Scientific Research Publishing

Open Journal of Obstetrics and Gynecology, 2017, 7, 117-128
http://www.scirp.org/journal/ojog
ISSN Online: 2160-8806
ISSN Print: 2160-8792

Clinical and Biochemical Changes in Polycystic Ovarian Syndrome Patients in Response to 3 Different Oral Hypoglycemic Drugs: A Double Blind Randomized Controlled Study

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How to cite this paper: El-Halwagy, A.S., Al-Gergawy, A.A., Eleslam, E.S. and Abd Elbar, E.S. (2017) Clinical and Biochemical Changes in Polycystic Ovarian Syndrome Patients in Response to 3 Different Oral Hypoglycemic Drugs: A Double Blind Randomized Controlled Study. *Open Journal of Obstetrics and Gynecology*, **7**, 117-128.
http://dx.doi.org/10.4236/ojog.2017.71013

Received: January 2, 2017
Accepted: January 15, 2017
Published: January 18, 2017

Abstract

Introduction: This study was done to evaluate other oral hypoglycemic medications; especially the new ones in the management of PCOS patients as alternatives to the standard medication used for this purpose Metformin. **Patients and Methods:** 105 patients were enrolled and randomly distributed into 3 groups according to sequence of computer-generated block-random numbers. Each group included 35 patients. This randomized double blind case controlled study was conducted at Tanta University Hospital from December 1, 2015 to October, 1, 2016. In group A (study group 1) the patients received Pioglitazobe 30 mg once a day for 6 months while in group B (study group 2) the patients received Vildagliptin 50 mg once daily. In Group C (control group) the patients received Metformin 500 mg tds. for 6 months. The clinical outcome measures of the study were the improvement in the regularity of the menstrual cycle, the BMI and the improvement in the modified Ferriman-Gallwey (F-G) score for hirsutism. The biochemical outcome measures will be the change in the Serum Free testosterone, dehydroepiandrosterone (DHEA), fasting insulin level, Glcosylated hemoglobin (Hb A1c) and fasting Low Density Lipoproteins (LDL) levels. **Results:** Pioglitazobe in the study group 1 patients showed a significant reduction of BMI ($p = 0.016$), Ferriman-Gallwey score ($p = 0.003$), free testosterone level ($p = 0.003$), DHEA level ($p = 0.001$), fasting insulin level ($p = 0.036$) and Hb a1c level ($p = 0.000$), and also significant reduction of menstrual irregularities ($p = 0.035$). When compared to Metformin in the control group 3, there were significant reduction of BMI ($p = 0.010$), Ferriman-Gallwey score ($p = 0.002$), free testosterone level ($p = 0.034$), Hb a1c ($p = 0.000$) level and significant reduction of menstrual irregularities ($p = 0.004$) only. This means that the clinical and metabolic effect of Pioglitazobe is better than Metformin in PCOS patients. On the contrary there were disappointing results of the new drug Vildagliptin in group 2; the patients in this group

showed significant reduction of BMI ($p = 0.001$), Ferriman-Gallwey score ($p = 0.046$) and Hb a1c ($p = 0.000$) level only. Non significant effect on menstrual irregularities and non significant reduction of LDL level are noticed. But there is elevation of Ferriman-Gallwey score, free testosterone level, DHEA level and fasting insulin level. **Conclusion:** Pioglitazobe is an effective and safe alternative to Metformin in the management of PCOS patient although further studies including larger number of patients should be done while Vildagliptin should be omitted for use in PCOS patients.

Keywords

PCOS, Pioglitazobe, Vildagliptin, Metformin

1. Introduction

Polycystic ovary syndrome is one of the most common endocrinopathies, with 5% -10% incidence among women in the child bearing age [1]. PCOS is diagnosed by diverse manifestations including chronic anovulation or oligo-ovulation, hyperandrogenism (clinical or biochemical) and polycystic ovaries seen by ultrasound [2]. PCOS is the most prevalent etiological factor of female infertility and is also associated with increased risks of diabetes mellitus, cardiovascular disorders, and endometrial cancer [3]. Although it is not yet fully understood, insulin resistance and its compensatory hyperinsulinemia are thought to play a key role in the pathogenicity of PCOS [2] [3]. The incidence of insulin resistance in PCOS is substantially higher in weight- and age-matched women without PCOS [4] and is a consistent feature of PCOS in both normal and overweight women. Insulin resistance also appears to play a significant role in the pathogenesis of the hyperandrogenism and infertility of PCOS [5]. Women with anovulation, hyperinsulinemia, and hyperandrogenism are at greater risk of developing diabetes with an age of onset 30 years earlier than in the general population [6]. Hyperinsulinemia increases the risk of cardiovascular disease both directly and by its impact on lipid metabolism [7].

