

# Impact of glitazones on metabolic and haemodynamic parameters in patients with type 2 diabetes mellitus

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## ABSTRACT

**Introduction:** Diabetes mellitus is a common disorder associated with a number of metabolic abnormalities such as insulin resistance, dyslipidaemia and high blood pressure. These abnormalities are recognised risk factors for cardiovascular diseases. Insulin-sensitising drugs exert an effect on these cardiovascular risk factors. The present study was done with the objective of elucidating the differences in glycaemic control, plasma lipid levels and blood pressure in diabetic patients who were prescribed glitazones in combination with sulphonylureas.

**Methods:** Patients were randomly assigned to receive either pioglitazone or rosiglitazone in addition to glimepiride in an open-labelled study. Fasting and postprandial blood glucose levels, glycosylated haemoglobin, fasting lipid profile and blood pressure were recorded at baseline and at various intervals until the end of the study period at 12 weeks.

**Results:** A total of 56 patients (28 in the pioglitazone group and 28 in the rosiglitazone group) completed the study. There was no significant difference in the baseline values of various parameters between the two treatment groups. The efficacy of the two treatment groups was similar in terms of the maintenance of blood glucose levels (fasting blood glucose, p-value is 0.10; postprandial blood glucose, p-value is 0.95; glycosylated haemoglobin, p-value is 0.30) and the effect on blood pressure (systolic blood pressure, p-value is 0.45; diastolic blood pressure, p-value is 0.95), while the pioglitazone group showed significantly better efficacy in improving the lipid profile compared to the rosiglitazone group (total cholesterol, p-value is 0.002; triglycerides, p-value is 0.002; low density lipoprotein, p-value is 0.005; and high density lipoprotein, p-value is 0.43).

**Conclusion:** The two drugs showed a similar effect on blood glucose levels and blood pressure. However, the pioglitazone group was superior to the rosiglitazone group in improving the lipid profile.

**Keywords:** blood pressure, diabetes mellitus, glimepiride, lipid profile, pioglitazone, rosiglitazone

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## INTRODUCTION

Type 2 diabetes mellitus is a rapidly-expanding health problem characterised by insulin resistance and impaired pancreatic  $\beta$ -cell function. By the year 2025, the number of people with diabetes mellitus is expected to increase to 300 million and more than 90% of those will have type 2 diabetes mellitus.<sup>(1)</sup> Cardiovascular disease (CVD) is the main cause of morbidity and mortality in such patients.<sup>(2)</sup> Strategies that deal with cardiovascular risk factors alongside improving the glycaemic control are desirable. Antihypertensive and lipid-lowering therapies have been shown to decrease the incidence of CVD in patients with type 2 diabetes mellitus.<sup>(3)</sup> Those anti-diabetic medications that concomitantly also improve the cardiovascular profile of such patients appear to be more appropriate therapies.

Thiazolidinediones (glitazones) were approved in the late 1990s, and appear promising with respect to the preservation of the  $\beta$ -cell function and the potential for CVD prevention.<sup>(4)</sup> The two drugs of this class, viz. pioglitazone and rosiglitazone, are being widely used in the management of diabetes mellitus as an add-on therapy. There is provisional data to suggest that these drugs exert a range of effects on aspects of metabolic syndrome that might decrease the risk of atherosclerotic CVD.<sup>(5)</sup> A recent study, the Pioglitazone Effect on Regulation of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE), has suggested that pioglitazone significantly lowers the rate of progression of coronary atherosclerosis.<sup>(6)</sup> The individual differences between these two drugs have not been clearly defined in

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**Table I. Follow-up schedule of patients in the pioglitazone and rosiglitazone groups.**

	FBG	PPBG	HbA <sub>1c</sub>	Lipid profile	Blood pressure
Baseline	√	√	√	√	√
Week 2	√	√			
Week 4	√	√			√
Week 6	√	√		√	√
Week 12 end-point	√	√	√	√	√

FBG: fasting blood glucose; PPBG: postprandial blood glucose; HbA<sub>1c</sub>: glycosylated haemoglobin.

