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ScienceDirect
Metabolism Clinical and Experimental 58 (2009) 373 – 378
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Relationship between changes in insulin sensitivity and associated cardiovascular disease risk factors in thiazolidinedione-treated, insulin-resistant, nondiabetic individuals: pioglitazone versus rosiglitazone

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Received 7 June 2008; accepted 31 October 2008

Abstract

This study compared the effects of administering rosiglitazone (RSG) vs pioglitazone (PIO) on cardiovascular disease risk factors in insulin-resistant, nondiabetic individuals with no apparent disease. Twenty-two nondiabetic, apparently healthy individuals, classified as being insulin resistant on the basis of a steady-state plasma glucose concentration of at least 10 mmol/L during the insulin suppression test, were treated with either RSG or PIO for 3 months. Measurements were made before and after drug treatment of weight; blood pressure; fasting and daylong glucose, insulin, and free fatty acid (FFA) levels; and lipid and lipoprotein concentrations. Insulin sensitivity (steady-state plasma glucose concentration) significantly improved in both treatment groups, associated with significant decreases in daylong plasma concentrations of glucose, insulin, and FFA. Diastolic blood pressure fell somewhat in both groups, and this change reached significance in those receiving PIO. Improvement in lipid metabolism was confined to the PIO-treated group, signified by a significant decrease in plasma triglyceride concentration, whereas triglyceride concentration did not decline in the RSG-treated group, and these individuals also had increases in total (P = .047) and low-density lipoprotein cholesterol (P = .07). In conclusion, RSG and PIO appear to have comparable abilities to improve insulin sensitivity and lower daylong glucose, insulin, and FFA concentrations in nondiabetic, insulin-resistant individuals. However, despite these similarities, their effects on lipoprotein metabolism seem to be quite different, with beneficial effects confined to PIO-treated individuals.
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1. Introduction

There are currently 2 thiazolidinedione (TZD) compounds, rosiglitazone (RSG) and pioglitazone (PIO), that can be used to treat patients with type 2 diabetes mellitus (2DM). Both drugs are presumed to act by improving insulin sensitivity and appear to be equally effective as antihyperglycemic agents [1,2]. Despite this apparent similarity in the ability to improve glycemic control, it appears that their effects on dyslipidemia in patients with 2DM are quite different; and the disparity between their effects on lipid metabolism has been said to be independent of their ability to improve insulin sensitivity [1-4]. On the other hand, the studies cited above have all been performed in patients with manifest hyperglycemia. Although insulin sensitivity is decreased in patients with 2DM, the metabolic characteristics as regards circulating glucose, insulin, and free fatty acid (FFA) concentrations are quite different in these subjects as compared with nondiabetic, insulin-resistant, hyperinsulinemic individuals [5,6]. Therefore, the difference in the effects of RSG and PIO on dyslipidemia in patients with 2DM does not need to be the same as in nondiabetic, insulin-resistant individuals. Furthermore, previous studies comparing the effects of PIO and RSG on insulin sensitivity and lipoprotein metabolism have used surrogate estimates of insulin-mediated glucose uptake (IMGU). To the best of our knowledge, comparisons between the ability of RSG and PIO to enhance insulin sensitivity and improve lipid metabolism have not been performed in insulin-resistant, nondiabetic individuals using a specific method to quantify IMGU. This study is an effort to accomplish that goal.

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doi:10.1016/j.metabol.2008.10.011

2. Methods

The experimental population consisted of 22 individuals selected from a larger number of individuals who had responded to advertisements in local newspapers describing our interest in studying the relationship between insulin resistance and cardiovascular disease (CVD). To be eligible for this study, volunteers had to be in apparent good health and taking no medication known to affect carbohydrate metabolism. Stanford University's Human Subjects committee approved the study protocol; all subjects gave written informed consent for participation; and potential participants were screened at Stanford General Clinical Research Center by medical history, physical examination, and clinical laboratory analyses. Blood pressure was measured using a Dinamap automatic blood pressure recorder (GE Healthcare, Tampa, FL). Before the blood pressure measurements, patients were seated quietly for 5 minutes in a chair with feet on the floor and arm supported at heart level. Using an appropriately sized cuff, 3 blood pressure readings were taken at 1-minute intervals; and the mean of these readings was used for data analyses. Volunteers who were apparently healthy on the basis of these measurements were eligible for participation. More specifically, individuals were excluded if they had diabetes (fasting glucose concentration >6.9 mmol/L), laboratory evidence of anemia, or abnormal hepatic or renal function test results. Volunteers meeting these general eligibility criteria were then scheduled to come to the General Clinical Research Center after an overnight fast to assess their insulin sensitivity.

