

Glitazones and the Potential Improvement of Lipid Profiles in Diabetes Patients at High Risk for Cardiovascular Disease

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Abstract

Most deaths and hospitalizations in patients with diabetes are related to atherosclerotic vascular disease. An asymptomatic patient with type 2 diabetes has a cardiovascular risk comparable to that of a patient without diabetes who has a history of a myocardial infarction. The American Heart Association classifies diabetes as a coronary heart disease risk equivalent. Thus, it is important in patients with diabetes to aim for systolic blood pressures less than 130 mm Hg, using an angiotensin-converting enzyme inhibitor-based regimen. The target hemoglobin A_{1C} (HbA_{1C}) for those patients is < 7%. New oral insulin-sensitizing medications, known as thiazolidinediones or glitazones, are useful to improve glycemic control. Most patients with diabetes require 2 or more oral agents to achieve optimal glucose control. Glitazones generally lower HbA_{1C} by 1% to 2%. They also raise high-density lipoprotein cholesterol levels and lower triglycerides. Thus, they may potentially improve low-density lipoprotein (LDL) particle sizes by converting small, dense LDL particles into larger,

less atherogenic ones. Current data concerning the lipid effects of pioglitazone and rosiglitazone are reviewed in this article.

(*Am J Manag Care* 2000;6:S1247-S1256)

Despite advances in risk-factor modification in the past 2 decades, coronary artery disease (CAD) remains the leading cause of death in the United States. In 1997, CAD accounted for 953,110 deaths.¹ Cardiac morbidity and mortality disproportionately affect patients with diabetes; it is estimated that the overwhelming majority of deaths of patients with diabetes are attributable to coronary disease.^{2,3} A recent study by Haffner et al⁴ demonstrated that patients with type 2 diabetes who have never experienced a cardiac event have the same risk of myocardial infarction as those patients who do not have diabetes but who have been diagnosed with heart disease. Although inadequately controlled hyperglycemia certainly may contribute to the risk of atherosclerotic disease, prospective trials to date have demonstrated a much stronger relationship between improved glycemic control and decreased microvascular morbidity.⁵ The benefit of reducing macrovascular mortality

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is less clear. The CAD risk associated with type 2 diabetes appears to be strongly affected by the interplay of the components of cardiovascular dysmetabolic syndrome, which include hypertension, dyslipidemia, central obesity, insulin resistance, and coagulation abnormalities.⁶⁻⁸ Each component of this syndrome promotes the progression of vascular disease.

The approach to reducing CAD risk in patients with diabetes involves both aggressive glycemic control and modifications of the above-mentioned concomitant risk factors. The goal of optimal glycemic control is challenging to achieve and maintain. Data from the United Kingdom Prospective Diabetes Study (UKPDS) trial demonstrate that worsening hyperglycemia is part of the natural disease progression of type 2 diabetes.⁹ Therefore, providers should expect that maintenance of euglycemia will require consistent medical follow up and modification of regimens over time. Eventually most patients will require multiple agents to achieve good glycemic control. Adequate control of glucose levels can lower triglyceride levels and thus improve dyslipidemia, as has been observed with metformin therapy.¹⁰

Thiazolidinediones (commonly known as glitazones) are a new class of insulin sensitizers available for glucose management in type 2 diabetes and also appear to have a beneficial effect on diabetic dyslipidemia. In animal trials, glitazones consistently lowered triglycerides and free fatty acid levels. Emerging data from human clinical studies appear to mimic some of the original findings in animal models. Uncertainty still exists about the exact mechanisms by which glitazones affect peripheral glucose uptake, circulating free fatty acid levels, and fat storage. The speculation is that glitazones affect both glucose control and the metabolic syndrome of insulin resistance,

including dyslipidemia and hypertension. Ongoing studies should elucidate the precise pharmacologic effects of glitazones and their clinical applications beyond glucose control.

Case Study

P.D. is a postmenopausal 54-year-old woman with a 15-year history of type 2 diabetes. Her glucose levels have been adequately controlled on a regimen of metformin 500 mg tid and glyburide 10 mg bid for the past 3 years.

However, recent elevations in her creatinine level (>1.4 mg/dL) prompted her provider to discontinue the metformin. P.D. understands the reason for changing her regimen and recognizes the need to achieve good glycemic control with a new combination of agents, but she is reluctant to accept her provider's recommendation to begin insulin therapy.

A review of her past medical history, current medications, and laboratory results reveals that P.D. is on appropriate agents to control her medical problems and to reduce her cardiovascular risk, except that she has a suboptimal cholesterol profile. Based on her medical history and baseline cholesterol values, her 10-year risk of a major cardiovascular event is high.