**Table II. Baseline characteristics of patients in the pioglitazone and rosiglitazone groups.**

	Pioglitazone group (n = 28)	Rosiglitazone group (n = 28)	p-value
FBG (mg/dL)	163.82 ± 59.92	171.57 ± 30.92	0.46
PPBG (mg/dL)	227.61 ± 73.22	228.79 ± 44.67	0.92
HbA <sub>1c</sub> (%)	7.932 ± 0.89	8.089 ± 0.66	0.30
TC (mg/dL)	217.39 ± 51.21	235.18 ± 48.07	0.18
TG (mg/dL)	161.46 ± 56.61	169.14 ± 64.72	0.61
LDL (mg/dL)	146.14 ± 45.27	160.64 ± 38.00	0.19
HDL (mg/dL)	38.96 ± 8.39	40.71 ± 7.52	0.39
Systolic BP (mmHg)	127.93 ± 15.40	124.86 ± 9.02	0.36
Diastolic BP (mmHg)	82.93 ± 9.65	82.79 ± 7.57	0.95
Weight (kg)	62 ± 4.50	60.10 ± 1.16	0.07

Data is expressed as adjusted mean ± standard deviation.

All the p-values was non-significant.

n: number of patients; FBG: fasting blood glucose; PPBG: postprandial blood glucose; HbA<sub>1c</sub>: glycosylated haemoglobin; TC: total cholesterol; TG: triglycerides; LDL: low-density lipoprotein; HDL: high-density lipoprotein; BP: blood pressure.

terms of their effect on lipid profile and blood pressure. The present study was undertaken to compare the effects of pioglitazone and rosiglitazone when administered with other hypoglycaemic agents, viz. glimepiride, on glycaemic control, lipid profile and blood pressure.

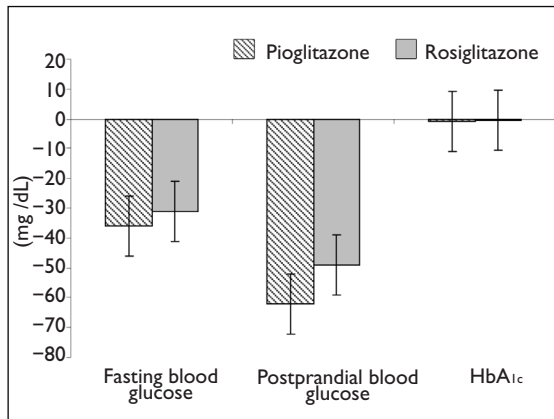
## METHODS

An open label, randomised comparison of a combination of pioglitazone and glimepiride with rosiglitazone and glimepiride in patients with type 2 diabetes mellitus was carried out in the year 2006. Patients attending the diabetic clinic of a teaching hospital were enrolled in the study. The protocol of the study was reviewed by the institutional review board and ethical clearance for the conduct of the study was given. Written informed consent was obtained from the participants before they were enrolled in the study. Patients who were included in the study, were of both genders in the 30–70 year age group, had type 2 diabetes mellitus, were prescribed sulphonylurea (glimepiride) and required an add-on therapy of glitazones due to a lack of proper glycaemic control. The patients were normotensives and did not take any medication for hypertension, nor were they taking any hypolipidaemic drugs. They were subjected to evaluation at the time of inclusion. After a complete medical history and physical examination were conducted, the following investigations were carried out:

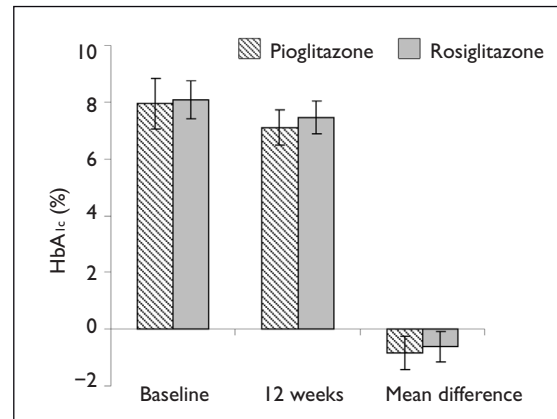
- (1) Baseline blood glucose levels: fasting blood glucose (FBG), postprandial blood glucose (PPBG) and glycosylated haemoglobin (HbA<sub>1c</sub>). PPBG levels were measured two hours after meals.
- (2) Lipid profile: total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL) and triglycerides (TG).
- (3) Blood pressure: systolic and diastolic. Right arm supine early morning blood pressure was measured.

The patients were randomised in the two groups by computer-generated random tables. The subjects were randomly prescribed either pioglitazone (Pioz) plus glimepiride (Amaryl) 2 mg orally, or rosiglitazone (Rezult) plus glimepiride (Amaryl) 2 mg orally. The dose of each drug was titrated in accordance with the patient's blood glucose levels. Most of the patients received pioglitazone at a dose of 30 mg/day and rosiglitazone 4 mg/day, which are mid-range doses for both drugs. The patients were also advised on non-pharmacological measures like lifestyle modification and proper diet. The study was conducted for a period of 12 weeks. The patients were followed up at weeks 2, 4, 6 and 12 (Table I).

The primary end points of this study were blood glucose levels, plasma lipids and blood pressure at 12 weeks. Blood glucose and lipid levels were estimated using a semiautomatic analyser. TC was estimated by the



**Fig. 1a** Bar chart shows the average change in the baseline values of fasting and postprandial blood glucose and HbA<sub>1c</sub> levels in the pioglitazone and rosiglitazone groups at the end of 12 weeks of treatment.



**Fig. 1b** Bar chart shows the levels of glycosylated haemoglobin in the pioglitazone and rosiglitazone groups at baseline and at 12 weeks.

cholesterol peroxidase method (CHOD-PAP method). TG was estimated by the GPO-ESPAS method using a fluid stable kit. HDL was measured by PEG precipitation and the enzymatic method. LDL was calculated by Friedwald's formula. Both systolic and diastolic blood pressure readings were recorded in the morning with the patient in the supine position and using his right arm. Statistical analysis was conducted. Paired *t*-test and Student's *t*-test were carried out to compare the two drugs using the Statistical Package for Social Sciences version 10.0 (SPSS Inc, Chicago, IL, USA). All statistical tests were carried out at a two-sided 0.05 significance level.

## RESULTS

A total of 63 patients who were in the 30–70 year age group, diagnosed with diabetes mellitus for less than three years and did not have any apparent symptoms of early diabetic complications, were enrolled in the study. Of these, three patients were excluded because of diabetic complications, two were non-compliant and two were lost to follow-up. 56 patients completed the study. The baseline characteristics of the two groups are shown in Table II. There was no significant difference in the baseline values of the different parameters of the two groups. The values at baseline and at 12 weeks were calculated for statistical significance.

In comparison to the baseline values, the mean fall in the FBG and PPBG levels at week 12 was significant in both groups ( $p < 0.05$ ). However, there was no significant difference between the two groups with regard to the change in FPG ( $p = 0.10$ ) and PPBG ( $p = 0.95$ ) (Fig. 1a). HbA<sub>1c</sub> levels also decreased significantly in the two groups of patients with no significant intergroup difference ( $p > 0.05$ ) (Fig. 1b). However, 37.9% of patients in the pioglitazone group and 17.8% in the rosiglitazone group

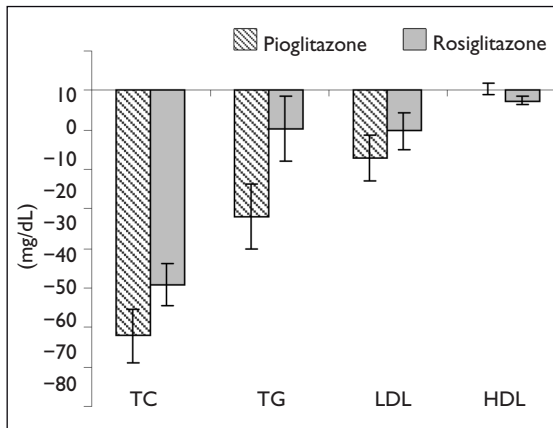
had HbA<sub>1c</sub>  $< 7.0\%$  at the end of the study.

