

Using Thiazolidinediones: Rosiglitazone and Pioglitazone in Clinical Practice

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Abstract

Type 2 diabetes is a disorder that has numerous components, including insulin resistance, an insulin secretory defect, and an increase in hepatic glucose production. Until recently, only the insulin secretory defect could be treated. Within recent years, the thiazolidinedione (TZD) class of drugs, which targets primarily insulin resistance, was released. Originally developed in Japan as triglyceride-lowering agents, TZDs were found to be more effective in lowering blood glucose levels instead. The actions of 2 TZDs—rosiglitazone and pioglitazone—are discussed and their glucose- and nonglucose-lowering effects are explained. Four case histories are presented to illustrate various patients' responses to TZDs in clinical practice. Although TZDs have been demonstrated to be effective in dealing with many different aspects of type 2 diabetes, further study, involving multiple clinical trials, is needed.

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It has long been known that type 2 diabetes is a disorder involving multiple components: insulin resistance, an insulin secretory defect, and an increase in hepatic glucose production. Patients with type 2 diabetes express varying degrees of these defects. The American Diabetes Association defines type 2 diabetes as a combination of resistance to insulin action and an inadequate compensatory insulin secretory response.¹ Until recently, physicians could treat only

the insulin secretory defect, either by increasing insulin secretion through use of insulin secretagogues or by the addition of exogenous insulin. Within the past few years several new drugs that target insulin resistance and/or hepatic glucose production have been made available for use in the United States.

The first of these drugs to be introduced was metformin, a member of the biguanide class.² Metformin has been available worldwide since 1957 and was introduced into the US market in 1995. Although it is not known exactly how metformin works, it is believed to primarily decrease hepatic glucose production^{3,4} and to a lesser degree, decrease peripheral insulin resistance.⁵ Most side effects associated with metformin are gastrointestinal and tend to be mild, including abdominal discomfort and diarrhea that occur in 20% to 30% of patients.^{6,7} Rarely, metformin can cause lactic acidosis. Conditions such as congestive heart failure and renal insufficiency increase the risk of lactic acidosis. Therefore the Food and Drug Administration (FDA) has specific guidelines for its use.⁸

The next category of antihyperglycemic agents available in the United States was the thiazolidinedione (TZD) class. This class includes troglitazone, rosiglitazone, and pioglitazone and acts by targeting insulin resistance primarily.

Pharmacology—General

The original TZD compounds were developed in Japan as triglyceride-lowering agents. However, these drugs were found to be more effective at lowering blood glucose levels than triglycerides, although some of these agents do improve the lipid profile as well. The first of these agents on the market was troglitazone, which was effective at lowering blood glucose levels with positive effects on plasma lipids⁹ as well as on blood pressure.¹⁰ These effects are very beneficial in patients with insulin resistance because insulin resistance is associated with dyslipidemia (low high-density lipoprotein [HDL] cholesterol, high triglyceride levels, and decreased low-density lipoprotein [LDL] particle size) and hypertension in addition to hyperglycemia.¹¹

Troglitazone was removed from the market in March 2000 because of concerns about liver toxicity. These concerns surfaced within a year after the drug was introduced to the market.¹² Through June 1998 the FDA received 560 reports of troglitazone-associated hepatotoxicity. In these cases, 24 patients suffered liver failure in which troglitazone appeared to be the likely cause.¹³ Because of the risk of liver toxicity and concerns

that postmarketing drug surveillance would not be adequate to identify all cases of liver failure,¹⁴ troglitazone was withdrawn from the market. Fortunately, 2 new TZDs, rosiglitazone and pioglitazone, had been introduced for use in the United States. These 2 agents had no signal for liver toxicity in their initial FDA submission.^{15,16} Two case reports were published on severe hepatotoxicity as a result of the use of rosiglitazone.^{17,18} However, 1 of these cases was subsequently believed to be a result of hypoxic liver damage¹⁹ and 1 was more likely a result of the use of zafirlukast,²⁰ which is more likely to cause hepatotoxicity than rosiglitazone. No further case reports of severe hepatotoxicity with either rosiglitazone or pioglitazone use have been published since these drugs became available in the United States more than a year ago.

