

## Pioglitazone attenuates cardiometabolic risk factors in non-diabetic patients with dyslipidemia

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### Abstract

**Objective:** To determine the effect of pioglitazone on cardiometabolic risk factors in non-diabetic patients with dyslipidaemia.

**Methods:** This prospective, randomised clinical trial was conducted at Sheikh Zayed Medical College and Hospital, Rahim Yar Khan, Pakistan, from August to October 2016, and comprised non-diabetic patients with dyslipidaemia. They were randomly divided into three groups. First and second groups were given a daily dose of tab pioglitazone 30mg and gemfibrozil 600mg, respectively, while the third group served as the healthy control. Body weight, body mass index and serum lipid profile were analysed pre- and post-treatment. SPSS 16 was used for data analysis.

**Results:** Of the 135 participants, there were 45(33.3%) in each group. After 12 weeks' treatment, the pioglitazone group showed a highly significant reduction in body weight ( $83\pm 10.5$  to  $76\pm 13.5$ kg) and body mass index ( $27.7\pm 4.4$  to  $25.5\pm 6.4$ kg/m<sup>2</sup>) ( $p\leq 0.01$ ) compared to the gemfibrozil group. The pioglitazone group showed a significant improvement in serum lipid profile after 12 weeks ( $p\leq 0.05$ ) while the gemfibrozil group showed a highly significant improvement in serum lipid profile ( $p\leq 0.01$ ).

**Conclusion:** Pioglitazone independently improved cardiometabolic risk factors, even in non-diabetics.

**Keywords:** Pioglitazone, Gemfibrozil, Dyslipidaemia, Lipid profile. (JPMA 67: 1884; 2017)

### Introduction

The number of deaths due to cardiovascular diseases is rising at an alarming rate in developing countries, especially Pakistan, as compared to developed nations. The strong impact of urbanisation and lifestyle modification to its underlying risk factors such as smoking, obesity, diabetes, dyslipidaemia and hypertension pose an enormous burden clinically as well as economically in developing countries. In addition, governments seem to have failed to control these risk factors because of lack of proper health awareness programmes and implementation of health reform policies in developing countries.<sup>1,2</sup>

Out of these modifiable risk factors, the role of dyslipidaemia as an initiation, progression as well as complication of atherosclerosis cannot be ignored. The screening of dyslipidaemic patients is essential because most of the patients remain asymptomatic unless it has been long standing. The most important hazards of long-standing dyslipidaemia is accelerated atherosclerosis which can manifest itself in a number of cardiovascular disorders like ischaemic heart disease, cerebrovascular disease and peripheral vascular disease.<sup>3</sup> About 80% of

deaths in low-income and middle-income countries is due to cardiovascular disease. The current therapeutic challenge is to implement the existence of effective primary prevention strategies in order to reduce the disease burden in these countries.<sup>4</sup>

Peroxisome proliferator activated receptors (PPARs) are nuclear receptor family that plays an integrative role in controlling the expressions of genes involved in inflammation, energy homeostasis, glucose and lipid metabolism. According to their two major sub-types, PPAR-alpha ( $\alpha$ ) is mainly located in liver, skeletal muscles and brown adipose tissue while PPAR-gamma ( $\gamma$ ) is expressed predominantly in brown and white adipose tissues. The standard lipid lowering drug gemfibrozil is an agonist of PPAR- $\alpha$  receptor that lowers plasma triglycerides and increase high-density lipoprotein (HDL) level while pioglitazone is PPAR- $\gamma$  receptor agonist which is widely prescribed as an oral anti-diabetic agent in both type 2 and 1 diabetes mellitus either alone or in combination with insulin and other anti-diabetic drugs.<sup>5</sup>

In addition, pioglitazone also acts as PPAR- $\alpha$  agonist and therefore it has favourable effect on serum lipid profile as compared to rosiglitazone which is PPAR- $\gamma$  agonist only.<sup>6</sup> A systematic review and meta-analysis of various observational studies in diabetic patients concluded that in comparison with rosiglitazone, pioglitazone had more beneficial effect on serum triglycerides, HDL cholesterol,