Insulin sensitizers are an alternative therapeutic way to the treatment of PCOS [6]. Although Metformin and Pioglitazobe reduce insulin resistance, they have different pharmacodynamics [8]. Metformin is a biguanide, which decreases hepatic glucose production, circulating insulin and intestinal glucose absorption, and improving peripheral tissue utilization of glucose. Pioglitazobe is a peroxisome proliferator-activated receptor gamma agonist which enhances the ability of muscles to metabolize glucose and improves insulin sensitivity without hypoglycemia [9] [10].

Vildagliptin is a strong and selective inhibitor of dipeptidyl peptidase-4 (DPP-4) that improves blood glucose control in type II DM by enhancing α- and β-cell response to glucose [11].

Multiple clinical studies proved that Vildagliptin improves blood glucose control in patients with type II DM when given as sole agent [12], or when given in combination with other antidiabetic medications, or with insulin [13]. Treatment with Vildagliptin has proven to have good overall safety profile [14] [15].

2. Patients and Methods

This study was conducted in the Department of Obstetrics and Gynecology, Tanta University on patients attending the outpatient clinic. The study was held in the period from December 1, 2015 to October, 1, 2016. The number of patients enrolled in the study was 105 patients after application of inclusion and exclusion criteria.

All women were thoroughly informed about the study aims and through discussion about the procedure, associated benefits and risks and assigned written consent.

2.1. Inclusion Criteria

The study inclusion criteria were: Age from 18 to 30 years, with diagnosed PCOS according to Rotterdam criteria [16] *i.e.* the presence of at least 2 of the following 3 criteria: 1) Oligo/anovulation, 2) clinical or biochemical signs of hyperandrogenism including hirsutism, acne, or increased serum Free testosterone, and 3) polycystic ovaries by ultrasound. Only the patients attending our clinics for PCOS symptoms other than infertility; namely obesity, hirsutism and menstrual irregularities will be included in this study.

2.2. Exclusion Criteria

The exclusion criteria were patients presented by DUB, patients with diabetes mellitus, abnormal liver function tests, known cardiac or renal disease, endocrinological diseases, chronic diseases, smoking, and also patients with infertility complains, suspicious of benign or malignant ovarian condition (indicated by ultrasound or proved by histopathology) were excluded from this study. In addition, of using of oral contraceptive drugs and other drugs related with ovarian function at least 3 months before research.

2.3. Baseline Examination

All patients were assessed by history taking, clinical examinations and were investigated by routine investigation to check for general condition. Patients were evaluated for hirsutism at baseline and at the end of the study using the modified Ferriman-Gallwey (F-G) score [17]. Women with an F-G value of 8 or greater were considered to be hirsute. Abdominal and Ultrasound was done to confirm diagnosis of PCOS and to check for other pelvic pathology.

2.4. Biochemical Assay

Fasting Serum (free testosterone, dehydroepiandrosterone (DHEA) and, insulin leves) were assessed by automated enzyme immune system AIA -1800st "TOSOH Bioscience". Glycosylated hemoglobin (Hb A1c) was assessed by HPLC (ADAMSTM"AIC HA-8180T (arkary), and ≥12 hours Fasting Serum Low Density Lipoproteins (LDL) levels calculation by Friedewald equation (SPINREACT cholesterol & triglyceride Kits).

The 105 patients included in the study were randomized in 3 study groups according to sequence of computer-generated block-random numbers. Neither the researchers nor the participants will know their study group.

In group A (study group 1) (35 patients) the patients received Pioglitazobe 30 mg once a day for 6 months while in group B (study group 2) (35 patients)the patients received Vildagliptin 50 mg once daily for 6 months. In Group C (control group) (35 pa-

tients) the patients received Metformin 500 mg tds. for 6 months.