Past Medical History

- Type 2 diabetes mellitus
- High blood pressure
- Hyperlipidemia
- Renal insufficiency
- Peripheral arterial disease; status: post right femoral-popliteal bypass
- Remote tobacco use

Current Medications

Metformin	500 mg tid
Glyburide	10 mg bid
Simvastatin	80 mg qhs
Ramipril	10 mg qd
Atenolol	50 mg qd
Aspirin	325 mg qd

Laboratory Findings at

Current Visit

Total cholesterol	170 mg/dL
Triglycerides	240 mg/dL
High-density lipoprotein cholesterol (HDL-C)	46 mg/dL
Low-density lipoprotein cholesterol (LDL-C)	104 mg/dL
Sodium	142 mEq/L
Potassium	5.4 mEq/L
Fasting glucose	128 mg/dL
Creatinine	1.6 mg/dL
Urea Nitrogen	19 mg/dL
HbA _{1c}	6.5%

P.D. and her provider decide to begin a trial of pioglitazone. Over the next 2 months, P.D. is titrated up to pioglitazone 30 mg/day and reports that her average glucose readings at home are consistently < 140. She has not experienced any hypoglycemic episodes on this new regimen. The first hemoglobin A_{1c} (HbA_{1c}) after 3 months of glyburide and pioglitazone therapy is equivalent to values previously obtained on glyburide and metformin. Moreover, P.D.'s lipid profile is somewhat improved on the pioglitazone therapy.

New Medication Regimen

Pioglitazone	30 mg qd
Glyburide	10 mg bid
Simvastatin	80 mg qhs
Ramipril	10 mg qd
Atenolol	50 mg qd
Aspirin	325 mg qd

Laboratory Findings at

4-Month Visit

Total cholesterol	160 mg/dL
Triglycerides	200 mg/dL
HDL-C	50 mg/dL
LDL-C	96 mg/dL
Sodium	142 mEq/L
Potassium	5.2 mEq/L
Fasting glucose	120 mg/dL
Creatinine	1.6 mg/dL
Urea nitrogen	19 mg/dL
HbA _{1c}	6%

Glitazones

In the United States, glitazones are indicated for both monotherapy and combination therapy in type 2 diabetes. However, because of their high cost relative to metformin and glyburide, they are generally not employed as first-line agents.¹¹⁻¹³ Their mechanism of action, however, makes them an attractive addition to the formulary for the management of diabetes. In a manner comparable to

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current recommendations for anti-hypertensive therapy, oral hypoglycemics from different classes can be used in combination to synergistically achieve euglycemia.

Glitazones are direct ligands for peroxisome proliferator-activated receptors (PPARs), which are predominately located in adipose tissue. Researchers have yet to elucidate the exact manner by which PPARs influence the glucose-lowering activity of glitazones, but their clinical use reduces serum free fatty acid levels and stimulates the storage of both fatty acids and glucose in adipocytes.¹²⁻¹⁵ High levels of circulating fatty acids are known to diminish insulin sensitivity,¹⁶ and so lowering fatty acid levels may enhance insulin action in peripheral tissues. Although glitazones may also directly affect insulin uptake in peripheral tissue, their action could primarily stem from this indirect mechanism.

Glitazone therapy reduces fasting and postprandial hyperglycemia by increasing peripheral tissue glucose uptake and decreasing hepatic glu-

cose output. Therapy with this agent also decreases both circulating glucose levels and circulating insulin levels, and enhances the action of insulin that is present. The predictable clinical benefit of glitazone use is a 1% to 2% reduction in HbA_{1c}, which makes it comparable in effectiveness to treatment with metformin or glyburide.^{12,17-20} The net improvement in glucose control is also additive when glitazones are combined with either of those other oral agents.

Glitazones are effective only in the presence of adequate insulin. Based on available clinical data, approximately 25% of patients may not respond adequately to glitazone therapy because of insulin deficiency.^{12,13,21} Used as a single agent, glitazone therapy rarely causes hypoglycemia.²²

Known and Potential Lipid Benefits

Research on glitazone agents has revealed potential desirable lipid profile effects. In both humans and animal models, glitazones modulate adipocyte action, enhance adipocyte differentiation, and decrease circulating free fatty acid levels. In animal studies, reproducible benefits of glitazones include decreased triglyceride levels and decreased free fatty acid levels.^{12,13,23-25} In human studies, benefits of glitazones include decreased triglyceride levels, reductions in LDL-C oxidation, and increased HDL-C levels.^{12,13,23,26-32} Regarding effects on lipid metabolism in humans, findings show that glitazones sometimes raise total cholesterol and increase LDL-C levels, possibly by lipolysis of triglycerides in very low-density cholesterol.^{12,30} However, if the LDL-C mass changes because the particles become larger and more buoyant, the LDL-C in fact may be less atherogenic. Early reports and data available in abstract form suggest some of the lipid benefits found in basic research might translate into clinical benefits.