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low-density lipoprotein (LDL) cholesterol and LDL particle size. The powerful renal PPAR- $\gamma$  agonistic effect of rosiglitazone causes more fluid retention in type 2 diabetics which is associated with myocardial infarction, congestive heart failure and death.<sup>7</sup> Moreover, pioglitazone was associated with favourable cardiovascular profile in diabetic patients such as reduction in blood pressure, silent inflammation and reduced all cause mortality as compared to rosiglitazone, metformin, 1st and 2nd generation sulphonylureas.<sup>8-11</sup> However, in diabetic patients, blood sugar control definitely improves diabetic dyslipidaemia and its associated complications. So it would be much better to conduct a study of pioglitazone in non-diabetic dyslipidaemic patients in order to see its independent effect on serum lipid profile so that it can be considered as an alternative drug in these patients who cannot tolerate anti-dyslipidaemic agents either due to their toxicity or potential drug interaction. The basic reason for comparison with gemfibrozil is that gemfibrozil is a standard lipid lowering agent that acts on PPAR- $\alpha$  receptor while pioglitazone is a dual agonist of both PPAR- $\alpha$  and PPAR- $\gamma$ . The current study was planned to compare the effect of both drugs in non-diabetic patients in order to see their independent effect on body weight, body mass index (BMI) and serum lipid profile.

## Patients and Methods

This prospective, randomised clinical trial was conducted at medical outdoor-1 of Sheikh Zayed Medical College/Hospital, Rahim Yar Khan, Pakistan, from August to October 2016, and comprised patients presenting with non-specific complaints. Approval was obtained from ethical committee of the institute. Informed consent was obtained from all participants. Initially, patients presenting with generalised weakness, headache, dyspnoea and pain in legs while walking, were enrolled. Of them, patients aged 28-65 years, having BMI  $\geq 27$  and borderline serum lipid profile based upon National Cholesterol Education Programme-Adult Treatment Panel (NCEP-ATP-111) guidelines were included.<sup>12</sup> Patients with history of alcohol use, smoking habits, pregnancy, oral contraceptive, lactation, hypothyroidism, hypertension, and any chronic diseases affecting heart, liver and kidney were excluded. Patients who were taking those drugs which effect serum lipid profile such as anti-dyslipidaemics, anti-diabetics, thiazide group diuretics, beta blockers and steroids were also excluded.

Patients were randomly divided into groups A, B and C. Group A received pioglitazone 30mg and group B received gemfibrozil 600mg once daily at night for 12 weeks, whereas group C served as the healthy control.

The patients were divided using a random number generated by an epidemiologist who was unknown to treatment modalities using a computer software programme. Patients were asked to do routine activities as usual. A digital weight scale was used to measure body weight in kilogram while BMI was calculated by standard formula weight in kilogram divided by height in metre square ( $\text{kg}/\text{m}^2$ ) before and after the treatment. Diabetic patients were asked to do fasting blood glucose by glucose oxidase peroxidase method at the start of study. A spectrophotometry principal was used to analyse lipid profile by semi automated clinical chemistry analyser.

The sample size was calculated primarily on the basis of anticipated percentage increase in HDL cholesterol level of 8% by pioglitazone at the end of study from baseline. It was calculated at 12-weeks using the formula: HDL-baseline HDL/baseline HDL $\times 100$ . Secondary end point was percentage change in all other major lipoproteins at 12 weeks from baseline. Anticipating 15% dropout rate, we estimated that a sample size of 45 per group would provide 80% power to detect this difference before and after the treatment with pioglitazone, by applying two-tailed  $\alpha$  of 0.05. Data was analysed by using SPSS 16. Numeric data values were presented as mean  $\pm$  standard deviation (SD). Student t-test was used for the statistical analysis of data.  $P < 0.05$  was considered statistically significant while  $p < 0.01$  was considered highly significant.

