polycystic ovary syndrome: association with obesity and IVF outcomes. J Endocrinol Invest. 2016;39(8):899-907.
26. Gupta A, Jakubowicz D, Nestler JE. Pioglitazone Therapy Increases Insulin-Stimulated Release of d-Chiro-Inositol-Containing Inositol phosphoglycan Mediator in Women with Polycystic Ovary Syndrome. MetabSyndrRelatDisord. 2016;14(8):391-96.
27. Shah D, Rasool S. PCOS and Metabolic Syndrome: The Worrisome Twosome? EndocrinolMetab Synd. 2015;4(2):1-7.
28. Rokade AV, Javdekar DP, Patange RP. Comparison of metformin and pioglitazone in PCOS. Journal of Evolution of Medical and Dental Sciences. 2013;2(15):2532-37.
29. Hwang KR,Choi YM, Kim JJ, Chae SJ, Park KU, Jeon HW. Effects of insulin-sensitizing agents and insulin resistance in women with polycystic ovary syndrome. ClinExpReprod Med. 2013;40(2):100-105.
30. NarsingRao L, Jacob JJ, Paul TV, Rajarathinam S, Thomas N, Seshadri MS. Effects of Pioglitazone on Menstrual Frequency, Hyperandrogenism and Insulin Resistance in Adoloscents and Young Adults with Polycystic Ovary Syndrome. J PediatrAdolesc Gynecol. 2009;22(2):91-95.
31. Devi AS, Anuradha J. Metformin and Pioglitazone in polycystic ovarian syndrome: A comparative study. IAIM. 2017;4(7):39-44.
32. Dawson AJ, Kilpatrick ES, Coady AM, Elshewehy AMM, Dakroury Y, Ahmed L, et al. Endocannabinoid receptor blockade reduces alanine aminotransferase in polycystic ovary syndrome independent of weight loss. BMC EndocrDisord. 2017;17(1):41.
33. Sangeeta S. Metformin and Pioglitazone in Polycystic Ovarian Syndrome: A Comparative Study.J ObstetGynaecol India. 2012;62(5):551-56.
34. Ganie AM, Hassan S, Nisar S, Shamas N, Rashid A, Ahmed I, et al. High-sensitivity C- reactive protein (hs-CRP) levels and its relationship with components of polycystic ovary syndrome in Indian adolescent women with polycystic ovary syndrome (PCOS). GynecolEndocrinol, 2014; 30(11):781-84.