

# Management of type 2 diabetes mellitus

## *Role of thiazolidinediones*

Jason Noble   Mark O. Baerlocher   Jay Silverberg, MD, FRCPC, FACP

### ABSTRACT

**OBJECTIVE** To review evidence supporting use of thiazolidinediones (TZDs) in management of type 2 diabetes mellitus (DM2).

**QUALITY OF EVIDENCE** A MEDLINE search found several randomized controlled trials (level I evidence). No systematic reviews of these trials were found in the Cochrane Library.

**MAIN MESSAGE** Thiazolidinediones lower hemoglobin A<sub>1c</sub> levels by as much as 1.0% to 1.5%. Effects can be seen in as little as 4 weeks, but full lowering takes 6 to 12 weeks. When used in combination with other diabetic agents, such as sulfonylureas and biguanides, TZDs' hypoglycemic effects appear to be complementary. Thiazolidinediones directly improve insulin sensitivity and recovery of pancreatic beta cell function. Nevertheless, there is no evidence indicating that TZDs are superior to other antidiabetic agents currently available or that TZDs reduce the long-term complications of DM2.

**CONCLUSION** Ongoing trials will further define the role of TZDs in management of diabetic patients. In current practice, cost is often a factor in the decision to prescribe TZDs.

### RÉSUMÉ

**OBJECTIF** Faire le point sur les données qui appuient l'utilisation des thiazolidinediones (TZD) dans le traitement du diabète de type 2 (D2).

**QUALITÉ DES PREUVES** Une recherche dans MEDLINE a permis de repérer plusieurs essais randomisés (preuves de niveau I). On n'a trouvé aucune revue systématique de ces essais dans la Cochrane Library.

**PRINCIPAL MESSAGE** Les TZD abaissent les niveaux d'hémoglobine A<sub>1c</sub> de 1,0-1,5%. Une baisse peut déjà être observée après 4 semaines, mais il faut de 6 à 12 semaines pour un effet complet. Lorsqu'on les combine avec d'autres anti-diabétiques comme les sulfonylurées et les biguanides, les TZD semblent avoir un effet hypoglycémiant complémentaire. Ils améliorent directement la sensibilité à l'insuline et aident au rétablissement de l'activité des cellules bêta du pancréas. Il n'y a toutefois pas de preuve qu'ils sont supérieurs aux autres anti-diabétiques actuellement disponibles ou qu'ils diminuent les complications à long terme du D2.

**CONCLUSION** La poursuite des essais permettra de définir la place des TZD dans le traitement du diabète. En pratique courante, le coût des TZD intervient souvent dans la décision de les prescrire.

This article has been peer reviewed.

Cet article a fait l'objet d'une évaluation externe.

*Can Fam Physician* 2005;51:683-687.

**T**ype 2 diabetes mellitus (DM2) is a chronic, progressive disease characterized by insulin resistance and pancreatic beta islet cell failure. Three specific abnormalities contribute to hyperglycemia in DM2: impaired insulin secretion, increased hepatic glucose production, and decreased insulin-stimulated uptake of glucose in peripheral tissues.

The United Kingdom Prospective Diabetes Study (UKPDS) showed that strict blood glucose control decreases the likelihood of complications from DM2.<sup>1</sup> Current management relies on controlling hyperglycemia, dyslipidemia, and hypertension. Although diet and exercise remain the cornerstone of managing hyperglycemia, single or combination antihyperglycemic agents are indicated if treatment targets are not met quickly (ie, within 2 to 3 months) as recommended by the Canadian Diabetes Association guidelines.<sup>2</sup>

Biguanides (eg, metformin) are first-line agents for glycemic control in DM2.<sup>2</sup> These agents act primarily by inhibiting hepatic gluconeogenesis and sensitizing hepatic and peripheral tissues to insulin. Biguanides have the added benefit of inducing weight loss and improving lipid profiles, which are desirable goals in most patients with DM2.<sup>3</sup> The UKPDS was the cornerstone investigation demonstrating that metformin significantly reduces the microvascular and macrovascular complications of DM2.<sup>3</sup> The virtues of metformin aside, combination therapy is often required to achieve adequate glycemic control.

In fact, recent Canadian Diabetes Association guidelines advocate for increased use of combination therapy<sup>2</sup> because using a combination of agents that act through different mechanisms might be superior to using a maximal dose of a single agent. Typically, when monotherapy fails, metformin is paired with a second agent, such as a sulfonylurea.

