Oral Hypoglycemic Agents:

What's New?

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Case Study

A 48-year-old non-smoking Caucasian male has been diagnosed with Type 2 diabetes for ten years. He has no other medical problems and, to his knowledge, has not developed any micro- or macro-vascular complications from his disease. After lifestyle modifications failed, metformin was added two years after the diagnosis. His glycosylated hemoglobin A1c (HbA1c) ranged between 6% to 8% over the next three years but subsequently increased despite maximal doses of metformin. Sulfonylurea (glyburide) was added to the regimen four years ago. He is currently on metformin, 1 g bid and glyburide, 10 mg bid. After the initial improvement with glyburide, his last three HbA1c readings over the preceding year have ranged between 8% to 9.5%. He is compliant with his diet and exercises at least 30 minutes, three times a week. His family history is remarkable for Type 2 diabetes in his father and one paternal uncle. The patient wishes to improve his glycemic control but is reluctant to start insulin therapy.

Patient Stats

Blood Pressure	136/78 mmHg
Body Mass Index	33
Electrolytes	Normal
Renal Function	Normal
Liver Enzymes	Normal
Fasting Glucose	8.7 mmol/L
HbA1c	8.8%
Total Cholesterol	5.85 mmol/L
Triglycerides	3.76 mmol/L
Low-Density Lipoprotein	2.87 mmol/L
High-Density Lipoprotein	1.5 mmol/L
Urine Microalbumin	22 g/l (0-19)
Pre-proliferative retinopathy on fundoscopy	
Presence of intact sensation to 10 g monofilament and vibration testing.	

In 1986, there were approximately 1.5 million people with diabetes in Canada. This figure is projected to increase to 3 million by 2010. In reality, this figure is an underestimate, as a significant number of individuals who have diabetes remain undiagnosed. The cause of this epidemic is multifactorial, including increased awareness and screening, obesity, sedentary lifestyle, poor eating habits, and, last but not

Table 1
Diagnostic Criteria for Diabetes and Glucose Intolerance

Category	Fasting plasma glucose mmol/L	Prostglandin two hours after 75 g glucose load mmol/L
Normal	< 6.0	< 7.8
Impaired fasting glucose	6.1-6.9	< 7.8
Impaired glucose tolerance	< 7.0	7.8-11.0
Diabetes Mellitus	> 7.1	>11.1

least, a continuous reassessment and reduction of threshold glucose levels used to diagnose diabetes.

In 1998, the diagnostic criteria for diabetes was revised and a fasting glucose of greater than 7 mmol/L was recommended to classify individuals with diabetes instead of the previous threshold of 7.8 mmol/L (Table 1). This revision was done because of the realisation that by using a fasting glucose cut-off of 7.8 mmol/L, a significant number of individuals, who otherwise would have been diagnosed with diabetes based on a two-hour glucose level from an oral glucose tolerance test, were being missed. As more information is being accumulated, it is becoming clear that the risk for micro-vascular and macro-vascular complications increases at levels of blood glucose much lower than what we believe, and, in all probability, a further revision of the diagnostic criteria in the future will be seen.

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What is Type 2 diabetes?

Both insulin resistance and defective insulin secretion are important in the development of Type 2 diabetes. Insulin resistance occurs at multiple sites, such as the skeletal muscle, adipocytes, and liver. Hyperglycemia further reduces insulin secretion from the pancreas through an effect known as glucotoxicity. The defects in insulin sensitivity and

insulin resistance are demonstrable several years before the onset of overt hyperglycemia. It is postulated that at the time of diagnosis, both insulin sensitivity and insulin secretion are reduced by as much as 50%. Although an oversimplification, insulin resistance may be viewed as the primary pathophysiologic defect in overweight or obese diabetics, whereas insulin deficiency appears to be the predominant defect in lean Type 2 diabetics. This mechanistic distinction is important in choosing the appropriate therapeutic agent. Interestingly, central obesity is related more to insulin resistance than the total body mass index (BMI) and an individual with a waist circumference of more than 90 cm can be assumed to have some degree of insulin resistance.

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What are the newer oral hypoglycemic agents?

The last few years have witnessed a remarkable increase in our armamentarium for treating Type 2 diabetes. Newer, once-a-day, slow release formulations of sulfonyureas, such as gliclazide MR and glymeperide, have been launched, which provide 24-hour glycemic control with perhaps a lesser risk of hypoglycemia and weight gain. Non-sulfonylurea