Pharmacology—Glucose Lowering

Rosiglitazone and pioglitazone share certain similarities, as well as some differences, when studied in research settings and when used in patients. Both drugs interact with the gamma subtype of the peroxisome proliferator-activated receptor gamma (PPAR- γ). PPAR- γ is a member of the nuclear receptor superfamily, which when stimulated regulates gene expression.²¹ Both drugs share a common thiazolidine-2,4-dione structure, but differ in their side chains, which causes differences in their effects.²² PPAR- γ receptors are found in adipose tissue, skeletal muscle, and liver. Activation of PPAR- γ nuclear receptors affects the transcription of a number of insulin responsive genes that are involved in the control of glucose and lipid metabolism. In addition to effects on glucose and lipid levels, TZDs increase adipocyte differentiation.²³ Both rosiglitazone and pioglitazone lower blood glucose levels. Although head-to-head trials have not been performed, it appears

Table 1. Effect on Fasting Blood Glucose Levels (mg/dL) by Rosiglitazone and Pioglitazone

Condition	Rosiglitazone	Pioglitazone
Monotherapy	38 to 58 (4 mg/day) 45 to 76 (8 mg/day)*	31 to 56 (30 mg/day) 58 to 80 (45 mg/day)
With Metformin	33 to 54	31 to 53
With Sulfonylurea	41 to 59	39 to 58

*Greatest glucose lowering if given as 4 mg twice per day.
Source: References 25, 26.

the glucose-lowering effects of these drugs is similar in patients with type 2 diabetes (Table 1). Rosiglitazone and pioglitazone differ in potency but not maximal clinical effectiveness. At maximal dose rosiglitazone is most effective when given as 4 mg twice per day, as compared with pioglitazone, which is given as 45 mg once per day.²⁴

Pharmacology—Nonglucose Effects

The nonglucose-lowering effects of these agents may be just as important, and perhaps even more important, as the glucose-lowering benefits. Rosiglitazone and pioglitazone seem to differ most clinically in their effects on lipids. Table 2 summarizes data from the package inserts of both drugs, reflecting the data obtained for FDA approval of these drugs for use in the United States.^{25,26} Their effects on lipid levels have now been shown in a variety of published clinical trials.²⁷⁻³⁰ Studies designed to compare the lipid effects of rosiglitazone and pioglitazone are under way. Overall, both agents raise HDL cholesterol levels. Rosiglitazone does this with no consistent change in triglyceride levels and often an increase in LDL cholesterol levels. Pioglitazone has been shown in trials to raise HDL cholesterol levels and lower triglycerides with essentially no change in LDL cholesterol levels. Table 3 summarizes data from the clinical experience of 1 practitioner, which are the only available head-to-head data on these drugs.³¹

Multiple effects of these drugs have been found. Both troglitazone and rosiglitazone reduce blood pressure in insulin-resistant patients.^{10,32} Pioglitazone has not yet been studied in terms of its blood pressure effects in humans but has a blood pressure-lowering effect in animal models.³³ TZDs cause an increase in fat cell differentiation with a redistribution of fat cells from the visceral (central) area to more subcutaneous regions.^{34,35}

A variety of positive effects on vascular risk factors has been shown. TZDs decrease neointimal hyperplasia after stenting and vascular injury.³⁶⁻³⁸ Troglitazone, and likely rosiglitazone and pioglitazone, increase LDL particle size³⁹ while decreas-

Table 2. Changes in Lipid Levels—Monotherapy Trials*

Drug/Dose	LDL Cholesterol	HDL Cholesterol	Triglycerides
Rosiglitazone vs placebo			
Rosiglitazone 4 mg/day	14.1%	11.4%	Changes variable and not statistically significant
Rosiglitazone 8 mg/day	18.6%	14.2%	Changes variable and not statistically significant
Placebo	4.8%	8%	Changes variable and not statistically significant
Pioglitazone vs placebo			
Pioglitazone 30 mg/day	5.2%	12.2%	-9.6%
Pioglitazone 45 mg/day	6%	19.1%	-9.3%
Placebo	4.8%	8.1%	4.8%

*Changes compared with baseline.

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Source: References 25, 26.

