

Benefit of Adding Pioglitazone to Statin Therapy in Non-Diabetic Patients with the Metabolic Syndrome

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ABSTRACT

Statins frequently do not control all of the lipid abnormalities found in patients with the metabolic syndrome. Pioglitazone (PIO), an insulin sensitizing agent, has been shown to have favorable lipid effects in diabetic patients. Little information is available regarding the effect of combined statin and PIO therapy in non-diabetic patients with the metabolic syndrome. We report our experience of adding PIO to statin therapy in non-diabetic patients with the metabolic syndrome. Pioglitazone was administered to 24 non-diabetic patients in our lipid clinic who were already on a statin yet continued to have significant lipid abnormalities. All patients had characteristic lipid abnormalities and clinical features of the metabolic syndrome. The treatment period was 59 ± 29 (range 7-123) weeks. Lipid profiles, fasting glucose, and alanine aminotransferase were assessed before and at least 6 weeks after pioglitazone was added to statin. Triglyceride levels decreased from 307 ± 295 mg/dL to 173 ± 129 mg/dL ($P=0.003$), non-high-density lipoprotein cholesterol (non-HDL) decreased from 151 ± 53 mg/dL to 130 ± 49 mg/dL, ($P=0.003$), and high-density lipopro-

tein cholesterol (HDL) levels increased from 42 ± 11 mg/dL to 45 ± 12 mg/dL, ($P=0.039$). The addition of PIO to statin in non-diabetic patients with metabolic syndrome produced significant additional benefits in the lipid profile over statin monotherapy. Favorable effects were seen in triglycerides, HDL, and non-HDL levels. Study limitations include: this is a small non-blinded observational study in which patients served as their own controls. The duration of combination therapy and type of statin employed were variable.

INTRODUCTION

The metabolic syndrome is an insulin resistant syndrome associated with accelerated arteriosclerosis and a particularly atherogenic lipid profile.^{1,2} This profile consists of an abundance of small, dense, low-density lipoprotein cholesterol (LDL) particles, elevated triglyceride levels, and depressed high-density lipoprotein (cholesterol) (HDL) levels.^{2,3} HMG-CoA reductase inhibitors (statins) remain the cornerstone of medical treatment.⁴ These agents significantly decrease total cholesterol levels, primarily by decreasing LDL and the number of LDL particles.⁵ Their effect on HDL and triglyceride levels is less impressive and consequently does not usually address all the abnormalities associated with the metabolic syndrome.^{6,7}

In contrast, fibrates and niacin have considerable beneficial effects on HDL and serum triglyceride levels. These agents are frequently used in combination with statins to address the multiple lipid abnormalities characteristic of the metabolic syndrome.⁷ However, concerns about side effects and added toxicity of using the agents in combination may limit their use or lead to a decrease in the statin dose.^{8,9}

Thiazolidinedione derivatives, such as pioglitazone (PIO) and rosiglitazone are insulin-sensitizing agents used to treat diabetes.¹⁰ These agents are nuclear re-

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ceptor ligands, which activate the peroxisome proliferative activated receptor gamma (PPAR γ) system.¹¹ The PPAR γ system is involved in insulin, glucose, and lipid metabolism.¹² PIO, in particular, has been shown to have beneficial lipid effects in diabetics by increasing HDL and lowering serum triglyceride levels.¹³ Recently, PIO has been shown to have similar beneficial effects in non-diabetic patients with the metabolic syndrome.¹⁴ Consequently, it is possible that PIO may further improve the lipid profile in non-diabetic patients with the metabolic syndrome who are suboptimally treated with statin therapy alone. Accordingly, we assessed whether the addition of PIO to statin in non-diabetic patients would provide additional benefits to the lipid profile.

METHODS

Our lipid clinic prospectively identifies all patients placed on a thiazolidinedione for possible future retrospective analysis. From this registry we identified patients who had typical features of the metabolic syndrome,¹⁵ and were on a stable dose of statin for at least 6 weeks prior to PIO treatment. Twenty-four non-diabetic patients met inclusion criteria for this retrospective analysis. All patients demonstrated suboptimal lipid control on statin therapy alone despite consultation on lifestyle modifications. Patient exclusion criteria included anyone with more than a single fasting glucose level above 125 mg/dL,¹⁶ use of hypoglycemic agents, and any acute coronary syndrome, percutaneous coronary intervention, coronary artery bypass grafting, or any major surgery in the past 12 weeks. We also excluded anyone who was taking any other lipid-lowering therapy such as a fibric acid derivative or niacin. The Aspirus Wausau Hospital Institutional Review Committee approved this retrospective analysis.