Thiazolidinediones (TZDs) have emerged recently as promising antidiabetic agents.<sup>4</sup> They offer a new

angle of attack in the pharmacologic management of DM2. They act primarily by decreasing insulin resistance in peripheral tissues, an aspect of DM2 not addressed by biguanide and sulfonylurea therapy. On a molecular level, TZDs act by binding to nuclear peroxisome proliferator-activated receptor-gamma cells in muscle, liver, and adipose tissue, facilitating uptake of glucose in the periphery and decreasing hepatic gluconeogenesis.<sup>4</sup> Also, both experimental and clinical evidence suggests that TZDs induce recovery of pancreatic beta cells and thereby improve insulin secretion.<sup>5,6</sup> In theory, since TZDs act by reducing insulin resistance (an underlying pathophysiologic feature of DM2), TZDs could have a crucial role in managing hyperglycemia and reducing complications of DM2.

As promising as TZDs are, they are relatively expensive, a factor that affects their role in management of diabetic patients. In this article, we review evidence supporting use of TZD antihyperglycemic agents, specifically rosiglitazone (Avandia) and pioglitazone (Actos), for treatment of DM2.

### Quality of evidence

MEDLINE was searched using the MeSH terms diabetes mellitus, type 2; treatment; pioglitazone; rosiglitazone; troglitazone; and randomized controlled trials. Also, the Cochrane Database of Systematic Reviews was searched using the same headings for systematic reviews and meta-analyses. No systematic reviews were found; several randomized controlled trials (RCTs) were found. Current evidence suggests that TZDs have a role in controlling hyperglycemia in patients with DM2. They can be used as first-line drugs, but national guidelines recommend them as second-line drugs. The RCTs reviewed were grouped into four areas: TZDs as monotherapy, TZDs compared with metformin, TZDs in combination with metformin, and TZDs in combination with sulfonylureas.

### Thiazolidinediones as monotherapy

Herz et al looked at the effectiveness of pioglitazone at doses of 30 and 45 mg in 297 patients with DM2.<sup>7</sup> The study demonstrated that 30 mg and 40 mg of pioglitazone were associated with a 0.8%

---

Mr Noble and Mr Baerlocher are students in the Faculty of Medicine at the University of Toronto in Ontario. Dr Silverberg teaches in the Department of Endocrinology at Sunnybrook and Women's College Health Sciences Centre in Toronto.

and 0.9% fall in HbA<sub>1c</sub>, respectively, at 16 weeks. Fasting serum insulin levels were also reduced, and insulin sensitivity was increased (as measured by the homeostasis model<sup>8</sup>). The homeostasis model is a method of evaluating insulin resistance that has been shown to be valid and reliable in several studies demonstrating good correlation (correlation coefficient 0.6 to 0.8) to criterion standard clamp studies.<sup>8-10</sup> Lipid profiles also seemed to improve, with increases in high-density lipoprotein (HDL) of 16% and 20% and reductions in triglycerides of 5% and 16%, respectively. Severe adverse reactions observed included edema, headache, pharyngitis, arthralgia, and increased body weight.

The largest trial investigating the role of rosiglitazone looked at the effect of 4- and 8-mg doses given to 959 patients for 26 weeks.<sup>11</sup> This study showed 0.8% and 1.5% reductions in HbA<sub>1c</sub> levels in the 4- and 8-mg groups, respectively. One third of patients achieved HbA<sub>1c</sub> levels <7% by the end of the study. Reductions in fasting plasma glucose were also observed. Statistically significant increases in weight and serum lipids were observed in all treatment groups and appeared to be dose related.

### Thiazolidinediones compared with metformin

A double-blind, 32-week RCT compared pioglitazone (30 mg to 45 mg) head-to-head with 850 mg to 2550 mg of metformin<sup>12</sup> in 205 patients. Pioglitazone and metformin were found equally effective in controlling blood glucose levels; both agents demonstrated a 3-mmol/L decrease in fasting blood glucose and a 1.3% decrease in HbA<sub>1c</sub> levels. Pioglitazone was associated with a 17% increase in insulin sensitivity; metformin was associated with a 9% increase. Fasting serum insulin levels decreased by 23% in the pioglitazone group but by only 1% in the metformin group. Pioglitazone raised HDL levels substantially more than metformin (0.22 vs 0.13 mmol/L). Metformin was associated with a significant decrease in low-density lipoprotein (LDL) (-0.2 mmol/L) not observed in the pioglitazone group. Pioglitazone was associated with a 0.7-kg gain in weight; metformin induced a 2.4-kg weight loss.