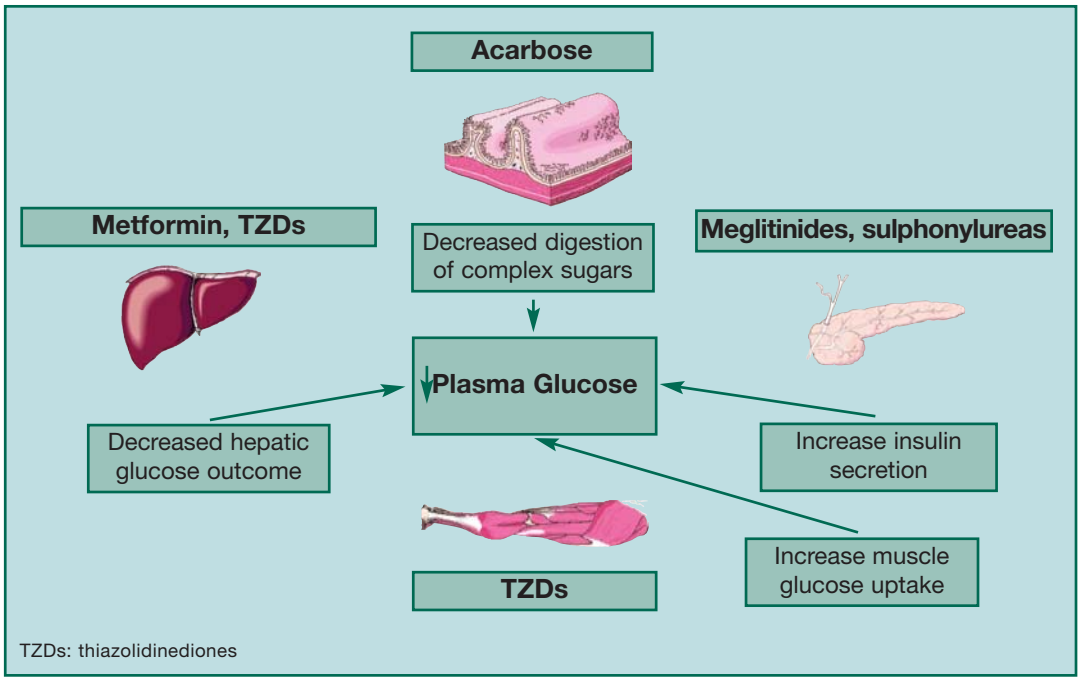

Figure 1. Sites of action of the oral hypoglycemic agents (OHAs).

insulin secretagogues, such as repaglinide and, more recently, nateglinide, to target postprandial hyperglycemia and insulin sensitisers, such as rosiglitazone and pioglitazone, have become available. From studies, such as the U.K. Prospective Diabetes Study, we have learned that the bottom line is intensive diabetes management. How we achieve that goal may not necessarily be important. One class of oral hypoglycemics is not necessarily better or more potent than the other. However, there are significant differences in the various classes of agents available in terms of their mechanisms of action, side-effects profile, and non-glycemic effects that can be exploited to suit an individual patient (Figure 1).

How do thiazolidinediones work?

The thiazolidinediones (TZDs) are an attractive option to treat patients with Type 2 diabetes, either as monotherapy or in combination with other oral hypoglycemic agents (OHAs). They have a unique mechanism of action and are generally safe and well-tolerated. It is argued that the thiazolidinediones are the first true insulin sensitisers. Although metformin is usually regarded as an insulin sensitiser, purists would argue that as metformin primarily inhibits hepatic glucose output, it is not necessarily an insulin sensitiser in

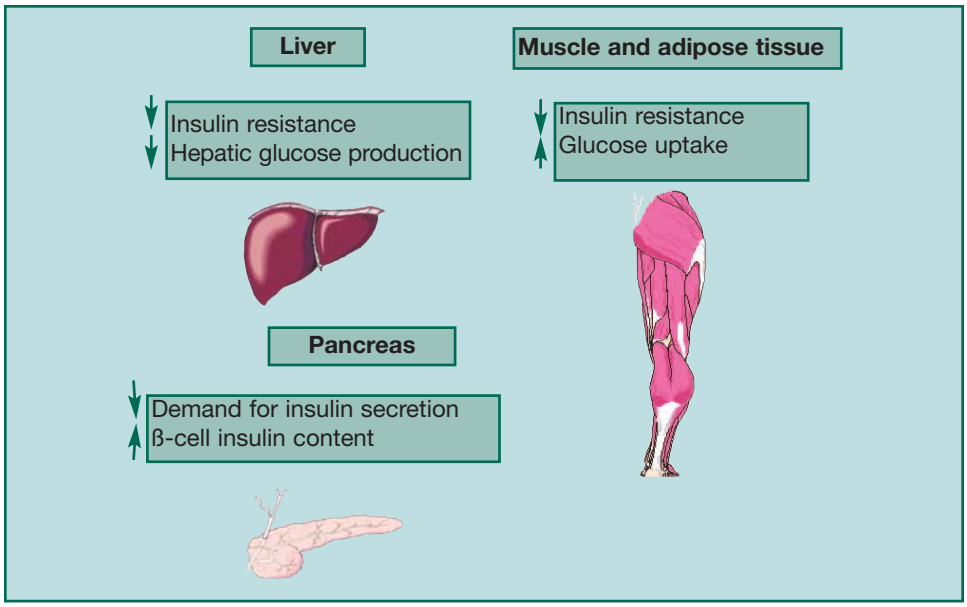

Figure 2. Effects/mechanism of action of thiazolidinediones.

the true sense of the word. The TZDs act as agonists on the perioxisome proliferator activated receptors (PPAR). They act primarily at the PPAR γ receptors, which are present on several tissues, such as the skeletal muscle, liver adipose tissue, heart, and kidney. They stimulate the transcription of various genes and cause protean effects including increase in glucose uptake, gluconeogenesis, adipocyte differentiation and fatty acid uptake (Figure 2). Beneficial effects on endothelial function, blood pressure, urinary albumin excretion and fibrinolysis have also been described.