In a small observational cohort report, comparative (baseline versus > 2 months of therapy) data on patients receiving either troglitazone 600 mg (35 patients), rosiglitazone 8 mg (36 patients), or pioglitazone 45 mg (30 patients) were reported. The benefits in terms of HbA_{1c} lowering were comparable and ranged from -1.57% to -1.93%. Patients on troglitazone showed a decrease in triglyceride levels and an increase in both HDL-C and LDL-C levels. Patients receiving rosiglitazone showed no decrease in triglyceride or LDL levels and a minute increase in HDL-C. Patients on pioglitazone showed a decrease in triglycerides, a modest decrease in LDL-C, and the largest increase in HDL-C.³³ Although these comparative data are noteworthy, we will review the available evidence on the individual glitazone agents from randomized, controlled trials in the following section.

Troglitazone. The strongest data showing the clinical benefits of glitazone therapy are with troglitazone, which is no longer available for clinical use. In a number of trials, troglitazone therapy at different doses decreased triglycerides and free fatty acid levels and in some instances increased HDL-C levels in patients with type 2 diabetes.²⁶⁻³² In a 48-week study of 154 patients randomized to either glyburide or troglitazone 800 mg/day, the troglitazone group had a significant reduction in triglycerides beginning with week 12 of therapy. The troglitazone group also showed a statistically significant increase in HDL-C by week 36.²⁷ Concerns about the overall impact of troglitazone therapy were raised because some studies showed an increase in LDL-C levels.³²

Rosiglitazone. Randomized, placebo-controlled, short-term trials of rosiglitazone treatment have demonstrated modest increases in HDL-C, LDL-C, and total cholesterol levels. In an 8-week trial of 303 patients,

rosiglitazone treatment at 4, 8, and 12 mg/day lowered free fatty acid levels and modestly raised total cholesterol, HDL-C, and LDL-C levels. Triglyceride levels and total cholesterol/HDL ratios were not altered.³⁴ Rosiglitazone treatment at 3 different dosages in another 8-week trial of 369 patients also resulted in significant increases in total cholesterol, HDL-C, and LDL-C levels. Free fatty acid levels were significantly decreased in both the 8 and 12 mg/day treatment groups. Triglyceride levels were significantly raised in the 12 mg/day dose group and were unchanged at the other dosage levels.³⁵

Longer-term randomized placebo-controlled studies of rosiglitazone used in conjunction with other hypoglycemic agents show similar effects on lipids, but these data must be interpreted with caution because 2 hypoglycemic agents are involved. In a 26-week trial of 574 patients already receiving sulfonylurea therapy, patients were assigned to the addition of either placebo, rosiglitazone 1 mg bid, or rosiglitazone 2 mg bid. In combination with sulfonylurea therapy, the addition of rosiglitazone at either dose resulted in a statistically significant decrease (both from baseline and compared with placebo) in nonesterified fatty acid levels, a significant increase in HDL-C levels, and also a significant increase in triglyceride levels,³⁶ which is surprising given the usual inverse relationship between triglycerides and HDL-C. In a 26-week trial of 348 patients already receiving metformin therapy, patients were assigned to the addition of either placebo, rosiglitazone 4 mg/day, or rosiglitazone 8 mg/day. In combination with metformin therapy, the addition of rosiglitazone at either dose resulted in a statistically significant increase in HDL-C levels, as well as a significant increase in both total cholesterol and LDL-C levels.³⁷

Pioglitazone. Data reported thus far on pioglitazone appear to suggest beneficial effects of pioglitazone therapy on lowering triglyceride and raising HDL-C levels. In a 26-week study of 408 patients randomized to either placebo or pioglitazone therapy at 7.5, 15, 30, or 45 mg/day dose levels, all pioglitazone-treated patients experienced statistically significant increases in HDL-C levels from baseline. Patients treated at the 15, 30, and 45 mg doses of pioglitazone also experienced a significant decrease in triglyceride

