

ORIGINAL ARTICLE

# Thiazolidinediones: comparison of long-term effects on glycemic control and cardiovascular risk factors

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## SUMMARY

**Objective:** To compare the long-term effects on HbA<sub>1c</sub>, lipid parameters, body weight, and hepatotoxicity after switching type 2 diabetes patients from troglitazone to either pioglitazone or rosiglitazone.

**Methods:** Of 125 study candidates from a previous prospective study, 100 patients (51 pioglitazone, 49 rosiglitazone) met criteria for comparing HbA<sub>1c</sub>, lipids, body weight, and incidence of hepatotoxicity over 2 successive observation periods (3.1 and 12.6 months).

**Results:** Mean absolute HbA<sub>1c</sub> decreased significantly, 0.53 and 0.27% in the pioglitazone and rosiglitazone groups, respectively, at the 12.6-month observation. Mean triglyceride (TG) decreased in the pioglitazone group at each interval with a cumulative decrease of 26.4% from baseline. In contrast, TG increased in the rosiglitazone patients by 43.3% at 3.1 months and then decreased (but remained above baseline) at

12.6 months. Mean high density lipoprotein (HDL) increased 22.1% with pioglitazone and 13.3% with rosiglitazone. In patients who had a baseline HDL < 35 mg/dL (0.91 mmol/L), pioglitazone-treated patients experienced a significant increase at each interval resulting in a 52.6% increase in HDL compared to a 26.9% increase for rosiglitazone patients. Patients in both treatment groups had similar weight increases at each interval and no hepatotoxicity was noted.

**Conclusion:** With pioglitazone or rosiglitazone, changes in glycemic control, lipid effects, and body weight appear to continue over time. Pioglitazone treatment resulted in decreased triglyceride levels, while rosiglitazone was associated with an increase in triglyceride levels. HDL increased in both treatment groups, but in patients with a baseline HDL < 35 mg/dL (0.91 mmol/L), pioglitazone improved the HDL to a greater extent than rosiglitazone.

## Introduction

Type 2 diabetes is associated with a two- to four-fold increased risk of coronary heart disease (CHD). Therefore, diabetes therapy should focus not only on providing long-term glycemic control, but also on treating other cardiovascular risk factors<sup>1,2</sup>. The thiazolidinediones offer a novel and unique approach for the treatment of diabetes. They improve glycemic control by reducing insulin resistance, which is believed

to be mediated through binding and activation of the peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ). This action improves target cell response to insulin, increasing glucose uptake in adipose tissue and skeletal muscle and decreasing hepatic glucose production<sup>3</sup>. In March 2000, the first thiazolidinedione available in the United States, troglitazone, was withdrawn from clinical use because of safety concerns regarding drug-induced hepatotoxicity<sup>4-6</sup>. At that time many of the type 2 diabetes patients in our private endocrinology practice

had been receiving maintenance therapy with troglitazone. In 2001 we reported results of a 3.2-month prospective observational study of patients who we had switched to one of the two newer thiazolidinediones (pioglitazone or rosiglitazone) after troglitazone's withdrawal<sup>7</sup>. That study demonstrated that pioglitazone and rosiglitazone provided similar glycemc (HbA<sub>1c</sub>) control, but had differing effects on lipids, particularly triglycerides and HDL. Other similar short-term observations have demonstrated varying lipid effects with thiazolidinediones<sup>8-24</sup>.

Long-term effects of thiazolidinediones (TZD) are of particular interest because patients will often be using them as continual therapy. Choosing between the two available thiazolidinediones should reflect consideration of both glycemc and lipid effects over a sustained therapeutic course. These glycemc benefits of thiazolidinediones are detected as early as the second week of therapy, with a previously reported maximal effect demonstrated at 10–14 weeks and maintained for 26 weeks<sup>12</sup>. Since therapeutic effects of these agents persist over time<sup>11</sup>, we retrospectively evaluated the previously described patients over a mean treatment duration of 12.6 months.

## Research design and methods

### Patients and Methods

After the withdrawal of troglitazone, we reported<sup>7</sup> the glycemc response of 144 patients with type 2 diabetes in our office-based endocrinology practice, who had been switched from troglitazone, and the lipid effects in the 125 patients in that group who had both glycemc and lipid data available. No other glycemc or lipid-lowering medication was changed. It was a prospective study, but the patients were not assigned to either agent by a randomized protocol. Medication selection was intended to alternate between the two agents but was influenced at the time by a number of factors, such as direct-to-consumer advertising, patient preference and formulary restraints.

The inclusion criteria for the 3.2-month prospective trial included transition to pioglitazone or rosiglitazone after the recommended 1-week washout period, and lack of additional glycemc medication or dose change. Patients were excluded if they had been receiving troglitazone for less than 4 months prior to the substitution, if they had not had at least two baseline HbA<sub>1c</sub> values while on maintenance troglitazone therapy, if there was a gap in therapy of greater than 3 weeks at

the time of conversion, if patient noncompliance occurred, or if the patient left the practice or died prior to the completion of laboratory assessments. To further satisfy the inclusion criteria for lipid evaluation, patients had to have a baseline lipid measurement at the time of the conversion and at least one subsequent lipid measurement without any change in lipid-lowering agent or dose.

### Long-term Observation

The 125 patients with both glycemc and lipid data available, as described above, were followed in our office-based private endocrinology practice. Our usual care was provided following the clinical practice recommendations of the American Association of Clinical Endocrinologists (AACE) and American Diabetes Association (ADA)<sup>1,2</sup>. The practice has an on-site clinical laboratory and an on-site diabetes patient education program (with two certified diabetes educators) recognized by the ADA. Diabetes disease management is facilitated for all diabetic patients in our practice by the use of DiaTrends (Overlook Software, Inc., Greensboro, NC, USA)<sup>25</sup>, a software tool designed to systematically track and improve the treatment of diabetes. Using this tool, we retrospectively evaluated these patients over a longer treatment duration. The general approaches to medical care, medical nutrition therapy and activity recommendations were not different for either cohort. These patients are the subjects of this report.

