

# Metabolic effects of a conversion from rosiglitazone to pioglitazone in Native American patients with type 2 diabetes

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In this retrospective electronic chart review, we evaluated the metabolic changes that occurred in Native American patients with type 2 diabetes who were treated with rosiglitazone and then converted to pioglitazone with no other changes in medication regimens for diabetes or dyslipidemia. Thirty-four patients were included in the analysis. After the conversion from rosiglitazone to pioglitazone, significant decreases in the levels of total cholesterol (10.1%), low-density lipoprotein cholesterol (11.7%), and triglycerides (15.3%) were seen. No significant changes occurred in weight, body mass index, fasting glucose, hemoglobin A<sub>1c</sub>, high-density lipoprotein cholesterol, blood pressure, or liver function tests. Significantly more patients achieved low-density lipoprotein cholesterol and triglyceride target goals when taking pioglitazone than when taking rosiglitazone. No drug discontinuations or adverse effects were reported among the evaluable population. These results are consistent with results of other studies evaluating these two drug therapies.

Type 2 diabetes is a growing epidemic. In the USA, approximately 1.5 million new cases of diabetes are identified each year (1). Related to this increased rate of diabetes is an increased rate of obesity. The International Obesity Taskforce has estimated that 1.1 billion adults are overweight, which includes 312 million who are classified as obese (2). Native Americans are at high risk of developing diabetes; they are 2.2 times more likely than non-Hispanic whites to have diabetes diagnosed (3). Approximately 107,775 Native Americans, or 14.5% of the population, receiving care from the Indian Health Service have diabetes (4).

Cardiovascular disease remains one of the most prevalent contributors to morbidity and mortality in the USA, accounting for 1 in every 2.7 deaths (5). The link between cardiovascular disease and diabetes is well defined, with stroke and heart disease death rates 2 to 4 times greater in diabetics than in nondiabetics. Because of this risk, diabetes is now recognized by the National Cholesterol Education Panel as a cardiovascular disease risk equivalent (6, 7). This elevated risk with diabetes is due not only to elevated blood glucose levels but also to elevated systolic and diastolic blood pressures, triglyceride levels, low-density lipoprotein (LDL) cholesterol levels, and total cholesterol levels and decreased levels of high-density lipoprotein (HDL) cholesterol (8). Evidence exists that microvascular and neurological

complications of type 1 and type 2 diabetes are better prevented and their progression slowed with improved glycemic control (9, 10). Macrovascular complications related to diabetes can be prevented by controlling lipid parameters and blood pressure in line with established goals (11–13). Recent data in type 1 diabetes have also suggested that intensive glycemic control may also decrease macrovascular complications over time (14).

Thiazolidinediones are unique oral agents utilized in the treatment of diabetes. They work primarily by decreasing insulin resistance at peripheral sites and secondarily by decreasing hepatic glucose output (15). Thiazolidinediones primarily target the peroxisome proliferator activated receptor (PPAR) gamma receptor, which is expressed mainly in the adipose tissue but which is also found in the muscle, liver, pancreas, and vasculature (15). PPAR gamma receptor agonists regulate the body's response by altering the transcription of genes controlling glucose and lipid metabolism (16). Thiazolidinedione use has been shown to reduce cardiovascular risk factors by having favorable effects on blood pressure, HDL cholesterol, LDL oxidation, fibrinogen, plasminogen activator inhibitor 1, microalbuminuria, intra-abdominal fat, carotid intima-media thickness, and cell wall inflammatory markers (15, 16).

Several studies have compared the lipid differences between the two available thiazolidinediones on the market, rosiglitazone and pioglitazone. These studies have observed a more favorable lipid profile with the use of pioglitazone vs rosiglitazone, resulting in an increase in HDL cholesterol, a decrease in triglycerides, and no change in either LDL or total cholesterol with

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The opinions expressed in this paper are those of the authors and do not necessarily reflect the views of the Indian Health Service.