## Results

Of the 130 patients initially enrolled, 90(69.2%) were included and were equally divided into groups A and B. Moreover, 45 healthy subjects formed group C as controls. So overall, there were 135 participants in the study. The tolerability profile of both drugs and patient's cooperation during the study was quite good. All patients in the treatment groups completed the study. No significant major risks and adverse effects were observed. However, 5(11.1%) patients in the pioglitazone group and

**Table-1:** Characteristics of study groups at baseline.

Baseline Characteristics	Pioglitazone Group (n 45)	Gemfibrozil Group (n 45)	Control Group (n 45)
Age(years)	27 $\pm$ 14	26 $\pm$ 17	29 $\pm$ 19
Sex Male/Female	25/15	23/17	20/20
Body weight(kg)	83 $\pm$ 10.5	85 $\pm$ 13.6	70 $\pm$ 12.92
BMI (Body Mass index $\text{kg}/\text{m}^2$ )	27.7 $\pm$ 4.4	28.5 $\pm$ 3.6	23 $\pm$ 6.8
Blood glucose fasting(mg/dl)	86 $\pm$ 18.4	83 $\pm$ 16.5	78 $\pm$ 13.5
Systolic blood pressure(mmHg)	124 $\pm$ 12.5	128 $\pm$ 14.2	110 $\pm$ 12.4
Diastolic blood pressure(mmHg)	78 $\pm$ 8.8	85 $\pm$ 7.5	82 $\pm$ 9.5

**Table-2:** Results of Pioglitazone and Gemfibrozil group (pre and post treatment).

Parameters	Pioglitazone Group (n 45)		Gemfibrozil Group (n 45)		Control Group (n 38)
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	
Body weight(kg)	83±10.5†	76±13.5**	85 ±13.6†	85.7 ±12.2	70±12.92
BMI(kg/m <sup>2</sup> )	27.7±4.4†	25.5±6.4**	28.5 ±3.6†	28.8 ±3.2	23±6.8
TC (mg/dl)	245±13.2†	198±16.45*	265±13.62†	182±11.45**	162±6.46
TG(mg/dl)	237±29.4†	192±32.45*	190±40.25†	136±36.25**	155±8.2
LDL-C(mg/dl)	148±16.78†	110±15.14*	165±12.5†	93±10.45**	115±8.4
HDL-C(mg/dl)	40.4±4.94†	46.6±4.5*	43±2.51†	53±1.82 **	55±3.2

BMI: Body mass index

TC: Total cholesterol

TG: Triglycerides;

LDL-C: Low density lipoprotein cholesterol

HDL-C: High density lipoprotein cholesterol

Results represent Mean ± SD

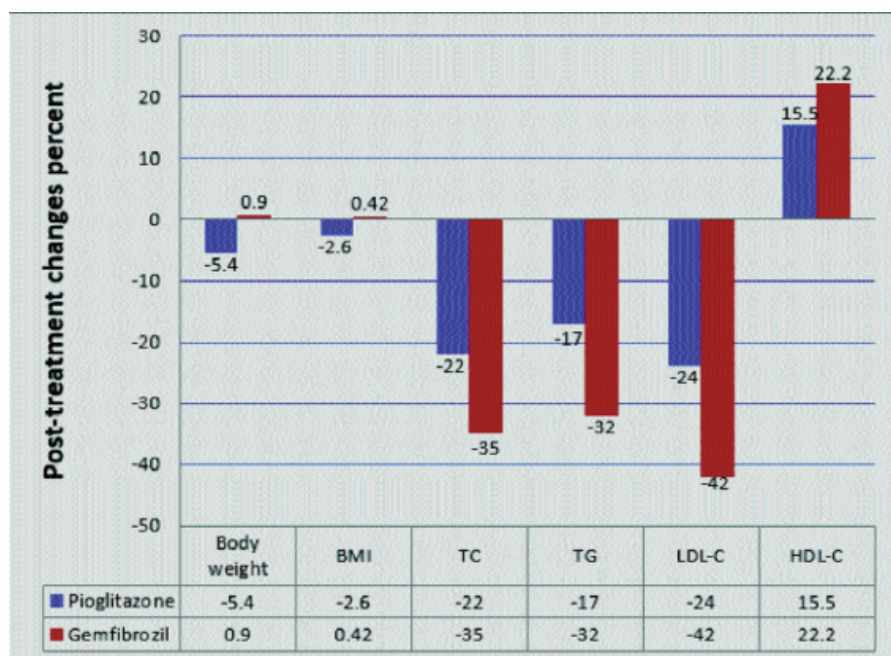
†Significantly (p<0.05) different with respect to control,