Sixty patients had been switched to pioglitazone and of these 9 were excluded (6 due to lack of data, 2 due to poor compliance and 1 due to lipid-lowering agent added). Sixty-five patients had been switched to rosiglitazone and 16 were excluded (10 due to lack of data, 1 due to death, 1 due to poor compliance and 4 due to starting additional glycemc medications).

Since dose equivalency was not available at the time of the conversion, clinical judgment was used in determining thiazolidinedione dose, with a tendency to switch to a higher dose for both agents. In contrast to the previously-reported 3.2-month interim observation, we permitted changes in the dose of an existing lipid-lowering agent during the extended observation. Specifically, 2 of the 51 patients in the pioglitazone group and 5 of the 49 patients in the rosiglitazone group had an increase in their lipid-lowering agent (atorvastatin) dose during the extended observation. All of these dose changes were a single increment from 10 to 20 or 20 to 40 mg daily. Potentially, this would favor the lipid effect in the rosiglitazone group, but this dose adjustment effect is estimated to be small (3–7% decrease in TG and 3 to –3% in HDL based on prescribing information)<sup>26</sup>. These patients were not

**Table 1.** Patient characteristics at baseline

	Pioglitazone (n = 51)	Rosiglitazone (n = 49)	p-value
Age (years)	67.0 ± 7.9	59.5 ± 10.9	< 0.01
Gender: M/F	31/20	25/24	0.42
Duration of diabetes (years)	14.5 ± 7.8	13.1 ± 8.0	0.38

**Table 2.** Concomitant medications

	Pioglitazone (n = 51)	Rosiglitazone (n = 49)
TZD monotherapy	7 (13.7%)	3 (6.1%)
Sulfonylurea or meglitinide	33 (64.7%)	33 (67.3%)
Metformin	13 (25.5%)	18 (36.7%)
Insulin	20 (39.2%)	21 (42.9%)
Alpha-glucosidase inhibitor	2 (3.9%)	0 (0.0%)
Statin	32 (62.7%)	20 (40.8%)
Fibrate	1 (1.9%)	2 (4.1%)

excluded from the study. In contrast, giving patients an additional or different lipid lowering agent would potentially have had a greater impact on their lipids. Therefore, when an additional or different lipid-lowering agent was started (7 of 51 pioglitazone patients and 9 of 49 rosiglitazone patients), the last lipid profile prior to that change terminated the observation for that patient, and this set of lipid values and its date of occurrence were included in the data analysis.

## Weights and Laboratory Testing

Body weight was measured on a single scale at the time of the office visits, and liver enzymes were obtained with a minimum frequency of every 2 months for the first 12 months according to guidelines.

All laboratory tests were done in the same laboratory using the same standard methodologies for the lipid analyses. There was a change in the HbA<sub>1c</sub> methodology due to an instrument change (switching from the Cobas Mira to the Bio-Rad Variant II). However, concordant measurements done with both assays gave similar results. Graphical observations of our entire patient population did not show any deviation, and data from the manufacturer and survey data from the College of American Pathologists confirmed the correlation of the results. Both HbA<sub>1c</sub> assay methods are certified by the National Glycohemoglobin Standardization Program and have a normal range of 4.1–6.0%. The mean of the two most recent HbA<sub>1c</sub> values obtained during the several months prior to each patient's thiazolidinedione conversion provided his or her baseline level. Subsequent (post-conversion) HbA<sub>1c</sub> and lipid measurements were obtained at 1–5 months for the interim observation and at 5–17 months for the extended observation.

## Statistical Analysis

Statistical analysis was conducted for each treatment effect (using each patient's last result within the observation period) compared to baseline on the basis that mean % change = 0 using the sign test. Comparison for the mean % change for pioglitazone vs. rosiglitazone was done using the Wilcoxon rank sum test.

## Results

### General Characteristics

Of the 125 patients (60 in the pioglitazone group and 65 in the rosiglitazone group) previously reported, there were 51 and 49 patients in the pioglitazone and rosiglitazone subsets, respectively, who met the glycemic and lipid criteria for the extended study as above. Baseline characteristics of the 100 patients in the extended observation are shown in Table 1. Both cohorts were statistically similar except the mean age of the pioglitazone patients was greater.

For the 51 patients switched to pioglitazone, the mean daily troglitazone dose had been 482.4 mg and the mean pioglitazone dose was 42.3 mg. Similarly, for the 49 patients switched to rosiglitazone, the mean daily troglitazone dose had been 508.2 mg and the mean daily rosiglitazone dose was 6.9 mg. The maximum dose was used for 84 and 73% of the pioglitazone and rosiglitazone patients, respectively. In the pioglitazone group, 1 (2.0%) patient was taking the 15 mg dose, 7 (13.7%) the 30 mg dose, and 43 (84.3%) the 45 mg dose. In the rosiglitazone group, 13 (26.5%) patients were taking the 4 mg dose and 36 (73.5%) were taking the 8 mg daily dose.

The vast majority of patients were on combination antihyperglycemic therapy. In the pioglitazone group, there were 7 (13.7%) patients receiving monotherapy, 33 (64.7%) on a sulfonylurea or meglitinide, 13 (25.5%) on metformin, and 20 (39.2%) on insulin. In the rosiglitazone group, 3 (6.1%) patients were receiving monotherapy, 33 (67.3%) a sulfonylurea or meglitinide, 18 (36.7%) metformin, and 21 (42.9%) insulin. Baseline statin was used by 32 patients (62.7%) in the pioglitazone group and 20 (40.8%) in the rosiglitazone group (Table 2).