The clinical outcome measures of the study were the improvement in the regularity of the menstrual cycle, the BMI and the improvement in the modified Ferriman-Gallwey (F-G) score for hirsutism. The biochemical outcome measures will be the change in the Serum free testosterone, dehydroepiandrosterone (DHEA), fasting insulin level, Glcosylated hemoglobin (Hb A1c) and Low Density Lipoproteins (LDL) levels.

2.5. Sample Size Calculation

Power analysis for a dependent sample *t*-test was conducted in G*Power to determine a sufficient sample size using an alpha of 0.05, a power of 0.80, a medium effect size (dz = 0.5), and two tails [18]. Based on the aforementioned assumptions, the desired sample size is 34 in each study arm.

All statistics were performed using MinitabVer.17 (Minitab Inc., USA).

3. Results

On comparing demographic, clinical and biochemical data of the study groups using one way ANOVA (Table 1) there was no significant difference (all p values are >0.05). Assessment of the effect of the drug Pioglitazobe on the study variables in group 1 (Table 2) using paired T test shows significant reduction of BMI, Ferriman-Gallwey score, free testosterone level, DHEA level, Fasting insulin level and Hb a1c level. But non significant reduction of LDL level is noticed.

Table 3 shows the effect of Pioglitazobe on the menstrual irregularities in group 1, Chi Square test shows significant reduction of oligomenorrhea and amenorrhea *i.e.* significant regaining of menstrual cyclicity.

Assessment of the effect of the drug Vildagliptin on the study variables in group 2 (Table 4) using paired T test shows significant reduction of BMI and Hb a1c level. Non significant reduction of LDL level is noticed. But there is elevation of Ferriman-Gallwey score, free testosterone level, DHEA level and Fasting insulin level.

Table 1. Comparison of the Pre-study variables between the 3 groups.

	Group 1 Pioglitazobe	Group 2 Vildagliptin	Group 3 Metformin	*p* value
Age	25.5 ± 4.0	24.5 ± 3.6	23.2 ± 4.3	0.058
BMI	27.5 ± 5.2	28.0 ± 5.1	25.8 ± 5.7	0.199
Ferriman-Gallwey (F-G) **score**	12.0 ± 7.4	11.8 ± 7.9	12.3 ± 7.4	0.961
Free testosterone (0.6 - 6.8 pg/ml)	4.4 ± 2.7	5.4 ± 2.5	5.5 ± 2.0	0.121
DHEA (44 - 332 µg/dL)	263.7 ± 117.4	271.9 ± 126.5	280.7 ± 132.2	0.852
Fasting Insulin (<25 µ IU/L)	27.9 ± 8.7	28.9 ± 8.1	29.8 ± 10.6	0.711
Hb A 1c (<5.7%)	4.4 ± 0.6	4.8 ± 0.7	4.7 ± 0.8	0.102
LDL (up to 140 mg/dl)	129.6 ± 27.3	133.6 ± 32.5	127.6 ± 28.9	0.691

Table 2. Comparison between pre- and post-study variables in group 1.

	Basal levels	Post study	*p* value
BMI	27.5 ± 5.2	27.0 ± 4.5	0.016*
Ferriman-Gallwey (F-G) **score**	12.0 ± 7.4	10.74 ± 6.12	0.003*
Free testosterone (0.6 - 6.8 pg/ml)	4.4 ± 2.7	3.9 ± 2.0	0.003*
DHEA (44 - 332 µg/dL)	263.7 ± 117.4	221.0 ± 82.2	0.001*
Fasting Insulin (<25 µ IU/L)	27.9 ± 8.7	25.4 ± 4.7	0.036*
Hb A1c (<5.7%)	4.4 ± 0.6	3.8 ± 0.7	0.000*
LDL (up to 140 mg/dl)	129.6 ± 27.3	127.6 ± 28.9	0.686

*Significant.

Table 3. The effect of Pioglitazobe on the menstrual irregularities in group 1.

		Oligomenorrhea	Amenorrhea	Regular cycles	X^2	*p* value
Before TTT	N	24	5	6	6.733	0.035*
	%	68.5%	14.2%	17.1%		
After TTT	N	15	4	16		
	%	42.8%	11.4%	45.7%		

*Significant.

Table 4. Comparison between pre- and post-study variables in group 2.