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levels from baseline.³⁸ Other data reported in abstract form mirror these findings. A 16-week study of 197 patients randomized to placebo or pioglitazone 30 mg/day found that pioglitazone treatment resulted in a 13% increase in HDL-C from baseline and a significantly higher increase than placebo. Pioglitazone therapy also led to a 28% reduction in triglycerides from baseline and a significantly greater decrease than placebo.³⁹

Finally, in a 24-week study of 260 patients randomized to placebo or 2 pioglitazone dose-escalating protocols (either pioglitazone 7.5 mg/day for 4 weeks, 15 mg/day for 4 weeks, and then 30 mg/day for 16 weeks, or pioglitazone 15 mg/day for 4 weeks, 30 mg/day for 4 weeks, and then 45 mg/day for 16 weeks), both pioglitazone treatment groups experienced a significant increase in HDL-C and a reduction in triglycerides from baseline. Changes in total cholesterol and LDL-C levels were not significantly different from placebo.⁴⁰

Randomized placebo-controlled studies of pioglitazone (data also

available only in abstract form) used in conjunction with other hypoglycemic agents show similar lipid effects. In one study, 560 patients poorly controlled on sulfonylurea therapy alone were randomized to the addition of either placebo, pioglitazone 15 mg/day, or pioglitazone 30 mg/day. The patients treated with the 30 mg/day dosage of pioglitazone showed a statistically significant 10% mean increase in HDL-C from baseline and a 15% decrease in triglycerides. Total cholesterol and LDL-C levels were not significantly changed.⁴¹

Another study of 328 patients poorly controlled on metformin therapy alone randomized patients to the addition of either placebo or pioglitazone 30 mg/day. The patients treated with the addition of pioglitazone showed a statistically significant 8% mean increase in HDL-C from baseline and a 21% decrease in triglycerides.⁴² Neither total cholesterol nor LDL-C levels were significantly changed. In summary, data on pioglitazone are only available in abstract form, but they suggest that this agent can increase HDL-C, lower triglycerides, and either raise or lower LDL-C.

Side Effects

The first agent in this class, troglitazone, was recalled in the United States because of rare cases of hepatic failure requiring liver transplantation and resulting in 61 deaths.⁴³⁻⁵¹ The 2 remaining drugs in the class, rosiglitazone and pioglitazone, have not been associated with confirmed reports of liver failure. Based on the data submitted as part of the Food and Drug Administration (FDA) approval process, elevations in hepatic enzymes occurred in 0.2% of patients receiving rosiglitazone therapy and in 0.25% of patients receiving pioglitazone therapy. However, in recent months, case reports of liver injury inconclusively attributed to rosiglitazone therapy have appeared in scientific publications.⁵²⁻⁵⁵ Because of the risk associated with trogli-

tazone therapy, the FDA has recommended that liver function be tested at regular intervals for all drugs in this class.

In addition to potential effects on liver function, glitazones can cause fluid retention and edema in some patients, and their use is therefore contraindicated in patients with persistent symptomatic heart failure (New York Heart Association Class III or IV).^{11,22,32} Studies of rosiglitazone have found between a 3% and 5% incidence of edema.¹¹ The side effect of anemia in some patients may be caused by hemodilution related to fluid retention. Patients on glitazone therapy may also experience weight gain independent of fluid retention, an undesirable side effect shared with insulin use.⁵⁶ In the case of glitazone-related weight gain, it may reflect increased body fat and/or fluid retention.¹¹ In a single study of 560 patients on sulfonylurea randomized to the addition of either placebo, pioglitazone 15 mg, or pioglitazone 30 mg, the combined occurrence of hypoglycemia, weight gain, and edema were 1%, 4%, and 5%, respectively.⁵⁷ Of special concern to women of childbearing age is the finding that glitazone use may cause ovulation and place women at increased risk of unexpected pregnancy.^{22,58}

Risk Factor Management in Type 2 Diabetes

Glycemic Control. Ideally, glycemic control in patients with type 2 diabetes will be achieved with a combination of dietary modifications including caloric restriction and reduced fat intake, regular exercise, and a combination of oral hypoglycemic agents or insulin therapy. The target goal for HbA_{1c} set by the American Diabetes Association (ADA) is < 7%,⁵⁹ but in some patients values close to normal (HbA_{1c} ≤ 6%) can be safely attained. In patients with type 1 diabetes, the results of the Diabetes Control and Complications Trial established the clinical standard that providers should

strive to achieve near normal glycemic control to reduce retinopathy, neuropathy, and nephropathy.⁶⁰ The most comprehensive long-term data about the benefits of aggressive glucose management in type 2 diabetes have been from the UKPDS. The UKPDS results demonstrated that each 1% reduction in mean HbA_{1c} resulted in a 21% risk reduction for any endpoint related to diabetes and a 37% risk reduction for microvascular complications.⁵