The mean baseline HbA<sub>1c</sub> for the 100 patients was 7.0%, which was very close to the target of less than 7.0% recommended by the American Diabetes Association<sup>2</sup>, but higher than the 6.5% currently recommended by the American Association of Clinical

**Table 3.** Weight, glycemic and lipid changes

	Baseline	3.1 months	12.6 months	Mean % change		
				0–3.1 months	3.1–12.6 months	0–12.6 months
Pioglitazone						
Weight (kg)	97.9 ± 18.5	99.3 ± 18.6	102.0 ± 19.6	1.5* ± 2.2	2.7* ± 4.0	4.1* ± 4.5
HbA <sub>1c</sub> (%)	7.07 ± 0.82	6.92 ± 1.03	6.54 ± 0.96	-2.0 ± 10.0	-4.6* ± 13.6	-7.4* ± 9.8
Cholesterol mg/dL	188.6 ± 27.0	179.7 ± 36.5	185.5 ± 39.7	-4.8*† ± 13.2	5.3† ± 24.7	-1.5 ± 16.4
mmol/L	4.88	4.65	4.80			
Triglycerides mg/dL	215.1 ± 146.0	179.5 ± 121.1	142.9† ± 83.9	-11.3*† ± 27.9	-13.8* ± 33.2	-26.4*† ± 30.0
mmol/L	2.43	2.02	1.61			
HDL mg/dL	47.3 ± 15.1	48.9† ± 13.9	55.1† ± 13.4	6.6*† ± 22.1	16.1* ± 21.5	22.1* ± 26.2
mmol/L	1.22	1.26	1.42			
LDL mg/dL	102.2 ± 25.5	95.8 ± 27.4	98.7 ± 26.5	-4.7† ± 21.7	5.5 ± 26.1	-1.9 ± 25.0
mmol/L	2.64	2.48	2.55			
Rosiglitazone						
Weight (kg)	102.6 ± 24.8	103.7 ± 25.5	105.6 ± 26.3	1.0 ± 3.9	1.8* ± 3.1	2.8* ± 4.7
HbA <sub>1c</sub> (%)	6.85 ± 0.73	6.90 ± 0.82	6.58 ± 0.99	0.4 ± 8.1	-3.9* ± 10.1	-3.8* ± 10.2
Cholesterol mg/dL	178.5 ± 30.0	194.4 ± 39.1	185.3 ± 38.7	9.9* ± 19.2	-3.4 ± 17.9	4.2 ± 15.4
mmol/L	4.62	5.03	4.79			
Triglycerides mg/dL	169.5 ± 91.3	247.1 ± 229.9	190.6 ± 129.7	43.3* ± 87.2	-13.6* ± 26.7	15.3 ± 56.6
mmol/L	1.91	2.79	2.15			
HDL mg/dL	44.2 ± 13.1	41.9 ± 12.3	48.6 ± 14.7	-3.6 ± 17.1	19.4* ± 27.8	13.3* ± 27.3
mmol/L	1.14	1.08	1.26			
LDL mg/dL	99.8 ± 25.0	106.3 ± 27.4	103.0 ± 30.8	9.3* ± 24.8	-3.5 ± 35.9	2.5 ± 24.1
mmol/L	2.58	2.75	2.66			

\**p* < 0.05 change in time period; †*p* < 0.05 pioglitazone v. rosiglitazone

Endocrinologists<sup>1</sup>. This mean HbA<sub>1c</sub> is similar to the overall mean HbA<sub>1c</sub> of 6.74% for type 2 diabetes patients in our practice at the time of the study.

Data were evaluated for these 100 patients at three time points: baseline (time of TZD conversion), interim (corresponding to the initial observation as previously described)<sup>7</sup> and the extended observation. The mean observation time for the interim and extended observations was 3.1 and 12.6 months, respectively (Table 3).

### Glycemic Control

From baseline to the interim observation, the absolute HbA<sub>1c</sub> decreased 0.15% for the pioglitazone patients and increased 0.05% for the rosiglitazone patients. Subsequently, there was a statistically significant decrease in

HbA<sub>1c</sub> values in both groups during the extended observation (Figure 1). The total absolute HbA<sub>1c</sub> decrease from baseline was 0.53 and 0.27% in the pioglitazone and rosiglitazone groups, respectively, but the difference between the two treatment groups was not statistically significant (*p* = 0.08).

### Cholesterol and LDL Changes

At the interim observation, the mean cholesterol decreased significantly from the pre-conversion value in the pioglitazone group compared to rosiglitazone, but at the final observation there was no difference between the pioglitazone and rosiglitazone groups. Similarly, LDL decreased at the interim observation for the pioglitazone patients but the LDL levels were similar at the final observation (Table 3).

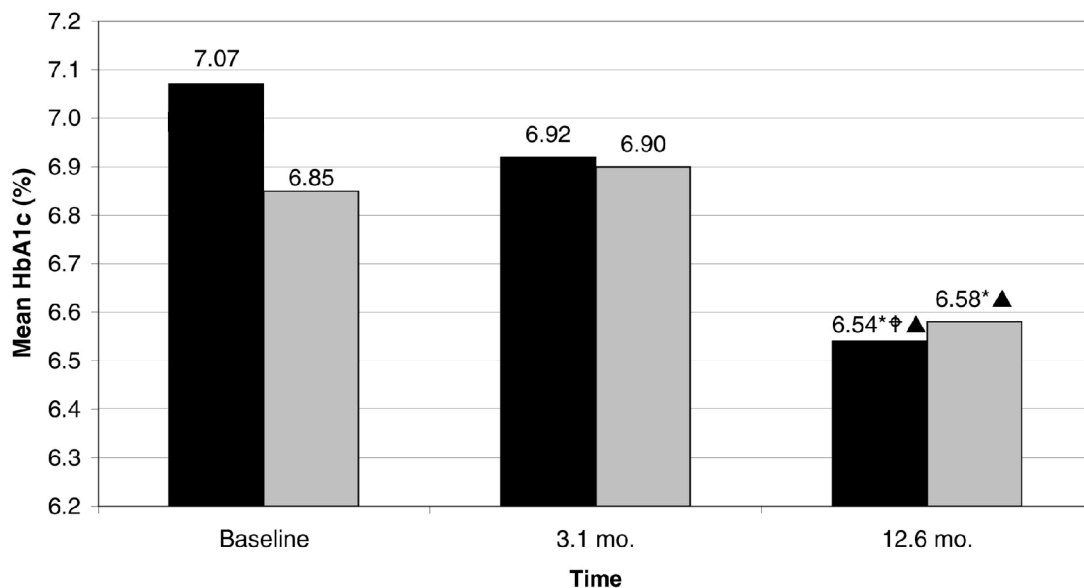


Figure 1. Glycemic changes after conversion to pioglitazone or rosiglitazone (\* $p < 0.05$  vs. baseline;  $\text{♠} p < 0.05$  vs. 3.1 months;  $\text{♠} p = 0.08$  pioglitazone vs. rosiglitazone)