Table 3. Comparison of Rosiglitazone and Pioglitazone

Parameter	Rosiglitazone (n = 36)	Pioglitazone (n = 30)
HbA _{1c} (%)	-1.89	-1.93
HDL Cholesterol (mg/dL) (%)	0.5 (1.1%)	6.5 (12.8%)
LDL Cholesterol (mg/dL) (%)	11.5 (11.2%)	-1.1 (-1.1%)
Triglycerides (mg/dL) (%)	47 (27.3%)	-21 (-10.1%)
Weight (kg)	0.5	2.6

HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Source: Reference 31.

ing potential atherogenic effects. Factors such as plasminogen activator inhibitor-1 (PAI-1) that increase risk for thrombosis are favorably impacted by TZDs.⁴⁰

A myriad of other nonglucose effects have been suggested for TZDs but data are available only from small studies and need to be validated in large-scale clinical trials. For instance, it is suggested that this class may have specific renal-protective effects⁴¹ and may also have positive effects on bone formation.⁴² Finally, they may aid in preserving beta-cell mass and preventing the development of hyperglycemia and macrovascular disease in patients at risk for diabetes.⁴³

Side Effects and Monitoring

When rosiglitazone and pioglitazone first became available, it was required that liver function be monitored every other month during the first year of use.^{25,26} These recommendations persist and should be followed, although rosiglitazone and pioglitazone do not appear to have the serious liver toxicity associated with troglitazone.

TZDs are associated with edema. The mechanism(s) for the edema are not well characterized. Rates range from 3% to 5% in monotherapy to 15% in patients on combination pioglitazone plus insulin therapy.²⁶ In most cases the edema is mild and is tolerated by the patients, but occasionally it is severe and the TZD must be discontinued. Rarely, patients may develop congestive heart failure.⁴⁴ Rosiglitazone and pioglitazone have not been studied in patients with New York Heart Association Class III and IV congestive heart failure and should not be used in these patients.

Cases

Although there are many potential benefits to TZD use, they should be more completely studied in long-term clinical trials. Because TZDs have now been on the market for several years,

physicians know how the agents work on an individual basis. The 4 cases below illustrate patients' responses in clinical practice.

Case 1: Adding a TZD to Metformin

B.L. is a 60-year-old white female with a 5-year history of type 2 diabetes. She was started initially on metformin and medical nutrition therapy with a good response. Her initial weight was 235 pounds (Ht = 5'4") and she subsequently lost 40 pounds while taking metformin. Her hemoglobin A_{1c} (HbA_{1c}) levels remained at 6% to 6.5%. She monitored her blood glucose levels 3 times per week before breakfast and 1 to 2 hours after dinner. She kept her fasting blood glucose (FBG) level between 80 and 140 mg/dL; her postprandial glucose levels were usually <160 mg/dL. Her lipids, even with weight loss and diet, revealed a total cholesterol of 224 mg/dL, triglycerides of 226 mg/dL, HDL cholesterol of 40 mg/dL, and LDL cholesterol of 139 mg/dL. An initial dose of atorvastatin 10 mg/day with dinner was increased to 20 mg/day to maintain her LDL cholesterol at <100 mg/dL. She also began taking aspirin daily. Her blood pressure was normal at 134/76 mm Hg.

Over 3 years her blood glucose levels and weight began to increase and her HbA_{1c} level increased to 8.5%. She was unable to lose weight; rosiglitazone 4 mg/day was added and increased to 4 mg twice a day to keep her HbA_{1c} level at <7%. After 6 months of rosiglitazone and metformin therapy her HbA_{1c} level was stable at 6.1%. She remained on the atorvastatin and daily aspirin and maintained an LDL cholesterol level of 98 mg/dL.

Comments

The United Kingdom Prospective Diabetes Study provided longitudinal data to show that type 2 diabetes is a

progressive disease.⁴⁵ Blood glucose levels tend to increase over time, particularly in patients who are on a single agent (monotherapy) for the treatment of diabetes. Now that more drugs are available for the treatment of type 2 diabetes, combination therapy increasingly can be used to lower blood glucose levels and to maintain near-normal blood glucose levels for many years.⁴⁶

The combination of a TZD with metformin is an effective approach for lowering blood glucose levels and possibly for lowering macrovascular disease risk. Both drugs work synergistically to decrease insulin resistance and to lower hepatic glucose production.^{27,30} Metformin also helps to limit weight gain associated with most therapies for treating diabetes.