Insulin-mediated glucose uptake was quantified by a modified version [7] of the insulin suppression test (IST) as described and validated by our research group [8,9]. After an overnight fast, an intravenous catheter was placed in each arm, one for the simultaneous 3-hour infusion of octreotide (0.27 μg/[m^2 min]), insulin (32 mU/[m^2 min]), and glucose (267 mg/[m^2 min]) and the other for obtaining blood specimens. Plasma glucose and insulin concentrations were measured every 10 minutes during the 150- to 180-minute period and averaged to determine the steady-state plasma glucose (SSPG) and insulin concentrations. Because steady-state plasma insulin concentrations are comparable in all individuals and glucose infusion is identical, the resultant SSPG concentration provides a direct measure of the ability of insulin to mediate the disposal of a given glucose load, that is, the higher the SSPG concentration, the more insulin resistant the individual. Measurements of IMGU with the IST have been shown to be highly correlated (r values >.9) with values obtained with the hyperinsulinemic, euglycemic clamp method [9].

Individuals whose SSPG concentration was at least 10 mmol/L were classified as being insulin resistant and were eligible for this study. This particular value provides a somewhat objective operational definition of insulin resistance because it is based on an SSPG concentration placing individuals in the most insulin-resistant third of an apparently healthy population [10], a distribution shown in prospective studies to identify individuals at increased risk to develop CVD [11,12].

In addition, on another morning after an overnight fast, daylong plasma glucose, insulin, and FFA concentrations were determined before and after test breakfast and lunch meals [13]. Each meal contained as percentage of daily calories 15% protein, 42% carbohydrate, and 43% fat. Breakfast was given at 8:00 AM and contained 20% of estimated daily caloric intake, and lunch was given at noon and contained 40% of estimated daily caloric intake. Blood was drawn at hourly intervals before and after the test meals from 8:00 AM to 4:00 PM.

Finally, on the mornings of the IST and the daylong meal profile, fasting blood samples were drawn for measurement of lipid and lipoprotein concentrations by the core clinical laboratory of Stanford Medical Center; and the lipid values from these 2 separate days were averaged. Low-density lipoprotein cholesterol (LDL-C) concentration was calculated by the Friedewald equation [14].

After the baseline studies outlined above were completed, subjects were assigned to treatment with either PIO or RSG. Pioglitazone was given at a dose of 15 mg once daily for 2 weeks, followed by 30 mg once daily for 2 weeks, and then 45 mg once daily for 8 weeks, whereas RSG was given at a dose of 4 mg once daily for 4 weeks followed by 4 mg twice daily for 8 weeks. Subjects in both treatment groups were instructed to maintain their usual diet and level of physical activity and return for follow-up visits every 2 weeks for the next 3 months. The International Physical Activity Questionnaire [15] was used to quantify the amount of habitual physical activity. At each visit, patients were weighed, their blood pressure was taken, and they were evaluated for both medication compliance and maintenance of baseline physical activity level. As best as could be determined, all subjects were compliant and maintained a constant level of physical activity. Alanine aminotransferase levels were also measured every 4 weeks during the study, and none of the subjects had any elevations of alanine aminotransferase levels that were 1.5 times the upper limit of normal. All baseline measurements were repeated after 3 months of treatment.

SPSS version 15.0 (SPSS, Chicago, IL) was used for data analyses. Summary data are expressed as mean ± SD or number of subjects. Triglyceride (TG) concentrations were log transformed to improve normality for statistical analyses. Between the 2 groups, means of baseline variables were compared by Student unpaired test; and differences in sex distribution were compared by Fisher exact test. Within each treatment group, before and after metabolic variables were compared by Student paired test. Treatment-associated changes (post − baseline) between the 2 groups were compared by Student unpaired test.