	Basal levels	Post study	*p* value
BMI	28.0 ± 5.1	27.3 ± 4.5	0.001*
Ferriman-Gallwey (F-G) **score**	11.8 ± 7.9	12.4 ± 7.1	0.046*
Free testosterone (0.6 - 6.8 pg/ml)	5.4 ± 2.5	5.6 ± 2.2	0.350
DHEA (44 - 332 µg/dL)	271.9 ± 126.5	353.1 ± 362.5	0.217
Fasting Insulin (<25 µ IU/L)	28.9 ± 8.1	31.4 ± 7.6	0.064
Hb A1c (<5.7%)	4.8 ± 0.7	4.2 ± 0.9	0.000*
LDL (up to 140 mg/dl)	133.6 ± 32.5	129.6 ± 27.3	0.596

*Significant.

Table 5 shows the effect of Vildagliptin on the menstrual irregularities in group 2, Chi Square test shows no significant change of the rate of oligomenorrhea and amenorrhea *i.e.* no significant regaining of menstrual cyclicity.

Assessment of the effect of the drug Metformin on the study variables in group 3 (Table 6) using paired T test shows significant **reduction** of BMI, Ferriman-Gallwey score, free testosterone level and Hb a1c level. But no significant **reduction** of DHEA level, Fasting insulin level. Also there is non-significant **elevation** of LDL level.

Table 7 shows the effect of Metformin on the menstrual irregularities in group 3, Chi Square test shows significant reduction of oligomenorrhea and amenorrhea *i.e.* significant regaining of menstrual cyclicity.

The following Figures 1-9 show comparison of the change of study variables between the study groups.

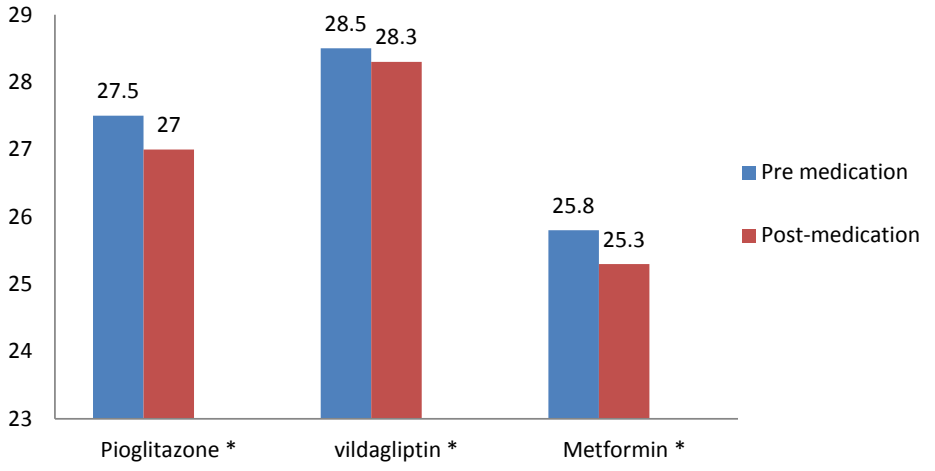

Figure 1. BMI. *Significant.