In addition to lowering blood glucose levels, it was important to address macrovascular risk factors in this case.⁴⁷ Aggressive treatment should be used to keep LDL cholesterol levels less than 100 mg/dL, if possible. After therapy with rosiglitazone is started, lipid levels should be remeasured to ensure there is no clinically significant increase in triglycerides and/or LDL cholesterol level. Daily aspirin should be recommended for most adults with type 2 diabetes.⁴⁸

Case 2: Adding a TZD to Insulin

L.H. is a 55-year-old African-American male with a 14-year history of type 2 diabetes. Initially he was given a sulfonylurea agent that stopped working, so he was started on twice-daily insulin. When he was referred for evaluation to the diabetes clinic, his HbA_{1c} level was 10% and he was on approximately 60 units of insulin per day. He had symptoms of mild peripheral neuropathy and had microalbuminuria on testing. He had no diabetic retinopathy and no known macrovascular disease.

Pioglitazone 30 mg was added to his insulin regimen. He was told to test his blood glucose levels at least twice per day, before breakfast and before dinner, and to report to his diabetes team if his blood glucose levels fell below 120 mg/dL. After approximately 2 weeks his blood

The combination of a TZD with metformin is an effective approach for lowering blood glucose levels and possibly for lowering macrovascular disease risk.

glucose levels began to fall and his insulin dose was lowered in 2- to 4-unit increments. After 2 months he still required insulin injections, so his dose of pioglitazone was increased to 45 mg/day. With this dose he was able to taper his insulin further and as a result began taking 20 units of insulin in the evening. He did not require a morning injection. During this period his HbA_{1c} level fell to 8% and he gained approximately 10 pounds.

To further lower his HbA_{1c} level, metformin was added to the pioglitazone and evening insulin. Metformin was increased to 1 g twice a day and he was able to stop taking insulin. The combination of pioglitazone and metformin therapy decreased his HbA_{1c} level to 7%. He was also given an angiotensin-converting enzyme inhibitor for microalbuminuria.

Comments

This case shows the gradual onset of the TZD's action. Often it takes 12 to 16 weeks to see the maximal effect of these drugs, but a decrease in glucose levels may occur within 1 or 2 weeks of starting the TZD. Patients

must monitor their blood glucose levels so appropriate adjustments can be made. Patients generally gain weight when they respond to a TZD and should be encouraged to adhere to recommended medical nutrition therapy and activity guidelines. In this case the patient was pleased that he was able to stop the insulin injections, although the primary goal of the addition of the TZD was to improve his HbA_{1c} level (which was accomplished).

Case 3: Treatment of Steroid-Induced Insulin Resistance

J.W. is a 53-year-old Asian businessman who had a 10-year history of type 2 diabetes treated with glyburide 5 mg/day. He did well but developed progressive kidney failure as a result of nondiabetic kidney disease. Eventually he required a renal transplant. After the transplant his blood glucose levels became markedly elevated, and he was started on twice-daily split/mixed insulin with NPH and regular insulin. Because he wanted to stop insulin injections, rosiglitazone 4 mg/day was prescribed and later increased to 4 mg twice a day. Normal blood glucose levels were achieved if insulin was decreased but not if insulin was discontinued. Glyburide was restarted and increased up to 20 mg/day. With the combination of rosiglitazone and glyburide his insulin dose was changed to once a day in the evening and was eventually discontinued. His prednisone dose was also tapered and stabilized at 5 mg/day. He was on a statin for treatment of his dyslipidemia. His lipids were well controlled with an LDL cholesterol level of 86 mg/dL and triglycerides level of 128 mg/dL. There was no change when rosiglitazone was added.

Comments

Insulin resistance occurs when patients take exogenous steroids. This patient had easily controlled

type 2 diabetes prior to his kidney transplant. Afterward he was started on immunosuppressive therapy that necessitated use of insulin. With the addition of rosiglitazone and eventually a sulfonylurea agent his insulin requirement was decreased while maintaining good glycemic control. Tapering his prednisone dose also helped to lower his need for exogenous insulin, but it was the combination of an insulin sensitizer with an insulin secretagogue that worked most effectively in this patient.