3. Results

Demographic characteristics of the 2 experimental groups are given in Table 1.

Table 1
Comparison of baseline anthropometric and metabolic characteristics (mean ± SD) of the PIO and RSG groups

Variable	PIO (n = 11)	RSG (n = 11)	P^a
Age (y)	54 ± 8	52 ± 7	.49
Weight (kg)	91.7 ± 12.4	94.9 ± 19.1	.65
Sex (F/M)	4/7	5/6	.70
Body mass index (kg/m^2)	31.9 ± 2.0	30.4 ± 3.6	.14
Waist circumference (cm)	101 ± 8	107 ± 14	.26
Systolic blood pressure (mm Hg)	136 ± 10	130 ± 14	.25
Diastolic blood pressure (mm Hg)	83 ± 6	78 ± 9	.68
Fasting glucose (mmol/L)	5.6 ± 0.7	5.7 ± 0.5	.53
SSPG (mmol/L)	12.2 ± 1.8	12.4 ± 0.3	.80
Total cholesterol (mmol/L)	5.2 ± 0.9	4.7 ± 0.9	.17
HDL cholesterol (mmol/L)	1.1 ± 0.2	1.0 ± 0.3	.91
LDL cholesterol (mmol/L)	3.5 ± 0.8	2.7 ± 0.9	.04
TG (mmol/L)	1.5 ± 0.9	2.2 ± 0.9	.09

HDL indicates high-density lipoprotein.
[a] *P* values are for the comparison of 2 groups by Student unpaired *t* test.

These results indicate that the only significant differences between the 2 groups at baseline were higher LDL-C concentrations in individuals assigned to treatment with PIO.

Table 2 presents the changes in anthropometric and metabolic variables that occurred in the PIO-treated group. It can be seen that, despite the significant increase in weight, subjects receiving PIO had a significant decrease in SSPG concentration. In addition, diastolic blood pressure and fasting plasma glucose and TG concentrations fell significantly in PIO-treated individuals.

A similar comparison in the RSG-treated group is seen in Table 3. In contrast to those receiving PIO, there was no weight gain in the RSG-treated individuals. The SSPG concentrations decreased significantly in these individuals, associated with a decrease in fasting glucose concentration. However, there was no significant change in plasma TG concentration; and the fall in diastolic blood pressure did not reach the conventional level of statistical significance. It should also be noted that both total (P = .047) and LDL-C (P = .07) increased somewhat in RSG-treated patients.

Table 4 provides a direct comparison of the effects of the 2 treatments on all the variables measured. In most instances, there were no differences between the changes in the 2 experimental groups. The exceptions were plasma total cholesterol and TG concentrations, with a significantly greater increase in cholesterol concentration in RSG-treated patients and a significantly greater decline in TG concentration in those receiving PIO.

Table 3
Anthropometric and metabolic characteristics (mean ± SD) before and after RSG treatment

Variable	Before (n = 11)	After (n = 11)	P^a
Weight (kg)	95 ± 19	95 ± 18	1.00
Waist circumference (cm)	107 ± 14	108 ± 11	.70
Systolic blood pressure (mm Hg)	130 ± 14	127 ± 12	.36
Diastolic blood pressure (mm Hg)	78 ± 9	75 ± 8	.06
Fasting glucose (mmol/L)	5.7 ± 0.5	5.3 ± 0.4	.008
SSPG (mmol/L)	12.4 ± 0.3	7.8 ± 3.1	<.001
Total cholesterol (mmol/L)	4.7 ± 0.9	5.1 ± 1.2	.047
HDL cholesterol (mmol/L)	1.0 ± 0.3	1.1 ± 0.3	.30
LDL cholesterol (mmol/L)	2.7 ± 0.9	3.1 ± 1.1	.07
TG (mmol/L)	2.2 ± 0.9	2.1 ± 1.0	.85

[a] *P* values are for the comparison of 2 groups by Student paired *t* test.

The results of the daylong measurements (total integrated response) of glucose insulin and FFA concentrations are summarized in Fig. 1. Despite the fact that these subjects were nondiabetic, both treatments led to a modest but statistically significant decrease in daylong plasma glucose concentration. In addition, daylong total integrated insulin and FFA responses were significantly lower after treatment with either PIO or RSG.