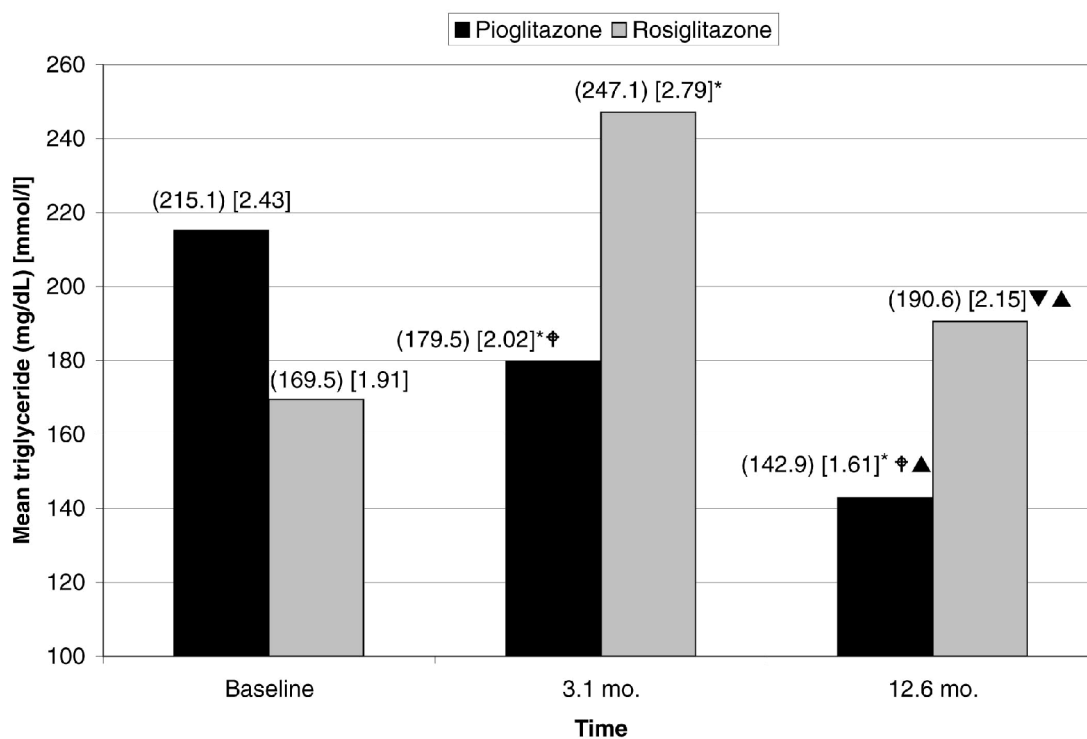


Figure 2. Triglyceride changes after conversion to pioglitazone or rosiglitazone (\* $p < 0.01$  vs. baseline;  $\text{♠} p = 0.06$  vs. baseline;  $\text{♠} p < 0.01$  vs. 3.1 months;  $\text{♠} p < 0.01$  pioglitazone vs. rosiglitazone)

## Triglycerides

Mean triglycerides were not statistically different at the index visit (Table 3). TG levels decreased significantly in the pioglitazone patients at both 3.1 months and at the extended observation. The rosiglitazone patients had a significant increase in the TG levels at the interim observation, although the levels later decreased. The net

result was a progressive decrease in TG levels in the pioglitazone patients and an overall improvement compared to the rosiglitazone patients (Figure 2).

## HDL

At each interval, HDL levels progressively and significantly increased from baseline in the group