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**Table 1. Pioglitazone dosages when converting from rosiglitazone**

Rosiglitazone dosage	Pioglitazone dosage
2 mg daily	15 mg daily
4 mg daily	15 mg daily
8 mg daily	30 mg daily
4 mg twice daily	45 mg daily

**Table 2. Baseline characteristics of the 34 study subjects (24 women and 10 men)**

Variable	Mean ± SD
Age (years)	57.8 ± 10.3
Duration of diabetes (years)	8.3 ± 4.9
Weight (kg)	110.7 ± 32.8
Body mass index (kg/m <sup>2</sup> )	39.8 ± 10.1

pioglitazone (17–20). None of these comparative trials directly addressed lipid findings in the Native American population.

This study investigated the metabolic effects of the conversion of rosiglitazone to pioglitazone in a population of Native Americans with type 2 diabetes.

## METHODS

This study was performed at Claremore Indian Hospital in northeastern Oklahoma, which has a Native American population of approximately 63,000. Claremore Indian Hospital is one of the largest hospitals in the Indian Health Service. It has nearly 175,000 outpatient visits and >4500 inpatient visits a year; >200,000 prescriptions are filled annually in the outpatient pharmacy. Recently, a change in the hospital formulary was made that mandated pioglitazone as the primary thiazolidinedione therapy to replace rosiglitazone due to purchasing costs and potential lipid benefits.

After the institutional review board approved the study, electronic charts were retrospectively reviewed for patients diagnosed with type 2 diabetes and receiving pioglitazone from May 2005 through April 2006. The following data were collected: age, gender, duration of diabetes, weight, body mass index (BMI), total cholesterol, HDL and LDL cholesterol, triglycerides, hemoglobin A<sub>1c</sub>, fasting plasma glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and systolic and diastolic blood pressure after the patient had received rosiglitazone for at least 12 weeks (baseline data) and then at least 12 weeks after conversion to pioglitazone (converted data). The dosages of pioglitazone after conversion from rosiglitazone were provided by the hospital's pharmacy and therapeutics committee (Table 1). The baseline data collected were compared with their respective converted data.

Inclusion criteria included a diagnosis of type 2 diabetes mellitus, treatment with a stable dose of rosiglitazone for 12

weeks prior to conversion, and treatment with a stable dose of pioglitazone for at least 12 weeks. Exclusion criteria included a change in any concomitant diabetes, thyroid, estrogen-containing, or lipid-lowering medication. Also, any patients using psychotropic medications, systemic glucocorticoids, or protease inhibitors during the study period were excluded.

The primary outcome was the change in fasting lipid profile (triglycerides and total, HDL, and LDL cholesterol). The secondary outcomes were changes in hemoglobin A<sub>1c</sub>, fasting plasma glucose, weight, BMI, AST, ALT, and blood pressure. The percentage of patients achieving glycemic, lipid, and blood pressure goals while receiving each thiazolidinedione was also compared. The American Diabetes Association (ADA) goals of therapy assessed in this study were hemoglobin A<sub>1c</sub> <7%, total cholesterol <200 mg/dL, triglycerides <150 mg/dL, LDL cholesterol <100 mg/dL, HDL cholesterol >40 mg/dL in men and >50 mg/dL in women, systolic blood pressure <130 mm Hg, and diastolic blood pressure <80 mm Hg.

Each patient served as his or her own control. The Wilcoxon signed-rank test was used to measure change from baseline to follow-up given the small sample sizes and the nature of the variables. McNemar's test was performed to assess whether there was a change in the proportion of patients meeting their goals for total, LDL, and HDL cholesterol, triglycerides, blood pressure, and hemoglobin A<sub>1c</sub>.