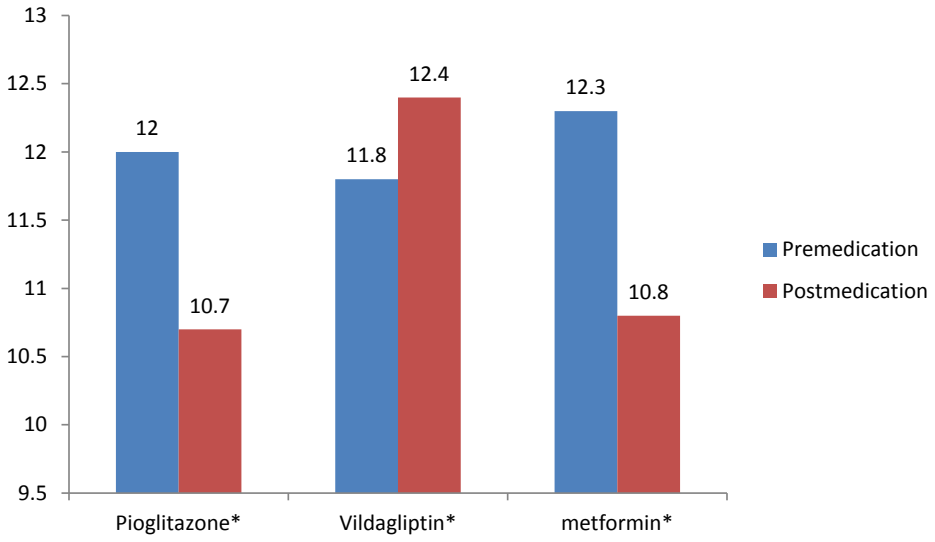

Figure 2. Ferriman-Gallwey score. *Significant.

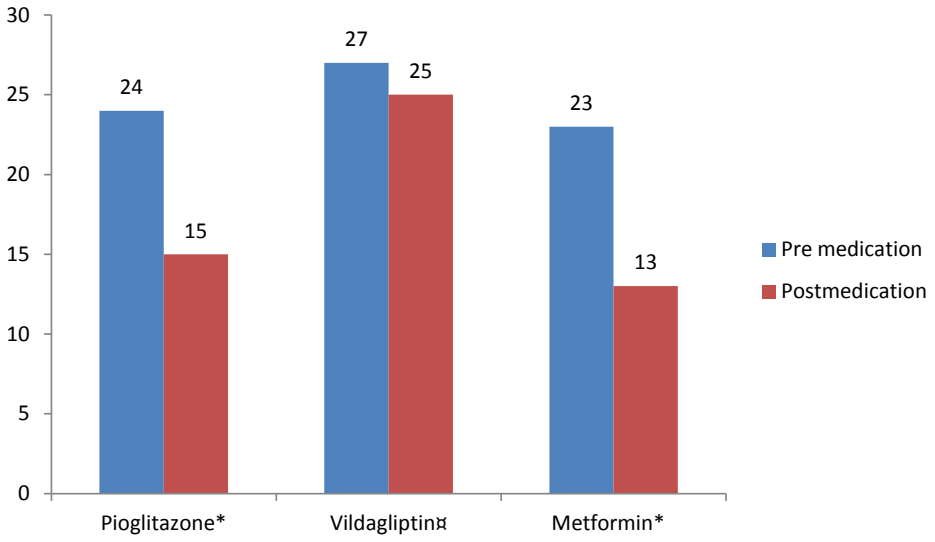

Figure 3. Cases with oligomenorrhea. *Significant. ¤Non significant.

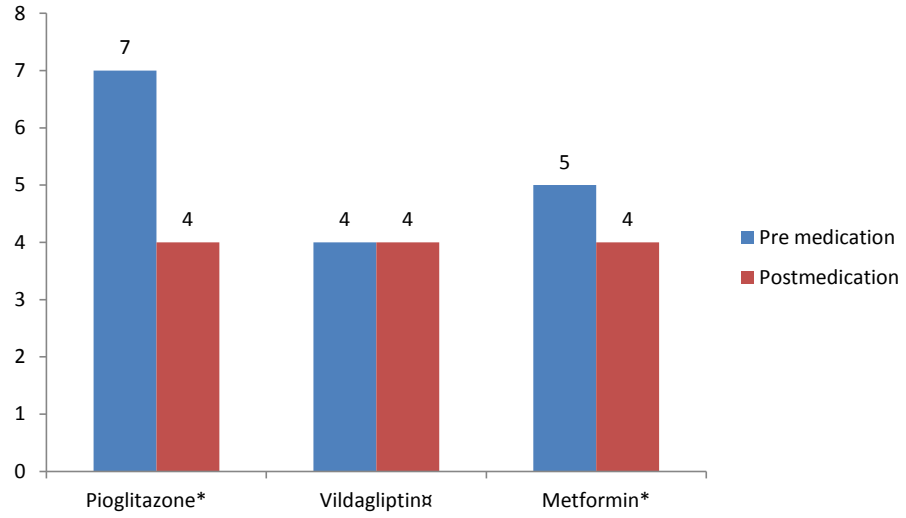

Figure 4. Cases with amenorrhea. *Significant. ¤Non significant.