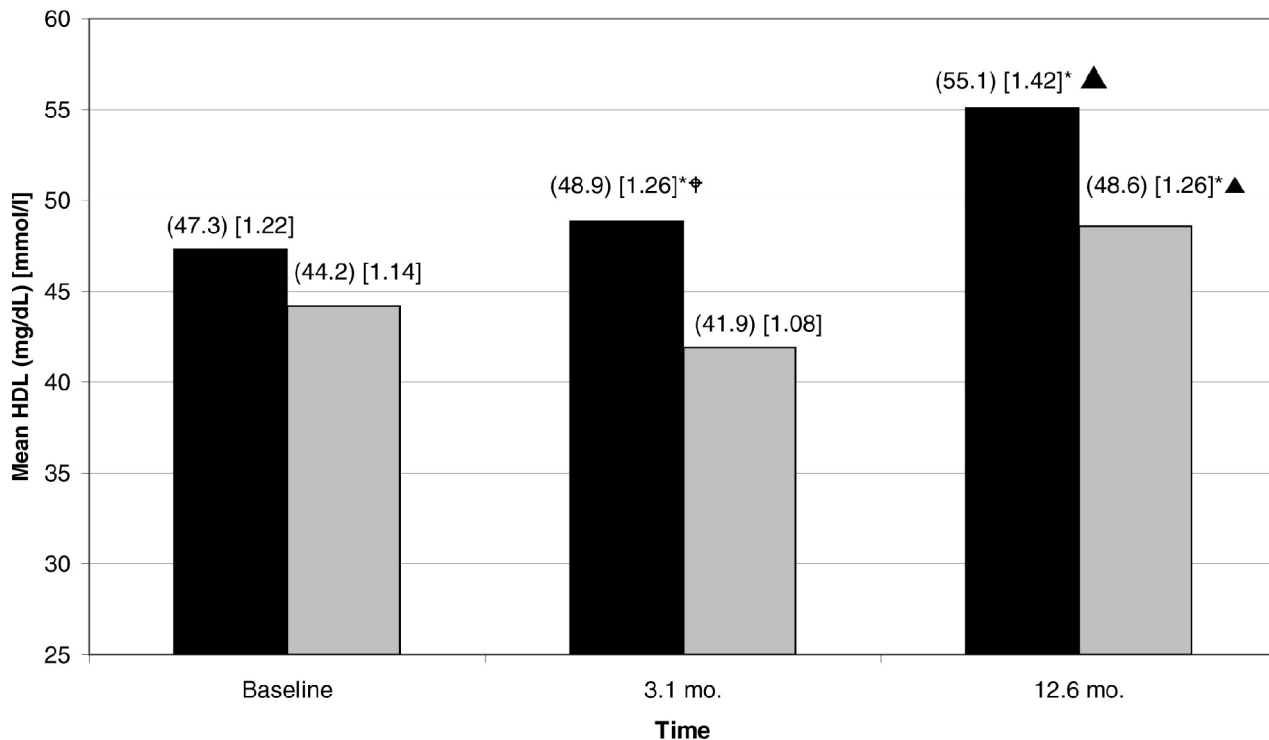


Figure 3. HDL changes after conversion to pioglitazone or rosiglitazone (\* $p < 0.05$  vs. baseline;  $\text{♠}$   $p < 0.01$  vs. 3.1 months;  $\text{♠}$   $p < 0.05$  pioglitazone vs. rosiglitazone)

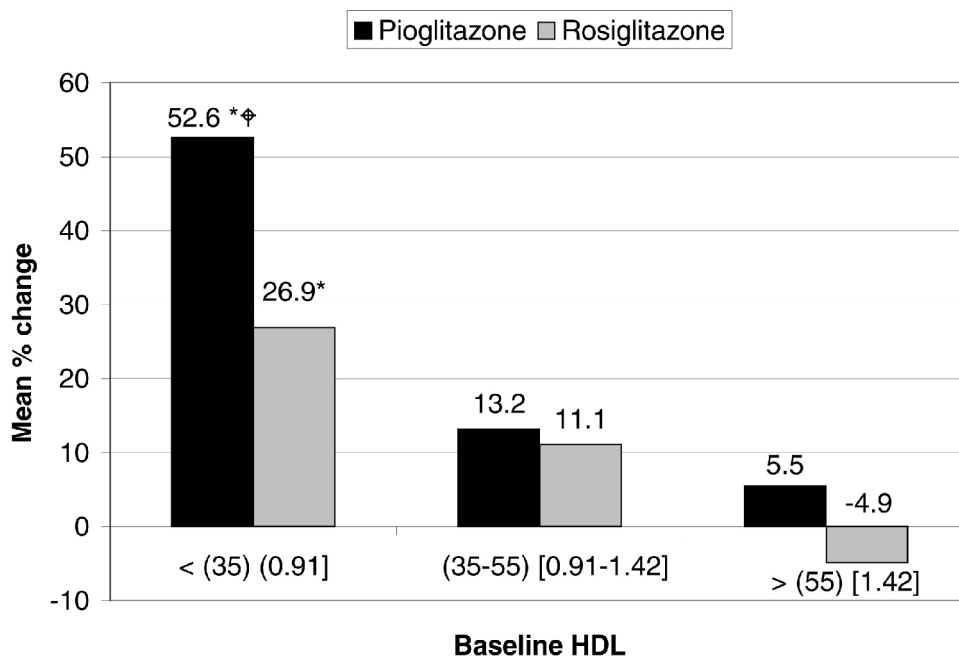


Figure 4. HDL changes 12.6 months after conversion to pioglitazone or rosiglitazone according to baseline HDL (\* $p < 0.01$  vs. baseline;  $\text{♠}$   $p < 0.01$  pioglitazone vs. rosiglitazone)

converted to pioglitazone. In contrast, HDL decreased initially in the patients converted to rosiglitazone, but then increased over time. At 12.6 months, both groups showed improvement in HDL (Figure 3).

The impact on HDL was greatest in patients with a baseline HDL level < 35 mg/dL (0.91 mmol/L) for both agents. For these patients, the HDL increased 52.6% in the pioglitazone patients ( $n = 15$ ) and 26.9% in the

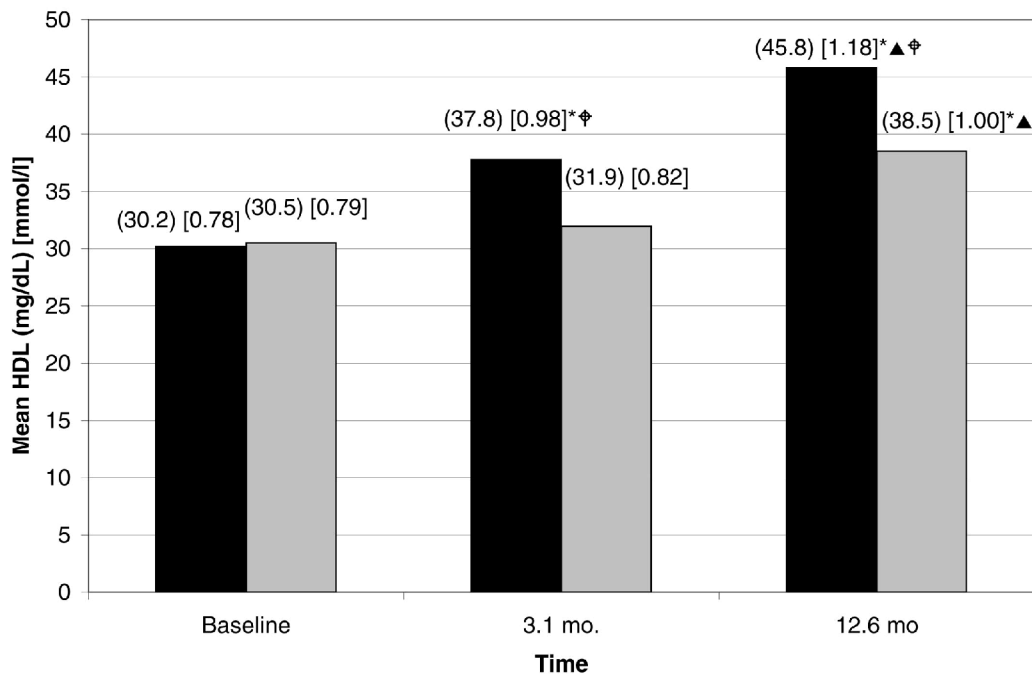


Figure 5. HDL changes after conversion to pioglitazone or rosiglitazone if baseline was < 35 mg/dL (\* $p < 0.01$  vs. baseline;  $\text{♠}$   $p < 0.01$  change from 3.1 months;  $\blacktriangle$   $p < 0.01$  pioglitazone vs. rosiglitazone change from baseline)