Case 4: Treatment of Polycystic Ovary Syndrome and Insulin Resistance with TZD Therapy*

B.M. is a 35-year-old white female who had been treated for infertility for the past 5 years. She had polycystic ovary syndrome (PCOS) and had undergone a wedge resection of one of her ovaries in an unsuccessful attempt to restore regular menstrual cycles. Over the course of the infertility treatment her weight had increased from 160 to 238 pounds. Her height was 5'3". She was unable to conceive and her menstrual cycles, which had been irregular in the past, had ceased entirely for 1 year. In addition, she had noted increasing hair growth on her chin and upper lip. She noted no striae or acanthosis nigricans. Her weight was primarily central in distribution, although she had gained some weight throughout. She had a grandmother with type 2 diabetes.

Her initial FBG level was 108 mg/dL with a fasting insulin level of 42 µU/mL. Prolactin and thyroid hormone levels were normal. She had an elevated luteinizing hormone:follicle-stimulating hormone ratio consistent with PCOS. She was informed of her insulin resistance and received instructions on

*Unlabeled/unapproved use of drug.

medical nutrition therapy and exercise. She felt somewhat better when she adhered to the diet, with less hunger and more energy. However, she had adopted an infant and was unable to follow the recommended lifestyle changes. She wanted to restore her normal menstrual cycles and determine if decreasing her insulin resistance could restore fertility. Therefore, she was started on pioglitazone 15 mg/day. After 3 months she did not menstruate, so the dose was increased to 30 mg/day. After 3 months on 30 mg menstruation had not occurred, although her FBG level had fallen to 92 mg/dL and her fasting insulin level to 21 μ U/mL. The dose of pioglitazone was increased to 45 mg/day. After 6 weeks on this dose her menstrual cycles returned and are now occurring every 28 to 32 days. She was informed that pregnancy could occur and to discontinue the pioglitazone immediately if she became pregnant.

Comments

This patient had marked insulin resistance. Her FBG to insulin ratio was initially 2:6, which is clearly <4:5 (the value suggested as a cutoff point for insulin resistance).⁴⁹ The use of troglitazone for the treatment of PCOS had been studied^{50,51} and was effective. Although there are no studies using the new TZDs, it would seem that a drug acting as an insulin sensitizer would lessen the features of PCOS, which are associated with insulin resistance. The restoration of fertility may be welcomed by women who desire pregnancy, but all women of reproductive age who are treated

with insulin sensitizers should be aware that pregnancy can occur and birth control should be used as indicated. If a woman becomes pregnant while taking any oral agent for the treatment of insulin resistance or diabetes, the oral drug should be discontinued and insulin prescribed as indicated by the patient's blood glucose levels.

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... REFERENCES ...

1. **American Diabetes Association.** Clinical Practice Recommendations 2001. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2001;24(suppl 1):S5-S20.
2. **Davidson MB, Peters AL.** An overview of metformin in the treatment of type 2 diabetes mellitus. *Am J Med* 1997;102:99-110.
3. **DeFronzo RA, Barzilai N, Simonson DC.** Mechanism of metformin action in obese and lean noninsulin-dependent diabetic subjects. *J Clin Endocrinol Metab* 1991;73:1294-1301.
4. **Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich JE.** Metabolic effects of metformin in non-insulin dependent diabetes mellitus. *N Engl J Med* 1995;333:550-554.
5. **Galuska D, Nolte LA, Zierath JR, Wallber-Henriksson H.** Effect of metformin on insulin-stimulated glucose transport in isolated skeletal muscle obtained from patients with NIDDM. *Diabetologia* 1994;37:826-832.
6. **DeFronzo RA, Goodman AM.** Efficacy of metformin in patients with noninsulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. *N Engl J Med* 1995;333:541-549.
7. **Garber AJ, Duncan TG, Goodman AM, Mills DJ, Rohlf JL.** Efficacy of metformin in type II diabetes: Results of a double-blind, placebo-controlled dose-response trial. *Am J Med* 1997;103:491-497.
8. Bristol-Myers Squibb. Glucophage Prescribing Information; Princeton, NJ.
9. **Fonseca VA, Valiquet TR, Huang SM, Ghazzi MN, Whitcomb RW.** The Troglitazone Study Group. Troglitazone monotherapy improves glycemic control in patients with type 2 diabetes mellitus: A randomised controlled study. *J Clin Endocrinol Metab* 1998;83:3169-3176.
10. **Ghazzi MN, Perez JE, Antonucci TK, et al.** Cardiac and glycemic benefits of troglitazone treatment in NIDDM. *Diabetes* 1997;46:433-439.