Dyslipidemia. Hyperlipidemia is common in patients with diabetes, and most often consists of elevated triglycerides, low levels of HDL-C, and increased levels of small, dense LDL-C. As a result, the presence of diabetes is considered a risk equivalent to having established CAD. The ADA recommends lipid-lowering medications in patients with diabetes mellitus to achieve an LDL-C < 100 mg/dL and triglyceride levels < 200 mg/dL.⁵⁹

Based on their efficacy and widely demonstrated benefit of improving cardiovascular outcomes, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, commonly known as statins, are generally used initially to reach the LDL-C goal. Statin therapy is associated with an approximate 20% to 40% reduction in subsequent cardiac events in patients with CAD.⁶¹⁻⁶³ In the subgroups of patients with diabetes in the Scandinavian Simvastatin Survival Study⁶¹ and the Cholesterol and Recurrent Events studies,⁶² the use of statins significantly reduced cardiovascular events. After the LDL-C target goal is reached with statin therapy, consideration should then be given to the judicious use of fibrates or niacin to optimize HDL-C and triglyceride values. Either of these agents should also lower CAD risk by converting the more atherogenic small, dense LDL-C particles commonly associated with diabetes into the less atherogenic, more buoyant particles.

Hypertension. Based on the accumulated evidence supporting the benefit of tighter blood pressure control in patients with diabetes, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure-VI guidelines recommend lowering blood pressure to < 130/85 mm Hg for all patients and setting a more aggressive goal of < 125/75 mm Hg if a patient with diabetes already has evidence of renal insufficiency as measured by proteinuria >1 g/day. In patients without contraindications, angiotensin-converting enzyme (ACE) inhibitors should preferentially be used because of their dual effect: lowering blood pressure and providing renal protection.⁶⁴ The prospective observational UKPDS 36 trial analyzed the relationship between systolic blood pressure (SBP) and microvascular and macrovascular outcomes in patients with diabetes and hypertension. In the 4801 patients followed for periods from 7.5 to 12.5 years, this study demonstrated that each 10-mm Hg reduction in mean SBP translated into a 12% risk reduction for any diabetes complication, 15% risk reduction in death related to diabetes, 11% risk reduction for myocardial infarction, and 13% risk reduction for microvascular complications.⁶⁵ UKPDS 38 tested microvascular and macrovascular outcomes in patients with diabetes and hypertension treated to an average blood pressure of 144/82 mm Hg (tight control) versus 154/87 mm Hg (less tight control). The tight control group experienced risk reduction benefits including 32% reduction in death from diabetes, 44% reduction in stroke, and 37% reduction in microvascular disease including retinopathy and microalbuminuria.⁶⁶

Conclusion

Accumulated clinical evidence indicates that providers should try to optimize blood pressure, lipid levels, and glycemic control in all patients with diabetes to lessen the morbidity

and mortality associated with atherosclerotic vascular disease. ACE inhibitor-based regimens should be strongly considered in any patient with diabetes who has a SBP > 130 mm Hg or a diastolic blood pressure > 85 mm Hg. The target HbA_{1c} for a patient with diabetes is < 7%, and the recent follow-up data from the UKPDS study suggest that microvascular and macrovascular complications of diabetes occur less frequently at HbA_{1c} levels in the range of 6%. Clearly, the benefits associated with these lower target values need to be balanced against the expense of multiple medications and the risk of hypoglycemia.

The class of medications known as glitazones seems to be effective in improving glycemic control. Typically they result in a 1% to 2% decrease in HbA_{1c} values. Better glycemic control will also optimize triglyceride values. The goal LDL-C for a patient with type 2 diabetes is < 100 mg/dL and the goal triglyceride level is < 200 mg/dL, although the new National Cholesterol Education Program guidelines will recommend a goal triglyceride level of < 150 mg/dL. In summary, all patients with diabetes should be treated aggressively with lifestyle modification and proven medications such as antiplatelet agents (eg, aspirin), antihypertensive agents (eg, ACE inhibitors), and lipid-lowering agents (eg, statins) if the LDL-C is > 100 mg/dL. A variety of oral agents, such as sulfonylureas, metformin, and glitazones, optimize glycemic control, which is vital to reduce the microvascular and macrovascular complications of this disease. Metformin and glitazones may also improve the control of dyslipidemia in patients with diabetes.

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