### Thiazolidinediones in combination with metformin

In a 16-week RCT, researchers compared treatment with pioglitazone (30 mg) plus metformin with placebo plus metformin in 249 patients with poorly controlled DM2 (HbA<sub>1c</sub> >8%).<sup>13</sup> Patients receiving the pioglitazone-metformin combination had lower HbA<sub>1c</sub> levels (0.83% decline), lower triglyceride levels (-9.7% vs +8.5%), increased HDL levels (+10.2% vs 1.5%), decreased insulin resistance (-16% vs +17.6%), and improved beta cell function (45% vs 39%) compared with the placebo plus metformin group at the study end point (homeostasis model for beta cell function). Adverse reactions in the pioglitazone group included edema (6%), increased body weight (average of 1 kg), and a slight decrease in hemoglobin and hematocrit levels.

Fonseca et al investigated the effect of rosiglitazone in combination with metformin in a 348-patient multicentre RCT.<sup>14</sup> Patients were randomized into three groups: 2500 mg of metformin plus placebo, 2500 mg of metformin plus 4 mg of rosiglitazone, and 2500 mg of metformin plus 8 mg of rosiglitazone. Hemoglobin A<sub>1c</sub> levels came down significantly in those receiving rosiglitazone, decreasing by 1.0% and 1.2% in the 4-mg and 8-mg groups, respectively. Reductions in fasting plasma insulin levels were noted in the rosiglitazone groups, along with improved insulin sensitivity (3.5% and 8% in the 4-mg and 8-mg groups, respectively). Pancreatic beta cell function improved by approximately one third in the rosiglitazone groups according to the homeostasis model. Significant increases in body weight and LDL levels (20%) were observed.

### Thiazolidinediones in combination with sulfonylureas

Kipnes et al conducted a 16-week, double-blind RCT of 478 patients to determine the effect of pioglitazone in combination with sulfonylurea agents.<sup>15</sup> Patients were allocated to three groups: 15 mg pioglitazone and sulfonylurea, 30 mg pioglitazone and sulfonylurea, and placebo plus sulfonylurea. Patients in the pioglitazone with sulfonylurea arm had significant, dose-related improvements in glycemic and lipid control compared with the

sulfonylurea monotherapy group. For the 15-mg and 30-mg pioglitazone groups, HbA<sub>1c</sub> levels decreased (-0.8% and -1.2%), fasting serum insulin levels fell (10.6% and 16.4%), triglyceride levels fell (6.4 and 15.9%), and HDL levels rose (5.0% and 12%). No significant change in LDL was noted in the pioglitazone groups.

## Discussion

Level I evidence clearly and consistently demonstrates that TZDs are effective in controlling hyperglycemia in patients with DM2. They significantly reduce fasting blood glucose, fasting insulin, and HbA<sub>1c</sub> levels whether they are used as monotherapy or in combination with metformin or sulfonylureas. There is some indication but no clear evidence that pioglitazone, in particular, seems to induce other secondary beneficial effects, including increasing HDL levels, decreasing triglyceride levels, and lowering blood pressure. Despite these favourable features, TZDs have also been shown to be associated with adverse effects. Most importantly, TZDs can cause fluid retention (especially when combined with insulin) and are contraindicated in patients with a history of congestive heart failure. Other adverse effects include weight gain (range 0.9 to 2.6 kg) and decreased hematocrit levels.

Current evidence suggests that TZDs have a role in treatment of hyperglycemia among patients with DM2. They are approved for use as first-line drugs, but national guidelines recommend them as second-line therapy.<sup>2</sup> The advantages of TZDs, including once-a-day dosing and potent antihyperglycemic effects, make them attractive therapeutic agents. But TZDs have not been shown to be superior to other diabetic medications, and most importantly, no long-term data currently exist, meaning that there is no evidence that TZDs reduce the microvascular and macrovascular complications of DM2.

Metformin, therefore, should remain the first-line therapy. For now, TZDs can be used in combination therapy for cases not adequately controlled with biguanide and sulfonylurea regimens. Patients started on TZDs should be monitored for signs of edema and anemia, and liver enzymes should be checked at initiation of TZD therapy and periodically thereafter according to the product monograph.

Cost is a concern when implementing TZD therapy. Because TZDs are the most recent important advance in DM2 care, they are relatively expensive (Table 1). In cost-benefit analyses, recent reports using economic models suggest that TZDs could reduce rates of complications by 23% to 36% and thereby be cost-effective treatment.<sup>16</sup> Actual cost-effectiveness depends on whether TZDs actually do have beneficial cardiovascular effects.