Note: Cases are used to illustrate key points of TZD use and are in some cases simplified or modified from the original. All are based on real patients. In all cases liver function tests were normal at baseline and were monitored every 2 months for the first year on the drug.

11. **Fagan TC, Deedwania PC.** The cardiovascular dysmetabolic syndrome. *Am J Med* 1998;105:77S-82S.
12. **Watkins PB, Whitcomb RW.** Hepatic dysfunction associated with troglitazone. *N Engl J Med* 1998;338:916-917.
13. **Misbin RI.** Troglitazone associated hepatic failure. *Ann Intern Med* 1999;130:330.
14. Center for Drug Evaluation and Research/ Food and Drug Administration. Meeting Number 74 of Endocrinologic and Metabolic Drugs Advisory Committee; May 19, 2000; Bethesda, MD.
15. Rosiglitazone. FDA review. Available at: www.fda.gov/cder/foi/label/1999/21071lblLBL.pdf. Accessed March 13, 2001.
16. **Rubin CJ, Schneider RL.** Pioglitazone liver enzyme profile is similar to placebo in US controlled clinical trials. *Diabetes* 2000;49(suppl 1):A123.
17. **Forman LM, Simmons DA, Diamond RH.** Hepatic failure in a patient taking rosiglitazone. *Ann Intern Med* 2000;132:118-121.
18. **Al-Salman J, Arjomand H, Kemp DG, Mital M.** Hepatocellular injury in a patient receiving rosiglitazone. *Ann Intern Med* 2000;132:121-124.
19. **Fried J, Everitt D, Boscia J.** Rosiglitazone and hepatic failure. *Ann Intern Med* 2000;132:164.
20. Correction. Liver injury and rosiglitazone [letter]. *Ann Intern Med* 2000;133:237.
21. **Spiegelman BM.** PPAR- γ : Adipogenic regulator and thiazolidinedione receptor. *Diabetes* 1998;47:507-514.
22. **Camp HS, Li O, Wise SC, et al.** Differential activation of peroxisome proliferator-activated receptor-gamma by troglitazone and rosiglitazone. *Diabetes* 2000;49:539-547.
23. **Lehmann JN, Moore LB, Smith Liver TA, Wilkison WO, Willson TM, Kleiwer SA.** An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator activated receptor γ (PPAR γ). *J Biol Chem* 1995;270:12953-12956.
24. **Philips LS, Grunberger G, Miller E, Patwardhan R, Rappaport EB, Salzman A.** Once and twice-daily dosing with rosiglitazone improves glycemic control in patients with type 2 diabetes. *Diabetes Care* 2001;24:308-315.
25. GlaxoSmithKline. Avandia Prescribing Information; Philadelphia, PA.
26. Takeda Pharmaceuticals America, Inc/ Eli Lilly and Company. Actos Prescribing Information; Lincolnshire, IL and Indianapolis, IN.
27. **Fonseca V, Rosenstock J, Patwardhan R, Salzman A.** Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus. *JAMA* 2000;283:1695-1702.
28. **Raskin P, Rappaport EB, Cole ST, Yan Y, Patwardhan R, Freed MI.** Rosiglitazone short-term monotherapy lowers fasting and post-prandial glucose in patients with type II diabetes. *Diabetologia* 2000;43:278-284.
29. **Aronoff S, Rosenblatt S, Braithwaite S, Egan JW, Mathisen AL, Schneider RL.** Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes. *Diabetes Care* 2000;23:1605-1611.
30. **Einhorn D, Rendell M, Rosenzweig J, Egan JW, Mathisen AL, Schneider RL.** Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: A randomized, placebo-controlled study. *Clin Ther* 2000;22:1395-1409.
31. **King AB.** A comparison in a clinical setting of the efficacy and side effects of three thiazolidinediones. *Diabetes Care* 2000;23:557.
32. **Bakris G, Dole JF, Porter LE, Huang C, Freed MI.** Rosiglitazone improves blood pressure in patients with type 2 diabetes mellitus. *Diabetes* 2000;49(suppl 1):388A.
33. **Kaufman LN, Peterson MM, DeGrange LM.** Pioglitazone attenuates diet-induced hypertension in rats. *Metabolism* 1995;44:1105-1109.
34. **Carey DG, Galloway G, Dodrell D, Richards J, Jones NP, Zhou B.** Rosiglitazone reduces hepatic fat and increases subcutaneous but not intra-abdominal fat deposits. Paper presented at: 36th Annual Meeting of the European Association for the Study of Diabetes; September 17-21, 2000; Jerusalem, Israel.
35. **Miyazaki Y, Mahankali A, Matsuda M, et al.** Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in patients with type 2 diabetes mellitus. *Diabetes* 2000;49(suppl 1):A299.
36. **Takagi T, Akasaka T, Yamamuro A, et al.** Troglitazone reduces neointimal tissue proliferation after coronary stent implantation in patients with non-insulin-dependent diabetes mellitus: A serial intravascular ultrasound study. *J Am Coll Cardiol* 2000;36:1529-1535.
37. **Law RE, Meehan WP, Xi XP, et al.** Troglitazone inhibits vascular smooth muscle growth and intimal hyperplasia. *J Clin Invest* 1996;98:1897-1905.
38. **Parulkar AA, Pendergrass ML, Granda-Ayala R, Lee TR, Fonseca VA.** Nonhypoglycemic effects of thiazolidinediones. *Ann Intern Med* 2001;134:61-71.
39. **Tack CJJ, Smits P, Demacker PNM, Stalenoef AFH.** Troglitazone decreases the proportion of small, dense LDL and increases the resistance of LDL to oxidation in obese subjects. *Diabetes Care* 1998;21:796-799.
40. **Freed M, Fuell D, Menci L, Heise M, Goldstein B.** Effect of combination therapy with rosiglitazone and glibenclamide on PAI-1 antigen, PAI-1 activity, and tPA in patients with type 2 diabetes. Paper presented at: 36th Annual Meeting of the European Association for the Study of Diabetes; September 17-21, 2000; Jerusalem, Israel.
41. **Nakamura T, Ushuyama C, Shimada N, Hayashi K, Ebihara I, Koide H.** Comparative effects of pioglitazone, glibenclamide, and voglibose on urinary endothelin-1 and albumin excretion in diabetes patients. *J Diabetes Complications* 2000;14:250-254.
42. **Okazaki R, Toriumi M, Fukumoto S, et al.** Thiazolidinediones inhibit osteoclast-like cell formation and bone resorption in vitro. *Endocrinology* 1999;140:5060-5065.