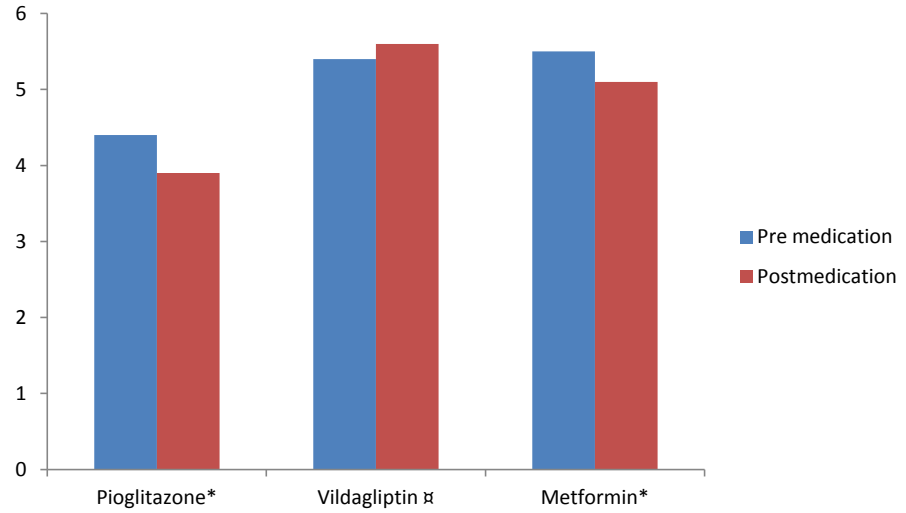

Figure 5. Free testosterone "pg/ml". *Significant. ¤Non significant.

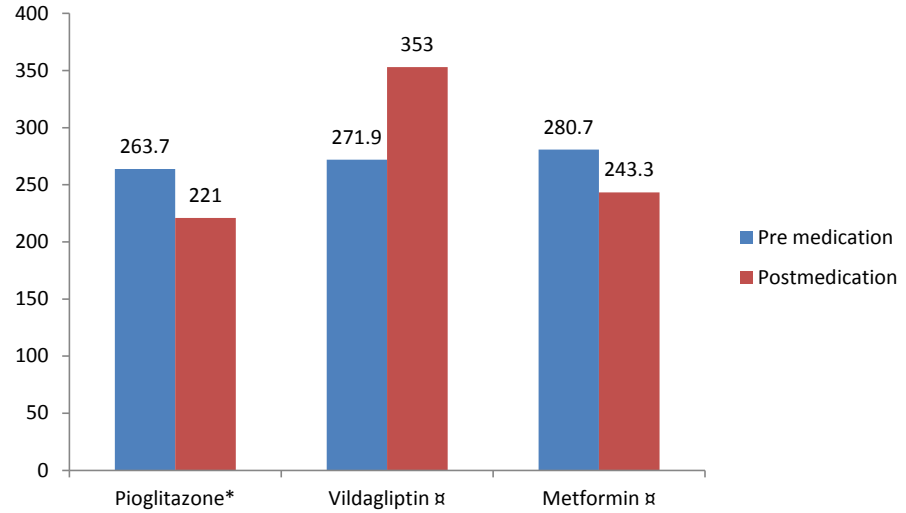

Figure 6. DHEA "µ g/dl". *Significant. ¤Non significant.

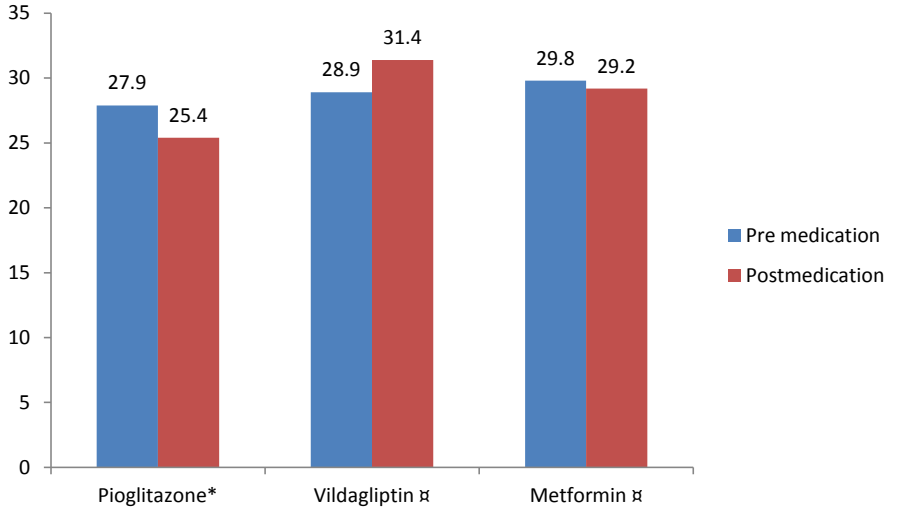

Figure 7. Fasting insulin "μ IU/L". *Significant. ¤Non significant.