**Table 1.** Cost comparison of popular antihyperglycemic medications (Canadian dollars)

MEDICATION AND DOSE	COST PER TABLET (\$)	MONTHLY COST (\$)
Metformin, 500 mg three times daily	0.12	10.80
Glyburide, 5 mg twice daily	0.07	4.10
Rosiglitazone	1.93	57.90
Pioglitazone	2.05	61.50

Source: Canadian Generic Pharmaceutical Association and the Sunnybrook and Women's College Health Sciences Centre drug inventory requisition


If clinicians decide to institute TZD therapy, which TZD should they use? To date, no comparative head-to-head trials show one TZD superior to the next. Current literature does, however, highlight differences among available TZDs.<sup>17,18</sup> Pioglitazone is associated with the largest weight gain. Rosiglitazone might cause elevations in both LDL and triglyceride levels, although these effects appear to respond well to statin therapy.<sup>19</sup> Because of the unique features of the available TZD agents, patients must be assessed on an individual basis to determine which agent is best in each case.

One of the hopes for TZDs is that, by reducing insulin resistance, they could raise the bar on DM2 therapy, going beyond blood glucose control to address underlying pathophysiologic processes. Since insulin sensitivity is an independent risk factor of vascular disease, diabetic agents that are mechanistically aimed at improving insulin sensitivity could theoretically reduce the vascular complications of DM2, although this has yet to be proven. Some data even suggest that improving insulin sensitivity has beneficial vascular effects independent of glycemic control.<sup>20</sup>

There is evidence that TZDs reduce urinary albumin excretion and levels of acute phase reactants,

such as C-reactive protein, and that these effects correlate with reduced insulin resistance.<sup>21,22</sup> As patients with DM2 are at much higher risk of vascular disease than others in the general population, TZDs might have an important role in managing these patients.<sup>18</sup> It must be kept in mind, though, that there is as yet no evidence that TZDs reduce rates of cardiovascular events.

## Conclusion

Thiazolidinediones are effective in controlling hyperglycemia in patients with DM2, both as monotherapy and in combination therapy. The proposed beneficial secondary effects of TZDs are attractive but as yet unproven. Ongoing trials investigating whether the antihyperglycemic and insulin-sensitizing effects of TZDs translate into a reduction in long-term complications of DM2 will determine whether their unique mechanism of action imparts a clinically beneficial effect on patient outcomes. 

**Correspondence to:** Dr Jay Silverberg, Sunnybrook and Women's College Health Sciences Centre, 2075 Bayview Ave, Suite H-149, Toronto, ON M4N 3M5