Lipid profile parameters showed significant differences between the two groups. TC in the pioglitazone and rosiglitazone groups changed and the difference between the two groups was significant ( $p = 0.004$ ) (Fig. 2). TG in the pioglitazone group ( $p = 0.0006$ ) decreased significantly in comparison to the rosiglitazone group ( $p = 0.255$ ) at 12 weeks with a *p*-value of 0.002. LDL cholesterol levels also showed a significant decrease ( $p = 0.005$ ) at the end of the study in the pioglitazone group, compared to the rosiglitazone group. HDL cholesterol increased non-significantly ( $p = 0.83$ ) in the pioglitazone group as compared to the rosiglitazone group, in which there was a decrease in the HDL levels ( $p = 0.03$ ). However, the intergroup change in the HDL cholesterol levels was not statistically significant ( $p > 0.05$ ) (Fig. 2).

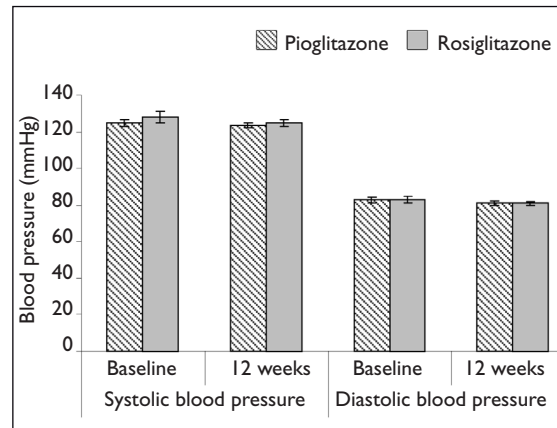
Systolic blood pressure in patients in the pioglitazone group and the rosiglitazone group showed a non-significant decrease ( $p = 0.079$  and  $p = 0.32$ , respectively). Likewise, the difference between the two groups was also not statistically significant ( $p = 0.45$ ). A similar trend was seen with diastolic blood pressure measurements (Fig. 3). There was an increase in the weight of the patients in the two groups but the difference between the two groups was not significant ( $p = 0.10$ ).

## DISCUSSION

Thiazolidinediones are generally administered along with other conventional drugs like sulphonylureas as an add-on therapy. In diabetic patients, the risk of cardiovascular death is 2–4 times higher than in the general population.<sup>(2)</sup> Since CVD disease is a major burden in patients with type 2 diabetes mellitus, data about the effect of thiazolidinediones on the modification of cardiovascular



**Fig. 2** Bar chart shows the average change in the baseline levels of total cholesterol, triglyceride, low- and high-density lipoproteins in the pioglitazone and rosiglitazone groups at 12 weeks of treatment.



**Fig. 3** Bar chart shows the change in the systolic and diastolic blood pressures of the pioglitazone and rosiglitazone groups at baseline and at 12 weeks.

risk factors is urgently needed. The present study is a comparative study of pioglitazone with rosiglitazone along with sulphonylurea (Glimeperide). The two drugs, pioglitazone and rosiglitazone, have demonstrated similar effects with regard to glycaemic control. The efficacy of the two drugs was similar in terms of the decrease in FBG, PPBG and HbA<sub>1c</sub> at 12 weeks. The addition of rosiglitazone or pioglitazone to the treatment schedule of patients whose glycaemic control with sulphonylurea was suboptimal was required for better glycaemic control. The two drugs have shown similar glucose-lowering effects in various studies and been shown to reduce HbA<sub>1c</sub> by around 0.5%–1.5%.<sup>(7)</sup>