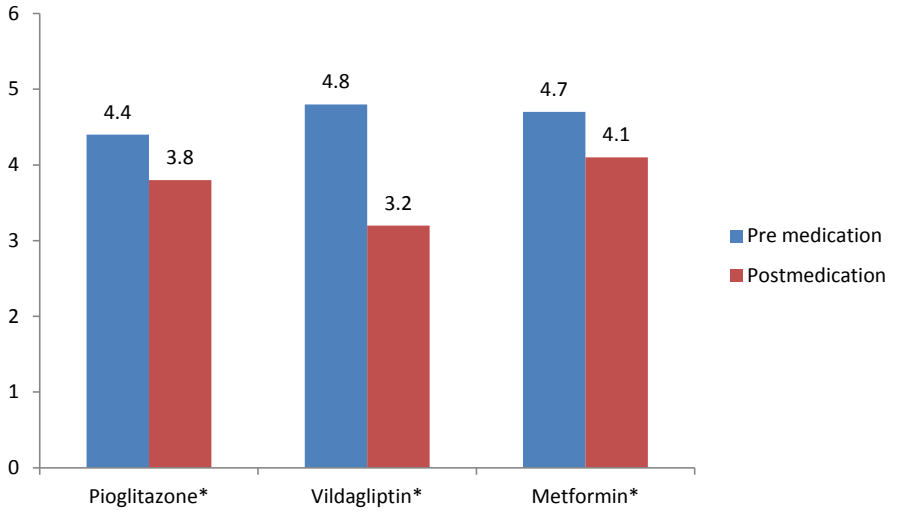

Figure 8. Hb A1c "gm%". *Significant.

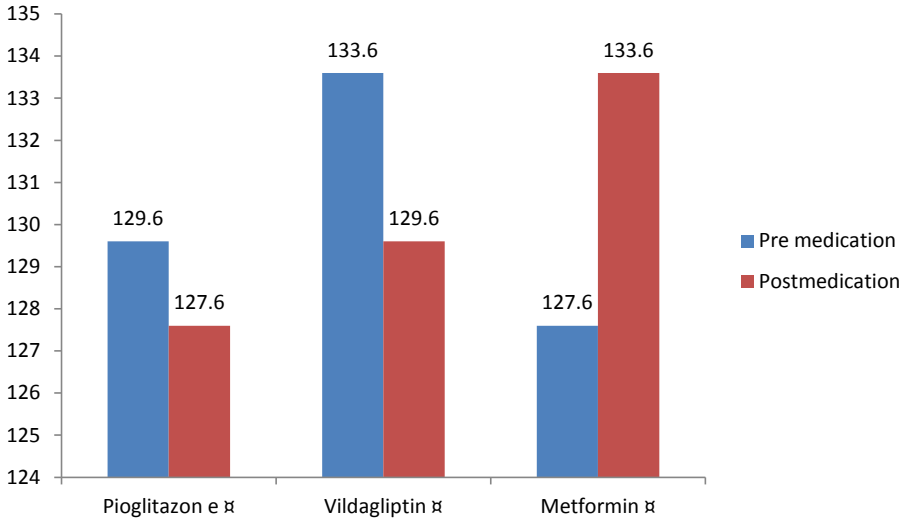

Figure 9. LDL "mg/dl". ¤Non significant.

Table 5. The effect of Vildagliptin on the menstrual irregularities in group 2.

		Oligomenorrhea	Amenorrhea	Regular cycles	X^2	*p* value
Before TTT	N	27	4	4	0.477	0.788
	%	77.1%	11.4%	11.4%		
After TTT	N	25	4	6		
	%	71.4%	11.4%	17.1%		

Table 6. Comparison between pre- and post-study variables in group 3.