\* Significantly (p<0.05) different with respect to pre treatment value

\*\* Highly significantly (p<0.01) different with respect to pre treatment value.

8(17.8%) patients in the gemfibrozil group complained of abdominal distress during the first week of therapy, but they recovered without any intervention. Also, 7(15.6%) participants in the control group did not complete the study due to loss of follow-up.

The mean age was 27±14 years in group A, 26±17 years in group B and 29±19 years in group C. The respective values for body weight were 83±10.5kg, 85±13.6kg and 85±13.6kg, and those of BMI were 27.7±4.4kg/m<sup>2</sup>, 28.5 ±3.6kg/m<sup>2</sup> and 23±6.8kg/m<sup>2</sup> (Table-1).



BMI: Body mass index

TC: Total cholesterol

TG: Triglycerides;

LDL-C: Low density lipoprotein cholesterol

HDL-C: High density lipoprotein cholesterol

**Figure:** Changes in parameters after treatment with Pioglitazone and Gemfibrozil.

After the 12-week treatment, body weight decreased from 83±10.5 to 76±13.5kg and BMI from 27.7±4.4 to 25.5±6.4kg/m<sup>2</sup> in group A (p<0.01). In group B, body weight decreased from 85±13.6 to 85.7±12.2 kg and BMI from 28.5±3.6 to 28.8±3.2 kg/m<sup>2</sup> (p>0.01). In group A, total cholesterol (TC) improved from 245±13.2 to 198±16.45mg/dl, triglycerides (TG) from 237±29.4 to 192±32.45 mg/dl, LDL cholesterol from 148±16.78 to 110±15.14 mg/dl and HDL cholesterol from 40.4±4.94 to 46.6±4.5mg/dl (p<0.05). In group B, TC improved from 265±13.62 to 182±11.45mg/dl, TG from 190±40.25 to 136±36.25mg/dl, LDL cholesterol from 165±12.5 to 93±10.45mg/dl, and HDL cholesterol from 43 ±2.51 to 53±1.82mg/dl (p<0.01) (Table-2, Figure).

### Discussion

To our knowledge, the current study was the first clinical trial conducted on non-diabetic patients by drugs which were acting on both PPAR-α and PPAR-γ receptors.

PPAR- $\alpha$  and PPAR- $\gamma$  receptors are widely distributed in adipose tissue and their agonists has a strong potential to treat obesity. Pioglitazone has a proven beneficial effect on all of those conditions that has strong association with obesity such as metabolic syndrome, hypertension, dyslipidaemia, non-alcoholic fatty liver disease, inflammation, cancers risks, heart disease risk and multiple reproductive disorders in various clinical studies.<sup>13</sup> In spite of these proven effects, it is assumed that pioglitazone increases body weight in diabetic patients. Most of the type 2 diabetic patients are overweight and obese at the time of diagnosis and most of them have low compliance with drugs and diet as compared to non-obese people. Moreover, weight gain is usually more pronounced with pioglitazone use in combination with sulphonylureas and insulin in diabetic patients. However, 50% patients cannot experience weight gain and even have weight loss if eucaloric diet and exercise plan have been maintained.<sup>14</sup> Research suggests that even if pioglitazone causes mild increase in body weight in diabetic patients, it is quite beneficial because it causes redistribution of body fat as it increases subcutaneous fat and decreases visceral fat, which has strong tendency to predispose to coronary heart disease.<sup>15</sup> On the contrary, pioglitazone caused a significant reduction in body weight and BMI in this study while gemfibrozil, which is PPAR- $\alpha$  agonist, failed to decrease body weight. This clearly showed that weight reduction property of pioglitazone is mediated through PPAR- $\gamma$  receptor in non-diabetics. It seems that pioglitazone increases insulin sensitivity even in non-diabetics which causes the reduction of body weight.