4. Discussion

The results of the current study are consistent with previous publications [1-4] in that, although the beneficial effects of RSG and PIO on glucose homeostasis seem to be comparable, their impact on lipid metabolism is not the same, in particular, the finding that plasma TG concentrations decrease in PIO-treated patients, but not in those receiving RSG. In contrast to the previous studies, our study sample was selected to be insulin resistant and without 2DM;

Table 2
Anthropometric and metabolic characteristics (mean ± SD) before and after PIO treatment

Variable	Before (n = 11)	After (n = 11)	P^a
Weight (kg)	92 ± 12	94 ± 13	.001
Waist circumference (cm)	101 ± 8	103 ± 10	.12
Systolic blood pressure (mm Hg)	136 ± 10	133 ± 12	.43
Diastolic blood pressure (mm Hg)	83 ± 6	77 ± 7	.02
Fasting glucose (mmol/L)	5.6 ± 0.7	5.2 ± 0.4	.05
SSPG (mmol/L)	12.2 ± 1.8	8.3 ± 2.2	<.001
Total cholesterol (mmol/L)	5.2 ± 0.9	5.0 ± 0.8	.37
HDL cholesterol (mmol/L)	1.1 ± 0.2	1.2 ± 0.2	.16
LDL cholesterol (mmol/L)	3.5 ± 0.8	3.3 ± 0.7	.62
TG (mmol/L)	1.5 ± 0.9	1.0 ± 0.7	.02

[a] *P* values are for the comparison of 2 groups by Student paired *t* test.

Table 4
Comparison of the changes (after − before) in anthropometric and metabolic characteristics (mean ± SD) after PIO and RSG treatment

Variable	PIO (n = 11)	RSG (n = 11)	P^a
Weight (kg)	2.2 ± 1.6	0.0 ± 3.3	.07
Waist circumference (cm)	2 ± 4	1 ± 10	.82
Systolic blood pressure (mm Hg)	-3 ± 11	-3 ± 11	.92
Diastolic blood pressure (mm Hg)	-5 ± 6	-3 ± 5	.32
Fasting glucose (mmol/L)	-0.4 ± 0.6	-0.4 ± 0.3	.99
SSPG (mmol/l)	-3.9 ± 2	-4.6 ± 2.3	.46
Total cholesterol (mmol/L)	-0.2 ± 0.7	0.4 ± 0.6	.04
HDL cholesterol (mmol/L)	0.1 ± 0.2	0.1 ± 0.2	.52
LDL cholesterol (mmol/L)	-0.1 ± 0.8	0.4 ± 0.6	.11
TG (mmol/L)	-0.4 ± 0.5	0.0 ± 0.5	.046

[a] *P* values are for the comparison of 2 groups by Student unpaired *t* test.