## RESULTS

One hundred seventy-three patients were identified as potential candidates for chart review; of these, 71 lacked adequate laboratory follow-up (i.e., they did not return for a physician visit within the study time frame), 67 had changes in medications, and 1 patient died. Thirty-four patients were deemed evaluable for study analysis. These patients were middle-aged (mean, 57.8 years), predominantly female (70.6%), and obese (mean BMI, 39.8 kg/m<sup>2</sup>) (Table 2). Sixty-two percent of patients were on statin therapy (average daily simvastatin dose of 40 mg). Of the 34 patients at baseline, 7 were on 2 mg of rosiglitazone per day, 15 were on 4 mg per day, 4 were on 8 mg daily, and 8 were on 4 mg twice daily.

The average time to follow-up for the population was 145 days (range, 85–206). The comparisons of total, LDL, and HDL cholesterol, triglycerides, hemoglobin A<sub>1c</sub>, fasting plasma glucose, systolic blood pressure, diastolic blood pressure, weight, and BMI at baseline and follow-up are presented in Table 3. Significant decreases were observed in the levels of total cholesterol (10.1%), LDL cholesterol (11.7%), and triglycerides (15.3%). HDL cholesterol levels increased by 6.4%, but this change was not statistically significant. No significant differences were observed for the variables of hemoglobin A<sub>1c</sub>, fasting plasma glucose, blood pressure, weight, and BMI.

The attainment of ADA goals of therapy is represented in the Figure. There was a significant increase in patients attaining an LDL goal of <100 mg/dL: from 55.3% at baseline to 76.5% at the conclusion of the study ( $P = 0.004$ ). There also was a significant increase in patients achieving the triglyceride goal of <150 mg/dL: from 29% to 55.9% ( $P = 0.007$ ).

None of the patients who were converted to pioglitazone discontinued the drug due to adverse effects, and no significant differences were observed in AST or ALT during the time period.

## DISCUSSION

After a conversion from rosiglitazone to pioglitazone in Native American patients with type 2 diabetes, we observed significant decreases in levels of total cholesterol (10.1%), LDL cholesterol (11.7%), and triglycerides (15.3%) without the loss of glycemic control or adverse effects. These changes allowed a significantly greater number of patients to reach their ADA goals of therapy for LDL cholesterol and triglycerides.

Previous clinical trials and analyses of thiazolidinedione use in non-Native American populations have identified similar differences in lipid effects. In these analyses with pioglitazone, a decrease in triglycerides of 14% to 26% was observed, whereas rosiglitazone has shown minimal decreases and in some cases an increase in triglycerides from baseline (15, 17, 19, 20). Regarding LDL cholesterol levels, pioglitazone has shown a minimal effect, whereas rosiglitazone has shown increases in the range of 8% to 16% (15, 20). Both drugs tend to increase the HDL cholesterol in the range of 5% to 13%, so the lack of difference between the groups in our study was not surprising.

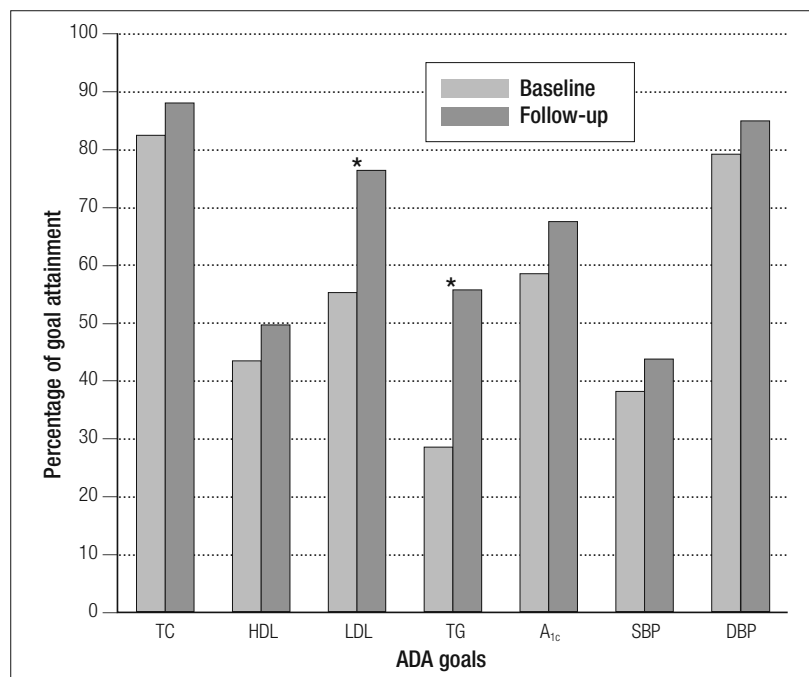
Two recent studies (21, 22) have addressed the issue of potential lipid differences between pioglitazone and rosiglitazone. In both of these studies, only 1.7% and 2.6% of the populations, respectively, were races other than Caucasian, Hispanic, Asian, or African American.