In this study, both pioglitazone and gemfibrozil caused a significant improvement in deranged serum lipid profile. Although most of the oral anti-diabetic drugs have beneficial effects on serum lipid profile in diabetic patients, the overall effect of pioglitazone is more pronounced as compared to rosiglitazone, metformin and sulphonylureas.<sup>8-11</sup> The anti-dyslipidaemic effects of pioglitazone mediated through PPAR- $\gamma$  and PPAR- $\alpha$  receptors activation include reduction of insulin resistance, decrease in lipoprotein lipase-associated lipolysis, reduced lipid uptake, inhibition of ApoC-111 synthesis an inhibitor of the action of lipoprotein lipase, decrease in the level of atherogenic dense LDL cholesterol and lipoprotein A. Increase in large buoyant LDL particles which are non-atherogenic induces the synthesis of Apo A-1 and Apo A-2, the major HDL cholesterol constituents to beneficially increase plasma HDL cholesterol level. In addition, PPAR activation enhances endothelial function, reduces inflammatory

cytokines and increases a diponectin release that further improve dyslipidaemia.<sup>16</sup>

However, there were limited studies conducted on pioglitazone in non-diabetic patients. Shokouh et al.<sup>17</sup> showed that pioglitazone not only improved lipid profile but also markers of systemic inflammation in non-diabetic patients with metabolic syndrome. Winkler et al.<sup>18</sup> concluded that pioglitazone significantly reduced atherogenic dense LDL particle size in non-diabetic patients with hypertension while similar study conducted by Campia et al.<sup>19</sup> revealed that pioglitazone not only improved lipid profile but also improved endothelial mediated vasodilatation and inflammation in non-diabetic patients with major cardiovascular risk factors. In another study, monotherapy of both pioglitazone and simvastatin has independent effect while their combinations have synergistic effect on atherogenicity of small dense LDL particles.<sup>20</sup> Moreover, pioglitazone has strong potential to stabilise the atherosclerotic plaque which stops its further progression in non-diabetic patients.<sup>21</sup>

Atorvastatin and pioglitazone have both independent as well as additive effects on improving lipid profile, various inflammatory markers, endothelial dysfunction and intima-media thickness (IMT) of the common carotid artery in non-diabetic population with high cardiovascular risk.<sup>22</sup> All these beneficial effects of statins involve the activation of both PPAR- $\alpha$  and PPAR- $\gamma$  receptors similar to pioglitazone.<sup>23</sup>

Given the beneficial effects of pioglitazone on body weight and lipid profile in non-diabetics, it is obvious that pioglitazone improved body weight and lipid profile by reducing insulin resistance through PPAR- $\gamma$  receptor activation. But when it acts through PPAR- $\alpha$  receptor, there is further improvement in lipid profile in non-diabetics. Our study showed that pioglitazone is not weak rather it is a strong agonist of PPAR- $\gamma$  receptor as gemfibrozil.

A number of drugs are currently under study for the treatment of dyslipidaemia. The new approach is to combine activation of both PPAR- $\alpha$  and PPAR- $\gamma$ , which is expected to combine the beneficial effects of PPAR- $\alpha$  and PPAR- $\gamma$  on lipid metabolism, without being restricted to type 2 diabetics.<sup>24</sup>

## Conclusion

Pioglitazone has a strong potential to improve cardiometabolic risk even in non-diabetics. So it can be considered as an alternative drug in those patients who cannot tolerate statins and other lipid lowering agents.

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