## References

- 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;352:837-53.
- Canadian Diabetes Association. Recommendations from the Canadian Diabetes Association. 2003 guidelines for prevention and management of diabetes and related cardiovascular risk factors *Can Fam Physician* 2004;50:425-33. Available at <http://www.diabetes.ca>. Accessed 2005 February 10.
- UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854-65.
- Parker JC. Troglitazone: the discovery and development of a novel therapy for the treatment of type 2 diabetes mellitus. *Adv Drug Deliv Rev* 2002;54(9):1173-97.
- Ovalle F, Bell DS. Clinical evidence of thiazolidinedione-induced improvement of pancreatic beta-cell function in patients with type 2 diabetes mellitus. *Diabetes Obesity Metab* 2002;4(1):56-9.
- Juhl CB, Hollingdal M, Porksen N, Prange A, Lonngvist F, Schmitz O. Influence of rosiglitazone treatment on beta-cell function in type 2 diabetes: evidence of an increased ability of glucose to entrain high-frequency insulin pulsatility. *J Clin Endocrinol Metab* 2003;88(8):3794-800.
- Herz M, Johns D, Reviriego J, Grossman LD, Godin C, Duran S, et al. A randomized, double-blind, placebo-controlled, clinical trial of the effects of pioglitazone on glycemic control and dyslipidemia in oral antihyperglycemic medication-naïve patients with type 2 diabetes mellitus. *Clin Ther* 2003;25(4):1074-95.
- Matthews DR, Hosker JB, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412-9.
- Emoto M, Nishizawa Y, Maekawa K, Hiura Y, Kanda H, Izumotani K. Homeostasis model assessment as a reliable index of insulin resistance in type 2 diabetic patients treated with sulphonylureas. *Diabetes Care* 1999;22:818-22.
- Katsuki A, Sumida Y, Gabazza EC, Murashima S, Furuta M, Araki-Sasaki R, et al. Homeostasis model assessment is a reliable indicator of insulin resistance during follow-up of patients with type 2 diabetes. *Diabetes Care* 2001;24(2):362-5.
- Phillips LS, Grunberger G, Miller E, Patwardhan R, Rappoport EB, Salzman A, et al. Once- and twice-daily dosing with rosiglitazone improves glycemic control in patients with type 2 diabetes. *Diabetes Care* 2001;24(2):308-15.
- Pavo I, Jermendy G, Varkonyi TT, Kerenyi Z, Gyimesi A, Shoustov S, et al. Effect of pioglitazone compared with metformin on glycemic control and indicators of insulin sensitivity in recently diagnosed patients with type 2 diabetes. *J Clin Endocrinol Metab* 2003;88(4):1637-45.
- 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. The Pioglitazone 027 Study Group. *Clin Ther* 2000;22(12):1395-409.
- Fonseca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus. *JAMA* 2000;283:1695-702.
- Kipnes MS, Krosnick A, Rendell MS, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. *Am J Med* 2001;111(1):10-7.
- Coyle D, Palmer AJ, Tam R. Economic evaluation of pioglitazone hydrochloride in the management of type 2 diabetes mellitus in Canada. *Pharmacoeconomics* 2002;20(Suppl 1):31-42.
- King AB. A comparison in a clinical setting of the efficacy and side effects of three thiazolidinediones. *Diabetes Care* 2000;23(4):557.
- Yale JE, Valiquett TR, Ghazzi MN, Owens-Grillo JK, Whitcomb RW, Foyt HL. The effect of a thiazolidinedione drug, troglitazone, on glycemia in patients with type 2 diabetes mellitus poorly controlled with sulfonylurea and metformin. A multicenter, randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001;134(9 Pt 1):737-45.
- Freed MI, Ratner R, Marcovina SM, Kreider MM, Biswas N, Cohen BR, et al. Effects of rosiglitazone alone and in combination with atorvastatin on the metabolic abnormalities in type 2 diabetes mellitus. *Am J Cardiol* 2002;90(9):947-52.
- Rewers M, Zaccaro D, D'Agostino R, Haffner S, Saad ME, Selby JV, et al. Insulin sensitivity, insulinemia, and coronary artery disease: the Insulin Resistance Atherosclerosis Study. *Diabetes Care* 2004;27(3):781-7.
- Bakris G, Viberti G, Weston WM, Heise M, Porter LE, Freed MI. Rosiglitazone reduces urinary albumin excretion in type II diabetes. *J Hum Hypertens* 2003;17(1):7-12.
- Sidhu JS, Cowan D, Kaski JC. The effects of rosiglitazone, a peroxisome proliferator-activated receptor-gamma agonist, on markers of endothelial cell activation, C-reactive protein, and fibrinogen levels in non-diabetic coronary artery disease patients. *J Am Coll Cardiol* 2003;42(10):1757-63.

## EDITOR'S KEY POINTS

- In current practice, oral hypoglycemics are first-line agents for treating diabetes. Metformin is first choice and sulphonylureas (glyburide) second choice when monotherapy fails.
- Recently a new class of oral hypoglycemics, the thiazolidinediones (TZDs)—rosiglitazone (Avandia) and pioglitazone (Actos)—have been introduced. These agents decrease insulin resistance in peripheral tissues.
- Thiazolidinediones are effective as monotherapy, and their once-daily dosing regimen is convenient. They might have secondary beneficial effects on lipids, but no long-term data show they reduce complications of diabetes, and they are costly.
- Thiazolidinediones can be used as second-line treatment or in an initial combination treatment when a metformin-glyburide combination has been ineffective. Physicians should watch their patients for fluid retention (congestive heart failure) and liver complications.

## POINTS DE REPÈRE DU RÉDACTEUR

- Les hypoglycémisants oraux sont couramment utilisés comme traitement de première intention du diabète. La metformine est le premier choix et les sulfonylurées (glyburide) le second en cas d'échec de la monothérapie.
- Récemment, une nouvelle classe d'hypoglycémisants oraux, les thiazolidinediones (TZD) crosiglitazone (Avandia) et pioglitazone (Actos), est apparue. Ces agents diminuent la résistance à l'insuline dans les tissus périphériques.
- Les thiazolidinediones sont efficaces en monothérapie et leur posologie quotidienne unique est pratique. Ils pourraient avoir des effets secondaires avantageux sur les lipides, mais ils sont coûteux et on n'a pas démontré qu'ils réduisent les complications à long terme du diabète.
- Les thiazolidinediones peuvent être utilisés comme agents de seconde intention ou pour débiter un traitement combiné lorsque la combinaison metformine-glyburide a été inefficace. Rétention liquidienne (insuffisance cardiaque) et atteinte hépatique sont des complications à surveiller.