The first study was designed to look at the effects of the thiazolidinediones on lipids specifically in patients with diabetes who were not receiving statin therapy (21). Over 800 patients with type 2 diabetes were enrolled in this study to receive either pioglitazone 30 mg daily for 12 weeks followed by 45 mg daily ( $n = 400$ ) or rosiglitazone 4 mg daily for 12 weeks followed by 4 mg twice daily ( $n = 402$ ). In the pioglitazone arm, triglyceride levels decreased by 12%, HDL cholesterol levels increased by 14.9%, and LDL cholesterol levels increased by 15.7%. In the rosiglitazone arm, triglyceride levels increased by 14.9%, HDL cholesterol levels increased by 7.8%, and LDL cholesterol levels increased by 23.3%. All changes were significant between the groups. Interestingly, the rise in LDL cholesterol was associated with an increase in particle size in both groups and a decrease in particle concentration only in the pioglitazone group.

**Table 3. Change from baseline to follow-up after conversion from rosiglitazone to pioglitazone**

Variable	Mean $\pm$ SD		P value
	Baseline	Follow-up	
Weight (kg)	110.7 $\pm$ 32.8	112.0 $\pm$ 32.2	0.25
Body mass index (kg/m <sup>2</sup> )	39.8 $\pm$ 10.1	39.9 $\pm$ 9.7	0.38
Blood glucose (mg/dL)	138.9 $\pm$ 49.9	129.1 $\pm$ 49.0	0.19
Hemoglobin A <sub>1c</sub> (%)	6.7 $\pm$ 0.9	6.8 $\pm$ 1.1	0.57
Total cholesterol (mg/dL)	181.2 $\pm$ 29.3	160.9 $\pm$ 35.3	0.002
High-density lipoprotein cholesterol (mg/dL)	39.3 $\pm$ 11.2	41.1 $\pm$ 10.0	0.09
Low-density lipoprotein cholesterol (mg/dL)	100.3 $\pm$ 24.0	86.7 $\pm$ 27.8	0.02
Triglycerides (mg/dL)	216.9 $\pm$ 115.9	167.2 $\pm$ 75.6	0.0004
Systolic blood pressure (mm Hg)	135.4 $\pm$ 20.5	133.7 $\pm$ 14.9	0.6
Diastolic blood pressure (mm Hg)	71.4 $\pm$ 10.2	70.3 $\pm$ 10.0	0.3
Aspartate aminotransferase (U/L)	19.1 $\pm$ 7.4	18.9 $\pm$ 8.8	0.9
Alanine aminotransferase (U/L)	39.5 $\pm$ 11.2	38.7 $\pm$ 11.7	0.54

Based on the results of the Heart Protection Study (11) and the recognition of the increased utility of statins in patients with diabetes, a subsequent study was designed to address the changes in lipids between the thiazolidinediones with stable statin therapy (22). This study was similar to ours in that patients receiving stable doses of both rosiglitazone and statin therapy were converted from rosiglitazone to pioglitazone. In this open-label study, 305 patients with type 2 diabetes on stable doses of rosiglitazone and statin therapy for over 90 days were converted to pioglitazone 30 mg daily with no change in statin