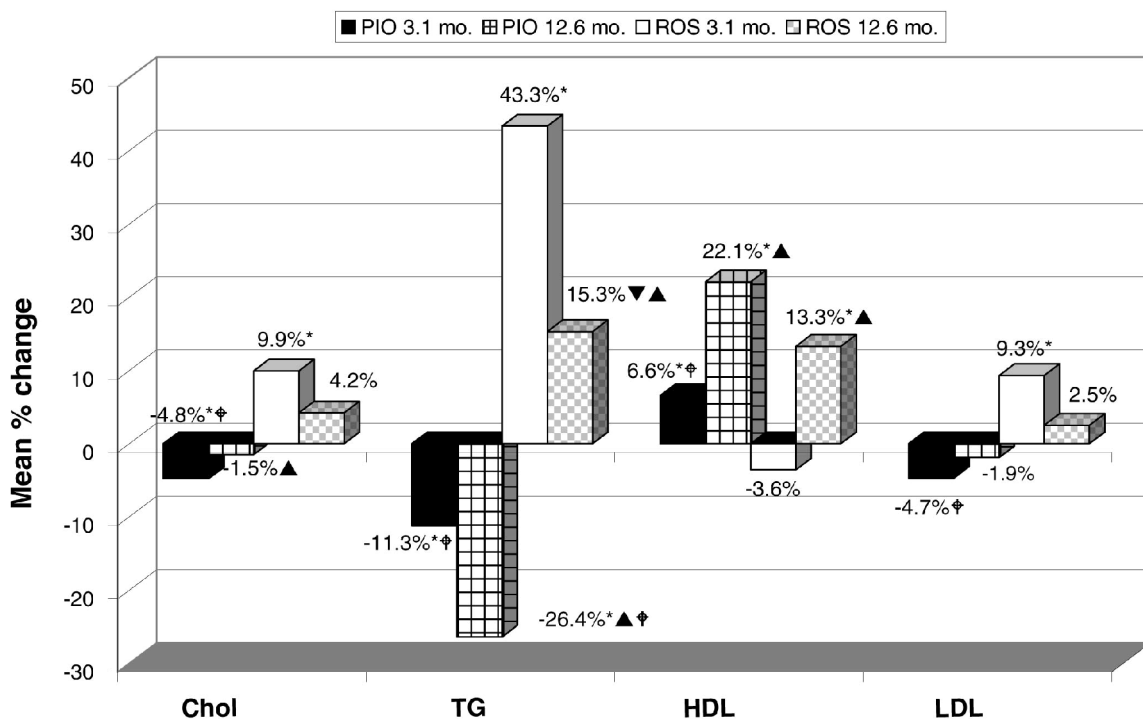
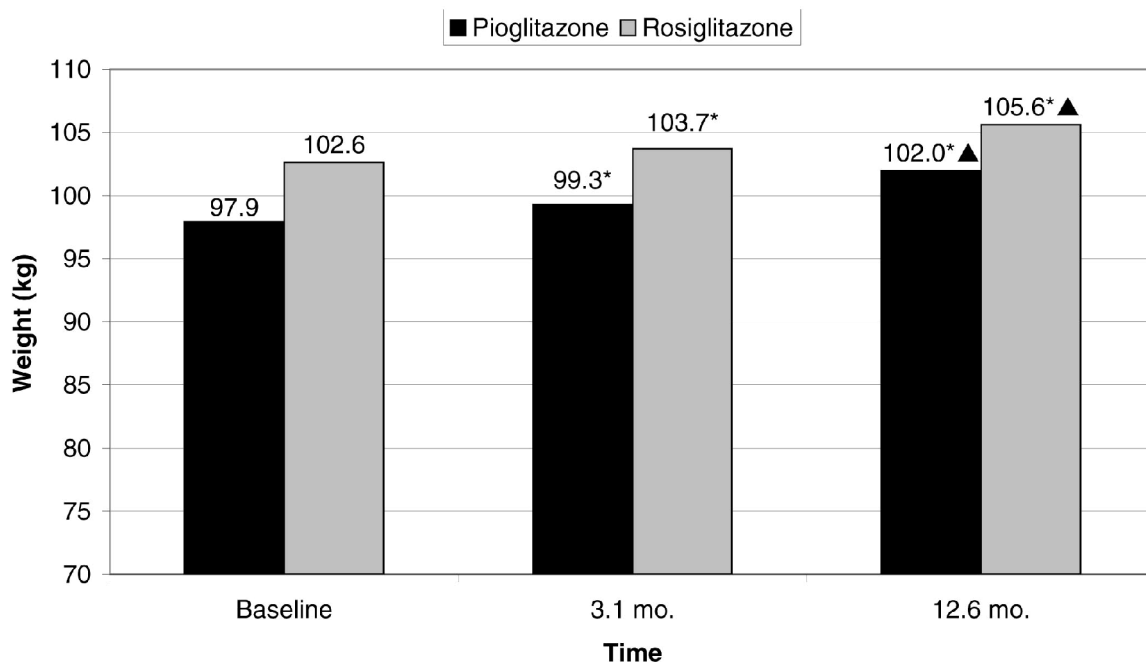


Figure 6. Aggregate lipid changes after conversion to pioglitazone or rosiglitazone (\* $p < 0.05$  vs. baseline;  $\text{♠}$   $p < 0.06$  vs. baseline;  $\text{♠}$   $p < 0.05$  vs. 3.1 months;  $\blacktriangle$   $p < 0.05$  pioglitazone vs. rosiglitazone)

rosiglitazone patients ( $n = 16$ ) after 12.6 months ( $p < 0.01$ ) (Figure 4). Progressive interval improvement in HDL occurred in both groups but was significantly better for the pioglitazone patients at both the interim and extended observation (Figure 5).