- 43. Buchanan TA.** Results of the TRIPOD Study. Paper presented at: The 60th Scientific Sessions of the American Diabetes Association; June 9-13, 2000; San Antonio, Texas.
- 44. Benbow A, Stewart M, Yeoman G.** Thiazolidinediones for type 2 diabetes. All glitazones may exacerbate heart failure. *BMJ* 2001;322:236.
- 45. UK Prospective Diabetes Study (UKPDS) Group.** Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:839-855.
- 46. Mudaliar S, Henry RR.** Combination therapy for type 2 diabetes. *Endocr Pract* 1999;5:208-219.
- 47. Goldberg RB.** Cardiovascular disease in diabetic patients. *Med Clin North Am* 2000;84:81-93.
- 48. American Diabetes Association.** Aspirin therapy in diabetes mellitus. *Diabetes Care* 2001;24(suppl 1):S62-S63.
- 49. Legro RS, Finegood D, Dunaif A.** A fasting glucose to insulin ratio is a useful measure of insulin sensitivity in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 1998;83:2694-2698.
- 50. Dunaif A, Scott D, Finegood D, Quintana B, Whitcomb R.** The insulin-sensitizing agent troglitazone improves metabolic and reproductive abnormalities in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 1996;81:3299-3306.
- 51. Ehrmann DA, Schneider DJ, Sobel BE, Cavaghan MK, Imperial J, Polonsky KS.** Troglitazone improves defects in insulin action, insulin secretion, ovarian steroidogenesis, and fibrinolysis in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 1997;82:2108-