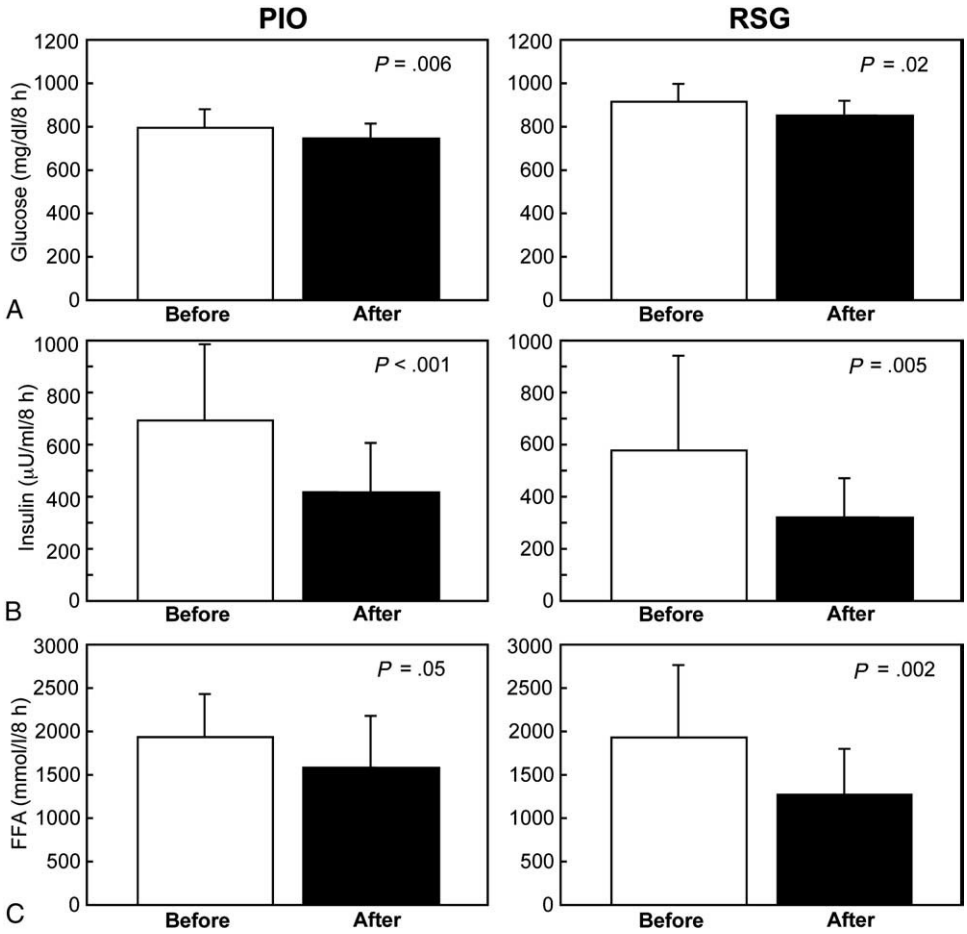

Fig. 1. Daylong glucose (A), insulin (B), and FFA (C) responses in insulin-resistant, nondiabetic individuals before and after treatment with PIO or RSG.

and the effect of the 2 compounds on IMGU was quantified with a specific measure of insulin action on muscle glucose uptake. As such, these data indicate that, although the 2 TZD compounds have a comparable ability to improve insulin sensitivity and daylong plasma glucose, insulin, and FFA concentrations, their effects on lipoprotein metabolism are significantly different. Furthermore, the disparity between the effects of PIO and RSG on glucose and lipoprotein metabolism, first shown in patients with 2 DM [1-4], is also seen in insulin-resistant, nondiabetic individuals.

Focusing on the difference between the effects of the TZD compounds on TG metabolism, the surprising observation is not that PIO-treated patients had a fall in TG concentration, but that those receiving RSG did not. Indeed, previous data in patients with 2DM have documented a modest increase in TG concentrations in RSG-treated patients [1-4]. The fact that TG concentrations were unchanged in the RSG-treated patients in this study may be due to the much smaller number of subjects we enrolled or due to the fact that these individuals were not diabetic nor were they selected because they were dyslipidemic [2,4].

There is considerable evidence that hypertriglyceridemia in insulin-resistant individuals, whether they are nondiabetic or have 2DM, results from an increase in hepatic very low-density lipoprotein (VLDL)–TG secretion, associated with an increased flux of FFA to the liver in the presence of normal or elevated plasma insulin concentrations [16-19]. Furthermore, it has been shown in insulin-resistant, nondiabetic individuals that lowering daylong plasma insulin concentration by changing macronutrient content [20,21] or enhancing insulin sensitivity by weight loss [22,23] will result in a fall in plasma TG concentrations

Because it is clear from the data in Table 4 and Fig. 1 that PIO and RSG both improve insulin sensitivity and lower daylong circulating insulin and FFA concentrations, it would be reasonable to anticipate that both drugs would also be associated with a fall in plasma TG concentrations. Unfortunately, the data necessary to explain why these metabolic changes only led to a decrease in TG concentrations in the PIO-treated group are not available. For example, it can be speculated that RSG has a direct effect on the liver that inhibits the ability of the combined beneficial effects of enhanced insulin sensitivity, lower plasma insulin concentrations, and a decrease in the FFA flux to the liver to bring about a decrease in hepatic VLDL-TG secretion and subsequent fall in plasma TG concentration. By inference, it then could be argued that this is not the case in PIO-treated individuals. However, isotope