### Summary of Lipid Effects

In patients switched from troglitazone, pioglitazone and rosiglitazone demonstrated different lipid effects at the interim (3.1 months) observation. At the extended



**Figure 7.** Weight changes after conversion to pioglitazone or rosiglitazone (\* $p < 0.01$  vs. baseline;  $\Delta p < 0.01$  vs. 3.1 months)

(12.6 months) observation these disparities diminished except for triglycerides (Figure 6). Triglyceride levels decreased with pioglitazone and increased with rosiglitazone. Both treatment groups ultimately had an increase in HDL levels, but there was particular benefit for those who had a baseline HDL  $< 35$  mg/dL (0.91 mmol/L), and that benefit was greater with pioglitazone than with rosiglitazone.

## Weight

Body weight increased similarly in both pioglitazone and rosiglitazone groups. After 12.6 months of treatment, there was a mean 4.1 kg (4.1%) weight increase in the pioglitazone patients and a mean 3.0 kg (2.8%) weight increase in the rosiglitazone patients. Weight increased significantly from baseline to the interim observation and further increased from the interim to the extended observation (Figure 7).

## Hepatic Function

Subsequent to the thiazolidinedione conversion, throughout the period of observation, no patient in either treatment group had an alanine aminotransferase (ALT) value  $\geq 3$  times the upper limit of normal, a commonly used marker of potential liver damage. (In fact, none had an ALT above the upper limit of normal.) Thus, no evidence of drug-induced hepatotoxicity or drug-induced elevations in serum ALT was observed.

## Discussion

Since type 2 diabetes is a cardiovascular disease risk equivalent, diabetes treatment should be directed towards both glucose control and reduction of other cardiovascular risk factors<sup>27</sup>. Utilizing a medication that improves both glucose and lipid levels would be advantageous. The thiazolidinediones, which reduce insulin resistance and improve glycemic control via binding and activation of PPAR- $\gamma$ , provide an important and unique approach to the management of diabetes and its associated metabolic abnormalities. Currently, there are two thiazolidinediones – pioglitazone and rosiglitazone – in clinical use. Troglitazone, the first available thiazolidinedione, was withdrawn from clinical use because of instances of severe hepatotoxicity<sup>4-6</sup>. However, reported cases of hepatotoxicity in patients taking pioglitazone or rosiglitazone are rare<sup>28-31</sup>, suggesting that the mechanism through which troglitazone caused hepatotoxicity is not a class effect but rather an effect specific to troglitazone. Hepatic injury due to thiazolidinediones is considered to be an idiosyncratic reaction, but its more frequent occurrence with troglitazone may be due to its unique tocopherol side chain<sup>32</sup>. In contrast to the similar glucose-lowering effect mediated by PPAR- $\gamma$  agonist activity of the thiazolidinediones, these agents have divergent lipid effects and thus appear to affect traditional cardiovascular risk factors differently. The mechanism for the difference in lipid effects between the two agents is not known but may be related to the finding that pioglitazone has more PPAR- $\alpha$  effect than does rosiglitazone<sup>33</sup>.

This observational study compared the results of switching patients from troglitazone to either pioglitazone or rosiglitazone after troglitazone was withdrawn from the market. Although this clinical situation is no longer directly relevant, it provided a unique opportunity to evaluate the two currently available thiazolidinediones in patients who had stable metabolic control and to observe lipid effects that were specific to each agent and not confounded by alterations in glucose toxicity. We previously reported the results of a prospective study in which glycemic control, lipid changes, weight gain, and lack of hepatotoxicity were described after a mean of 3.2 months after switching from troglitazone<sup>7</sup>. That study demonstrated similar glucose control with pioglitazone and rosiglitazone but divergent lipid effects. Herein, we retrospectively extended the evaluation of the patients we previously described. Baseline was defined as the time at which the patient was converted from troglitazone to either pioglitazone or rosiglitazone. There were two time periods: the interim period (3.1 months from baseline for the remaining 100 patients) which corresponds to the conclusion of the previous report (3.2 months for 125 patients), and the extended result, with a mean follow-up of 12.6 months after the conversion.

Each of the two thiazolidinediones was associated with better glycemic control with more prolonged use. During the first observation period (3.1 months from the time of conversion from troglitazone) there was no significant glycemic improvement. However, by the 12.6-month extended observation, both pioglitazone and rosiglitazone were associated with significantly improved HbA<sub>1c</sub> levels compared to baseline. This suggests that maximum benefit for glycemic control may not become evident for perhaps a year or longer in contrast to the 10–14 week maximal effect previously reported<sup>12</sup>. A possible mechanism for this may be improved beta cell function. This would provide rationale for continued use of thiazolidinediones even if the initial results do not achieve the therapeutic glycemic target.

Body weight increased similarly after the switch to pioglitazone or rosiglitazone. Again this effect continued over time, with a weight increase at the 3.1-month observation time and a further increase at 12.6 months (Figure 7). For reasons that are not entirely clear, edema occurs fairly commonly in people treated with thiazolidinediones<sup>34</sup>. Edema contributes to weight gain in some patients. The weight gain associated with thiazolidinediones is believed to be associated with a shift from visceral fat to the less metabolically active subcutaneous fat and with increased fat deposition in lower body depots<sup>35,36</sup>, but waist-hip ratios were not

monitored in this observation. The triglycerides decreased and the HDL increased in the pioglitazone group and the HDL increased in the rosiglitazone group even though both groups experienced weight gain. This improvement in traditional cardiovascular risk factors in spite of weight gain has also been seen with troglitazone<sup>37</sup>.