Diabetic dyslipidaemia is characterised by an increase in TG and a decrease in HDL.<sup>(8)</sup> Often the level of LDL is the same as that of non-diabetics.<sup>(7)</sup> Despite near normal LDL levels, LDL has been more atherogenic as compared to other lipid parameters. Any reduction in the level of LDL has beneficial effects on patients with dyslipidaemia and thereby reduces the risk of cardiovascular events. Pioglitazone significantly decreased TC, TG and LDL as compared to rosiglitazone. One of the earlier studies showed that pioglitazone decreased TG levels significantly, while rosiglitazone showed an increase in the TG levels.<sup>(9)</sup> In our study, both pioglitazone and rosiglitazone have decreased the levels of TG, and the decrease is statistically significant only in the former. Our study further re-emphasises the superiority of pioglitazone over rosiglitazone as far as better control over TG levels is concerned.

In the present study, there was a decrease in LDL levels in both groups but the decrease was significant only in the pioglitazone group. The results are in concordance with an earlier study which showed similar results.<sup>(10)</sup> In contrast to earlier studies, however, our study showed a

decrease in LDL levels, even in the rosiglitazone group, but this decrease was not statistically significant. As compared to earlier studies, HDL levels have increased in the pioglitazone group and decreased in the rosiglitazone group, but the difference between the two groups was not significant. Similar results have been shown in another study that concluded that the two drugs have an almost similar effect on plasma HDL cholesterol levels.<sup>(11)</sup> The mechanism responsible for the beneficial effect of pioglitazone is yet to be established but it may be due to its modest agonistic effect on peroxisome proliferator-activated receptor (PPAR)- $\alpha$ <sup>(12)</sup> in addition to PPAR- $\gamma$ .

Hypertension is 1–2 times more prevalent in patients with type 2 diabetes mellitus. Hypertension is associated with substantial insulin resistance, even in patients without diabetes mellitus. The United Kingdom Prospective Diabetes Study has shown that the control of hypertension in patients with diabetes mellitus improves both micro- and macrovascular outcomes.<sup>(13)</sup> Thiazolidinediones decrease insulin resistance, and may have a beneficial effect on blood pressure. Also, it is postulated that thiazolidinediones improve endothelial dependent vasodilation, decrease the calcium influx and the calcium sensitivity of contractile apparatus.<sup>(14)</sup> Both the drugs slightly decrease the systolic and diastolic blood pressures. It has been shown that rosiglitazone, when administered for 16 weeks, significantly decreased the systolic and diastolic blood pressures in hypertensive diabetic patients.<sup>(15)</sup> In a double-blind, placebo-controlled study with pioglitazone in non-diabetic patients with arterial hypertension, it was found that there was a non-significant decrease in systolic blood pressure but a significant decrease in diastolic blood pressure.<sup>(16)</sup> The patients in the present study were

not hypertensive, and that could be the reason for a non-significant fall in their blood pressure. Studies with a longer duration, and especially in diabetic patients who are also hypertensive, may provide more conclusive evidence.

Thiazolidinediones are a useful class of drugs with a beneficial effect on dyslipidaemias. A two drugs have differential effects on lipid metabolism. A meta-analysis by Nissen and Wolski showed that treatment with rosiglitazone increases the risk of myocardial infarction, and also increases in the risk of death from cardiovascular causes of borderline significance.<sup>(17)</sup> The potential factor put forth by the authors for this increased risk is the adverse effects of drugs on serum lipids. However, this is not a class effect, as shown in the PROactive Study which suggested that pioglitazone improves cardiovascular outcomes in patients.<sup>(18)</sup> This advantage of pioglitazone has been postulated to be due to a better metabolic profile in terms of glucose, HDL-cholesterol, TG concentration and a better blood pressure profile at the end of the study than at the beginning. In summary, pioglitazone holds a stronger position as compared to rosiglitazone in type 2 diabetes mellitus with cardiovascular risk factors in decreasing the cardiovascular complications.

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