kinetic studies by Nagashima and colleagues [24] in PIO-treated patients with 2DM indicated that the reason for the decrease in TG concentration was unlikely to be related to a decrease in hepatic VLDL-TG secretion, but rather the result of an increase in the fractional catabolic rate of VLDL-TG secondary to an increase in lipoprotein lipase–mediated lipolysis. Isotopic kinetic studies by Duez et al [25] demonstrated that administration of RSG to nondiabetic individuals with varying degrees of insulin sensitivity led to a tendency to an increase in TG production and a decrease in TG clearance. Taken together, these data could be interpreted to mean that the effects of the 2 compounds on lipoprotein metabolism differ primarily in that one tends to increase TG removal from plasma (PIO), whereas the other decreases TG removal rate (RSG). Compatible with this conclusion are the findings of Deeg et al [4] that "PIO treatment resulted in a decrease in apo C-III, whereas RSG caused an increase in apo C-III," findings that are consistent with the notion of differential effects of removal of TG-rich lipoproteins from plasma.

On the other hand, using different indices to assess TG secretion and catabolic rates, diametrically opposed conclusions were reached by Chappuis and colleagues [3] in their study comparing the effects of PIO and RSG on lipid metabolism in patients with 2DM. These authors demonstrated a disparity between the effects of the 2 compounds on fasting TG concentrations; but because these 2 compounds had similar effects on hepatic and lipoprotein lipase activity, the authors argued that the difference could not be secondary to increased TG lipolysis in PIO-treated patients. Furthermore, based on differences in the changes seen in TG concentrations in VLDL subfractions, most particularly a decrease in the TG content of VLDL-2 in PIO-treated patients, they concluded that the PIO administration decreased hepatic VLDL-TG secretion rate, whereas this was not true in RSG-treated patients. Although they did not compare RSG and PIO, Al Majali et al [26] described essentially comparable changes in VLDL subtractions in PIO-treated patients with 2DM; and they also concluded that hepatic TG secretion is decreased in PIO-treated patients with 2DM. Given these conflicting data, it seems reasonable to conclude that there is general agreement that PIO and RSG have different effects on TG metabolism; however, there is no unanimity as to why this is the case.

In conclusion, we believe this to be the first study comparing the effects in nondiabetic, insulin-resistant individuals of treatment with RSG vs PIO on insulin sensitivity, as quantified by a specific measure of IMGU, as well as determinations of fasting and postprandial glucose, insulin, FFA levels, and fasting lipoprotein concentrations. The results indicate that, although the 2 drugs had similar beneficial effects on insulin sensitivity, as well as fasting and postprandial glucose, insulin, and FFA concentrations, the changes in lipoprotein profile were quite different. Specifically, TG concentrations decreased in PIO-treated patients, without a significant change in total or LDL-C concentrations, whereas TG concentrations did not change in RSG-treated subjects, and both total and LDL-C concentrations were higher after treatment. Furthermore, the treatment-related effects on TG concentrations were significantly different between the 2 groups. In this context, there is evidence that lowering plasma TG concentrations with gemfibrozil is associated with a decreased CVD in nondiabetic individuals, particularly in those subjects who are insulin resistant [27]. Furthermore, Chappuis and colleagues [3] have shown that, whereas PIO-treated patients with 2DM had a fall in postprandial TG concentrations, the opposite was true of patients treated with RSG. Initially introduced by Zilversmit [28], the importance of the association between postprandial TG-rich lipoproteins and CVD risk has just recently been reemphasized [29,30]. The role, if any, of the disparate effects of PIO and RSG on lipid metabolism that contribute to the apparent modest benefit of PIO in decreasing myocardial infarction in patients with 2DM [31] or to the possibility that RSG might increase the risk of myocardial infarction in these patients [32] can only be speculated upon.

Acknowledgment

Supported in part by research grants from the National Center for Research Resources, National Institutes of Health (M01 RR-000070); CAPES (Research Funding Agency of the Brazilian Ministry of Education–Postdoctoral Scholarship for Nereida KC Lima: 1306-07-3); Glaxo-SmithKline Pharmaceuticals; and Takeda Pharmaceuticals.

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