Thiazolidinediones have been associated with heart failure and pulmonary edema<sup>38,39</sup> and are not recommended in patients with New York Heart Association (NYHA) Class III and IV cardiac status. Diabetes itself is also associated with ischemic cardiomyopathy and a greater incidence of heart failure<sup>40,41</sup>. Since ejection fractions and left ventricular mass do not change with thiazolidinediones, these agents may not have a direct causative role<sup>42,43</sup>. It is possible that in thiazolidinedione-treated patients with ischemic cardiomyopathy or other cardiac disease, other precipitating factors such as excess sodium intake and concomitant medications associated with fluid retention may unmask or exacerbate congestive heart failure as is often seen in other clinical settings<sup>44</sup>. None of the patients in this study developed clinically-evident congestive heart failure during the observation period.

Importantly, the extended observation time affected lipid changes also. After the switch to pioglitazone there was a decrease in cholesterol and LDL which was significantly different from the rosiglitazone group at the 3.1-month observation. This was no longer present at the 12.6-month observation. Differences between the two treatment groups were most evident for triglycerides and HDL. Triglycerides progressively decreased with each time interval after conversion to pioglitazone, whereas in the cohort converted to rosiglitazone the triglyceride levels initially increased significantly and then decreased. However, at 12.6 months the triglycerides were still higher than at baseline in the rosiglitazone group.

Similarly, the HDL levels progressively and significantly increased with each successive time interval after patients were switched to pioglitazone. In contrast, the patients switched to rosiglitazone experienced an initial decrease in HDL at 3.1 months and then an increase resulting in a significant improvement from baseline.

The difference between the groups in terms of HDL was more demonstrable in the patients who had an HDL < 35 mg/dL (0.91 mmol/L) at the time of conversion. After 12.6 months, that subgroup had a 52.6% increase in HDL ( $p < 0.01$ ) for the pioglitazone-treated patients compared to a 26.9% increase in the rosiglitazone-treated patients. Again, the HDL increased significantly at each successive time interval for the pioglitazone patients, but not for the rosiglitazone patients in this subgroup.

The hallmark of metabolic syndrome and type 2 diabetes is insulin resistance, which in turn is associated with additional cardiovascular risk factors such as hypertriglyceridemia and low HDL levels. Compared to the general population, people with metabolic syndrome or type 2 diabetes have a much greater risk of cardiovascular mortality. Reduction of insulin resistance and/or hyperglycemia would be expected to improve these associated cardiovascular risk factors. Perhaps the greatest strength of this study is that the patients, as a group, had a mean pre-conversion HbA<sub>1c</sub> of 7.0%, which is near the glycemic control target recommended in published clinical guidelines<sup>1,2</sup>, had no significant difference or change in glycemic control at the interim observation, and had statistically significant but only modest (and similar) improvements in glycemic control at the 12.6 month observation. This would imply that the differing effects of the two thiazolidinediones on triglycerides and HDL may to a large degree be independent of glycemic control changes and specifically not mediated by any improvement in glucose toxicity.

In a study of men with coronary heart disease and low levels of HDL, gemfibrozil reduced triglycerides by 31%, increased HDL by 6%, and was associated with a 22% decrease in mortality<sup>45</sup>. These lipid effects parallel the differences noted in our observation between pioglitazone and rosiglitazone (triglycerides, 42%, and HDL, 9%), suggesting perhaps that pioglitazone has a gemfibrozil-like effect that is not shared by rosiglitazone. It remains to be established if this is a PPAR- $\alpha$  effect.

Other studies comparing the two current thiazolidinediones with attention to glycemic control, weight change and lipid effects are described in four abstracts<sup>16-19</sup>, five additional published manuscripts<sup>20-24</sup> and one meta-analysis<sup>46</sup>. Of the published manuscripts, three are smaller studies with 20-127 subjects in single clinical settings without pharmaceutical sponsorship<sup>20-22</sup> and two are larger multicenter reports with 829 and 1115 subjects, respectively, with sponsorship<sup>23,24</sup>. All of them had higher baseline HbA<sub>1c</sub> levels (7.9-8.7%) than our study, and all except one<sup>22</sup> had improved glycemic control which could confound the lipid response. All of them had an improvement in triglycerides<sup>20-24</sup> and most<sup>21-24</sup> had an improvement in HDL with varying statistical significance. All five studies<sup>20-24</sup> and the meta-analysis<sup>46</sup> concluded that pioglitazone had a more favorable lipid effect than rosiglitazone.

This observational study has several limitations. The unexpected need to rapidly switch patients off troglitazone following its abrupt withdrawal from the market, along with direct-to-consumer advertising and formulary restraints resulted in a lack of pure randomization and somewhat more patients receiving

rosiglitazone than pioglitazone. Nevertheless both cohorts were statistically similar aside from the mean older age in the pioglitazone group. Another problem in the design of the study is that more of the rosiglitazone patients had an increase in their dose of lipid-lowering medications. But if anything this would have tended to improve the lipids in the rosiglitazone group, so perhaps the lipid difference between the two thiazolidinediones was underestimated in this observation. Finally, since this study represents findings in a clinical practice which is approaching the metabolic targets recommended in published guidelines, it may not be appropriate to extrapolate the findings to other clinical settings.

## Conclusion

Both pioglitazone and rosiglitazone provided improved glycemic control in patients who were converted from troglitazone. This improvement was not seen at 3.1 months but was apparent after 12.6 months of observation. There was similar weight gain in both groups; this was observed at 3.1 months and continued into the 12.6 month observation. No hepatotoxicity was noted in either group.

The two thiazolidinediones had divergent effects on triglyceride levels, with an improvement in the pioglitazone group compared to the rosiglitazone group. This persisted even at the extended observation. HDL levels increased in both groups but the greatest impact on HDL was seen in the patients who had a baseline HDL < 35 mg/dL (0.91 mmol/L). In this subset the pioglitazone patients had a progressive increase at each observation interval and this increase was significantly greater than in the rosiglitazone patients.

Irrespective of the mechanism, these differences in lipid effects offer clinicians a reason to consider selecting one agent over the other. Whether these differences will affect clinical cardiovascular outcomes remains to be established. However, until such outcome studies are available, it seems prudent to consider the differential effects on traditional cardiovascular risk factors when deciding which thiazolidinedione to use.

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