Lipid levels were obtained in the fasting state, and measurements were made in a hospital or office laboratory certified by the College of American Pathologists or by the Department of Health and Human Services. For each patient, baseline lipid levels, serum alanine aminotransferase (ALT), weight, and body mass index (BMI) were collected by chart review before and after PIO was initiated. LDL levels were calculated with the Friedewald equation.¹⁷ We excluded 4 patients from LDL calculations due to the inaccuracy of the Friedewald equation at triglyceride levels >400 mg/dL.¹⁸ They were included in all other calculations. Non-HDL cholesterol was derived by subtracting HDL from total cholesterol. Glucose was measured using the oxidation method.¹⁹

PIO, ranging from 15 to 45 mg/day, was administered

as a single daily dose while maintaining constant statin dosage. Initial and subsequent PIO dosage was based on clinical circumstances. Cost considerations had a significant influence on PIO dose, and consequently, when necessary, pill splitting was utilized to decrease patient cost. Initial dose was typically 15-22.5mg (half of a 30 or 45 mg tablet). Follow-up lipids dictated dose modifications. Because all patients had persistent abnormalities with initial dosing as defined by Adult Treatment Panel III criteria,¹⁵ all patients were eligible for upward dose titration to a maximum of 45 mg/day. Patients were monitored for any adverse side effects of the medication. If there were no adverse effects, the PIO dosage was increased to the maximum of 45 mg/day whenever possible. However, because cost became a limiting factor for several patients, they were precluded from 1 tablet per day therapy. In these patients, the maximum dose achieved was 22.5 mg/day. In no instance did toxicity or intolerance of PIO itself prevent us from using 45 mg.

Once PIO was started, neither the statin agent nor dose was altered during the time course of this analysis. Baseline measurements (statin only) were compared to those obtained when the patients were on the maximum dose of PIO. In many cases, more than 1 set of measurements was obtained while the patient was taking PIO. In this situation the baseline measurements were compared with the most current data. We also noted the usage of concurrent antihypertensive medications including angiotensin enzyme inhibitors, angiotensin receptor blockers, thiazide diuretics, and beta-blockers.

Statistical Analysis

For all continuous variables, a mean and standard deviation was calculated and the results compared by paired t-tests. Differences were considered significant at $P < 0.05$. Percent changes from baseline were also derived.

RESULTS

Table 1 illustrates the clinical characteristics, pharmacologic data, and treatment duration. All patients were considered high-risk for future atherosclerotic events by having either established coronary artery disease (CAD) or numerous risk factors suggesting high risk as defined by Adult Treatment Panel III guidelines.¹⁵ Eighty percent of patients had a history of symptomatic CAD, and 75% were hypertensive. Atorvastatin and simvastatin were the most frequently used statins.

Table 2 and Figure 1 illustrate the effects of adding PIO to a stable dose of statin. The largest beneficial effects were seen in triglyceride and HDL levels. Although there was no significant effect on LDL, we did observe

Table 1. Clinical Characteristics and Pharmacology Data

Male/female	15/9
Age	67 ± 3
Health History	n (%)
History of CAD	20 (80)
Hypertension	18 (75)
Concomitant Antihypertensive Medications	n (%)
Beta Blocker	20 (83)
Angiotensin Converting Enzyme	6 (25)
Angiotensin Receptor Blocker	3 (13)
Hydrochlorothiazide	3 (13)
	No. patients, dose mgs/day (mean±SD)
Statin	
atorvastatin	8, 34 ± 22 mgs/day
simvastatin	8, 45 ± 23 mgs/day
lovastatin	4, 40 ± 16 mgs/day
pravastatin	2, 40 ± 0 mgs/day
fluvastatin	1, 80 ± 0 mgs/day
rosuvastatin	1, 10 ± 0 mgs/day
PIO dose mgs/day	35 ± 9 mg
Duration on PIO (weeks)	59 ± 29 weeks
Duration range	7 – 123 weeks

CAD=coronary artery disease; PIO=Pioglitazone.