	Basal levels	Post study	*p* value
BMI	25.8 ± 5.7	25.3 ± 5.0	0.010*
Ferriman-Gallwey (F-G) **score**	12.3 ± 7.4	10.8 ± 5.5	0.002*
Free testosterone (0.6 - 6.8 pg/ml)	5.5 ± 2.0	5.1 ± 1.3	0.034*
DHEA (44 - 332 µg/dL)	280.7 ± 132.2	243.3 ± 103.5	0.057
Fasting Insulin (<25 µ IU/L)	29.8 ± 10.6	29.23 ± 9.5	0.645
Hb A1c (<5.7%)	4.7 ± 0.8	4.1 ± 0.7	0.000*
LDL (up to 140 mg/dl)	127.6 ± 28.9	133.6 ± 32.5	0.374

*Significant.

Table 7. The effect of Metformin on the menstrual irregularities in group 3.

		Oligomenorrhea	Amenorrhea	Regular cycles	X^2	*p* value
Before TTT	N	23	7	5	10.944	0.004*
	%	65.7%	20.0%	14.2%		
After TTT	N	13	4	18		
	%	37.1%	11.4%	51.4%		

*Significant.

4. Discussion

The primary objective of the study is to evaluate other oral hypoglycemic medications; specially the new ones in the management of PCOS patients as alternatives to the standard medication used for this purpose Metformin. We used many indices to assess the improvement in the clinical and metabolic condition of the patients.

Pioglitazobe in the study group 1 patients showed a significant reduction of BMI, Ferriman-Gallwey score, free testosterone level, DHEA level, Fasting insulin level and Hb a1c level, and also significant reduction of menstrual irregularities. But non significant reduction of LDL level is noticed. When compared to Metformin in the control group 3 in which there were significant reduction of BMI, Ferriman-Gallwey score, free testosterone level and Hb a1c level. But no significant reduction of DHEA level, Fasting insulin level. Also there is non-significant elevation of LDL level. This means that the clinical and metabolic effect of Pioglitazobe is better than Metformin in PCOS patients.

On the contrary there were disappointing results of the new drug Vildagliptin in group 2, the patients in this group showed significant reduction of BMI and Hb a1c

level only. Non significant effect on menstrual irregularities and non significant reduction of LDL level is noticed. But there is elevation of Ferriman-Gallwey score, free testosterone level, DHEA level and Fasting insulin level. This can be explained by that Vildagliptin is a selective, reversible, competitive inhibitor of dipeptidyl peptidase-4 (DPP4). DPP4 is involved in the inactivation of many neuropeptides, cytokines, chemokines, and gastrointestinal hormones. Two important hormones involved in glucose homeostasis and inactivated by DPP4 are glucose-dependent insulinotropic polypeptide (GIP) and GLP-1. GIP and GLP-1 are incretins, which are hormones released from the gut that stimulate insulin secretion in response to food intake. GLP-1, the most potent insulinotropic hormone, enhances glucose-dependent secretion of insulin from pancreatic β-cells and inhibits glucagon secretion. Inhibition of DPP4, results in increased levels of active GLP-1 and subsequent enhancement of insulin release *i.e.* Vildagliptin increases insulin release rather than improves insulin sensitivity which explains most of the disappointing results of the group 2 in the current study.

To the best of our knowledge there was only one study on Vildagliptin in PCOS patients. ZHAO Xiaolan and FENG Lin [19] published this study in which they compared 2 groups; a study group received Vildagliptin in combination with Metformin for 6 months versus a control group received Metformin only. They concluded that Metformin combine with Vildagliptin can effectively improve the levels of endocrine,sugar and fat metabolism in patients of polycystic ovary syndrome (PCOS) with abnormal glucose metabolism, which is effective and safe. The contradiction with our results can be explained by that they used the Vildagliptin in combination with Metformin.

Limitation

The Limitation of this study is the small sample size.

5. Conclusion

Pioglitazobe is an effective and safe alternative to Metformin in the management of PCOS patient although further studies including larger number of patients should be done while Vildagliptin should be omitted for use in PCOS patients.

Declaration of Funding

This study was not funded.

Declaration of Financial/Other Relationships

The authors of this manuscript have no relevant financial relationships to disclose.

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