**Figure.** American Diabetes Association goal attainment at baseline (on rosiglitazone) and at follow-up (after conversion to pioglitazone). TC indicates total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglycerides; A<sub>1c</sub>, hemoglobin A<sub>1c</sub>; SBP, systolic blood pressure; DBP, diastolic blood pressure. \* $P < 0.01$ .

dosage. The authors observed a 15.2% reduction in triglyceride levels ( $P < 0.0001$ ), a 9% reduction in total cholesterol levels ( $P < 0.0001$ ), a 1.8% increase in HDL cholesterol levels ( $P < 0.05$ ), and a 2.2% increase in LDL cholesterol levels, which was associated with increases in LDL cholesterol particle diameter and decreases in particle concentration (both  $P < 0.0001$ ).

Our data along with recent studies have demonstrated that the two thiazolidinediones are associated with different lipid profiles. It has been shown that both rosiglitazone and pioglitazone have high affinity for the PPAR gamma receptor, but pioglitazone has a stronger affinity for the PPAR alpha receptor than does rosiglitazone (16). This receptor binds the fibrin acid derivatives and allows positive changes in the lipid profile to occur, such as a 30% decrease in triglyceride levels, a 5% to 15% decrease in LDL cholesterol levels, and a 10% to 15% increase in HDL cholesterol levels (23). This increased receptor affinity by pioglitazone may explain the greater improvement in lipid profile.

Does this difference correlate to a difference in outcomes between the two drugs? No study to date has addressed this issue. Data in patients with type 2 diabetes and evidence of macrovascular disease show that the addition of pioglitazone to existing therapy as a secondary prevention measure showed a significant 16% reduction in the secondary combined endpoint of mortality, myocardial infarction, and stroke when compared with placebo (24). Pioglitazone has also been shown to slow the progression of carotid intima-media thickness, a marker of coronary atherosclerosis, when compared with glimepiride over 18 months (25). Recently, some concern has arisen with rosiglitazone due to a meta-analysis revealing a 43% increased risk of myocardial infarction with rosiglitazone use (26). A prospective study has not yet been performed to confirm that result.

The attainment of ADA goals of therapy is an important marker for outcomes in patients with diabetes. In the STENO-2 study, an intensive program to attain goals of therapy for the multiple risk factors in patients with type 2 diabetes compared with conventional therapy resulted in a >50% reduction in cardiovascular and microvascular events (27). The conversion from rosiglitazone to pioglitazone in our study allowed us to attain our lipid goals for LDL cholesterol and triglycerides in a higher proportion of patients, which may help prevent cardiovascular complications in the long term.

The lack of difference in hemoglobin A<sub>1c</sub>, fasting plasma glucose, blood pressure, weight, and BMI is consistent with other trials comparing the two thiazolidinediones (15, 17, 19, 20). Interestingly, the conversion utilized in our study was not consistent with that of other crossover studies, but still no difference was observed in hemoglobin A<sub>1c</sub> or fasting plasma glucose (18, 20). The difference was primarily with the conversion of 8 mg daily to 30 mg daily and of 4 mg daily to 15 mg daily. Some conversion studies have dosed the drugs based on total daily dose, where 8 mg per day (8 mg daily or 4 mg twice daily) was changed to 45 mg and where 4 mg per day (4 mg daily or 2 mg twice daily) was changed to 30 mg.

This study is not without limitations, including the fact that a retrospective analysis cannot definitively demonstrate cause

and effect. Another limitation is the small number of patients included due to the large number of lack of follow-ups. The patients who were included in the trial were very well controlled from a cardiovascular standpoint; this study did not represent patients with uncontrolled diabetes.

The overall benefits of thiazolidinedione therapy are becoming more apparent as studies examining cardiac outcomes (24), cardiac surrogate markers (25), changes in inflammatory markers (15, 21, 28, 29), and glycemic durability have been reported (30) with positive effects. Some concern has recently arisen with rosiglitazone, but no prospective study has been performed to confirm this (26). Future head-to-head outcome studies will need to be performed to determine if the lipid differences between the thiazolidinediones have an effect on cardiovascular outcomes.

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