Table 2. Effect of Adding PIO to a Statin (n = 24)

Component	Pre-PIO	Post-PIO	P value
Total cholesterol (mg/dl)	192 ± 52	175 ± 48	0.013
HDL Cholesterol (mg/dl)	42 ± 11	45 ± 12	0.039
Non-HDL Cholesterol (mg/dl)	151 ± 53	130 ± 49	0.003
LDL Cholesterol (mg/dl)	93 ± 23	89 ± 19	0.520
Triglycerides (mg/dl)	307 ± 295	173 ± 129	0.003
Fasting Glucose (mg/dl)	119 ± 12	108 ± 14	0.012
ALT (u/l)	34 ± 16	35 ± 12	0.775
Weight (kg)	95 ± 14	94 ± 14	0.931
BMI (range 25-38)	32 ± 3	32 ± 4	0.986

PIO=Pioglitazone; HDL=high-density lipoprotein; LDL=low-density lipoprotein; ALT=Alanine aminotransferase; BMI=body mass index.

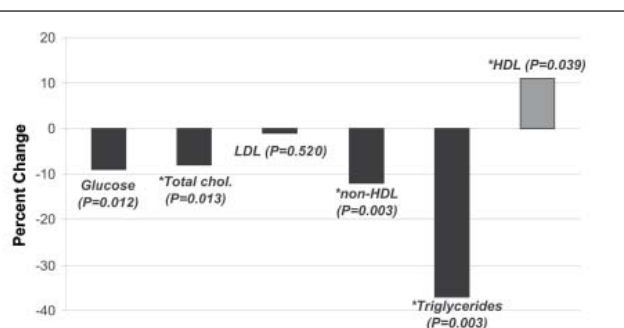


Figure 1. Percent change with addition of PIO. Significance at 95% CI.

a significant decrease in non-HDL cholesterol. Glucose levels also decreased significantly; however, no case of suspected or confirmed hypoglycemia was observed. There was no effect on alanine aminotransferase (ALT), weight, or body mass index (BMI). Two patients noted mild peripheral edema but continued to take PIO. Two other patients ultimately stopped PIO for financial reasons. Otherwise PIO was continued in all patients without reported adverse effects or toxicity.

DISCUSSION

We found that the thiazolidinedione PIO, when added to statin in non-diabetic patients with the metabolic syndrome, significantly improved the lipid profiles over statin therapy alone. The effect of PIO was most marked on the triglyceride and HDL fractions of the lipid profile. Similar effects have been reported with PIO in diabetic patients.¹⁵ In agreement with Szapary et al,¹⁴ our results demonstrate that it is not necessary to have diabetes for this beneficial effect to occur. Because of cost constraints, we were not able to use the maximum dose of 45 mg in several patients. Had that been possible, it is likely we would have noted even more powerful effects. As is, the magnitude of the triglyceride and HDL effect is similar to what has been historically reported when a fibrate is added to statin in patients with similar lipid profiles.^{6,7}

Because thiazolidinediones are insulin sensitizing agents rather than insulin secretagogues, hypoglycemia is rare.^{10,20} We observed no symptoms suggestive of hypoglycemia in our study group. Also, we observed no statistically significant increase in weight, which has been a troubling side effect in thiazolidinedione-treated diabetic patients.²¹ This finding is in accord with Szapary et al, who also saw no significant increase in body weight in a larger sample of non-diabetic patients on PIO.¹⁴

Rosiglitazone, another available thiazolidinedione insulin sensitizing agent, also has beneficial lipid effects. In diabetics, these lipid effects appear to be much less pronounced than PIO.²⁰ Our lipid clinic also experienced this phenomenon in our diabetic patients (personal observation, Cardiovascular Associates of Northern Wisconsin lipid clinics) and consequently we chose PIO rather than rosiglitazone as the adjunct therapy in these non-diabetic patients.

In addition to favorable insulin, glucose, and lipid effects, thiazolidinediones appear to have potent anti-inflammatory properties and improved endothelial function via activation of the PPAR γ system.²² Numerous lines of research have suggested activation of this sys-

tem may protect against atherosclerosis.¹¹ Recently, PIO has been shown to reduce atherosclerotic events in high-risk diabetic patients.²³ This effect may make PIO an acceptable adjunct agent when lipid abnormalities of the metabolic syndrome are not adequately treated with statin therapy alone.

LIMITATIONS

Our investigation represents a real life experience in a lipid clinic setting in which patients served as their own controls. Consequently it was not subjected to the controls of blinding or randomization. PIO is not approved by the Food and Drug Administration for treating lipids and little information is available in non-diabetic patients. Consequently, our use of PIO in this situation is considered "off label." To our knowledge, our results represent the only lipid study done with PIO and statin therapy in the non-diabetic with metabolic syndrome. Clearly, additional studies in larger sample sizes are warranted to further assess the role of thiazolidinediones in management of the atherogenic lipid profile accompanying the metabolic syndrome.

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