Troglitazone was the first TZD available, which was subsequently withdrawn because of several cases of fulminant hepatotoxicity. Rosiglitazone was the second and pioglitazone was the next TZD available. They are similar in many respects, however, differences between these agents have emerged, primarily with respect to their nonglycemic effects. These differences may be due to the activation of other PPAR receptors (α,β) and activation/inhibition of different genes. As far as their antihyperglycemic effect is concerned, it is postulated to be secondary to an increase in the production and recruitment of glucose transporter 4 (Glut 4) molecules, which help to stimulate glucose uptake into the cells, primarily in the skeletal muscles.

What is the efficacy of TZDs?

In terms of their glycemic effects, both rosiglitazone and pioglitazone are comparable. A 1.5% to 2% reduction in HbA1c in drug naïve patients and 1%, and 1.5% reduction in previously treated patients can be expected.

The non-glycemic effects of the TZDs, particularly the effects on lipids, have been a focus of recent interest. Rosiglitazone, in general, has been shown to have either a neutral effect on triglycerides or causes a slight increase in their levels. Pioglitazone has been demonstrated to decrease triglyceride levels by up to 25%. Rosiglitazone may cause an elevation of low-density lipoprotein (LDL) cholesterol, whereas pioglitazone has a neutral effect. However, most of the increase in LDL with rosiglitazone is accounted for by the large buoyant LDL particles, which supposedly are not atherogenic. Both these agents have been shown to increase high-density lipoprotein (HDL) levels as much as 15%. Whether these effects on lipids are clinically relevant or not is a matter of much speculation.

A TZD would be a good choice for the patient in the case study, either rosiglitazone 4 mg a day or pioglitazone 15 mg a day can be added to his metformin and glyburide.

What are the side effects of TZDs?

The main side effects seen in clinical practice are those related to fluid retention and weight gain. Fluid retention may manifest as lower extremity edema, hemodilution-anemia, and in susceptible individuals, congestive heart failure (CHF). These agents should be used cautiously, if at all, in patients with or at risk of CHF. The prevalence of edema occurs in up to 6% of patients treated with TZDs and can occur in up to 15% of patients in whom TZDs are combined with insulin. A low sodium diet may reduce the frequency and severity of the fluid retention.

Weight gain is another major side effect seen with the TZDs. An average of 2 kg to 4 kg of weight increase is seen in both rosiglitazone and pioglitazone. Part of the weight gain may be due to the fluid retention and partly due

to the mobilisation of fat from the intra-abdominal/visceral sites to the subcutaneous tissue. Recent data suggests that the PPAR agonists cause adipocyte differentiation and entrapment of the circulating fatty acids into the adipocytes through activation of the enzyme glycerol kinase. It would seem paradoxical that an agent that increases weight is associated with an improvement in insulin sensitivity. The mobilisation of fat from the abdominal/visceral sites (which is known to independently increase insulin resistance) to the extra-abdominal/subcutaneous sites may explain the paradox.

Hepatotoxicity is seen much less frequently with newer TZDs as compared to troglitazone. Elevation of aminotransferases greater than three times the upper limit of normal is seen in less than 0.5% of patients on the newer TZDs. These agents should not be used in patients with known liver disease. In other patients, it is recommended to monitor liver enzymes every two months while on therapy.

What are the indications of TZDs?

Both rosiglitazone and pioglitazone, as monotherapy, are approved for treatment of Type 2 diabetes. Rosiglitazone is also approved in combination with sulfonylureas and metformin. Because of concerns with fluid retention and precipitation of CHF in susceptible individuals, combination with insulin is neither approved nor recommended. The starting dose of rosiglitazone is 4 mg once a day and pioglitazone 15 mg once a day. The maximum effective dose of rosiglitazone is 4 mg twice daily, and of pioglitazone is 45 mg once a day. Several weeks are often required to see the complete effects of these medications and, as such, the dose should be increased after at least six to eight weeks if required.

Unfortunately, these medications are expensive and are subject to provincial formulary restrictions. At this time, I generally limit their use as second- or

third-line agents in patients who have not reached their targets with metformin and/or insulin secretagogues. A TZD would be a good choice for the patient in the case study, either rosiglitazone 4 mg a day or pioglitazone 15 mg a day can be added to his metformin and glyburide. As the patient also has hypertriglyceridemia, I may prefer the use of pioglitazone in this particular patient.

Take-home message

The TZDs are a relatively new class of OHAs and their mechanism of action makes them an attractive choice for use in patients with Type 2 diabetes. As their non-glycemic effects, such as the beneficial effects on lipids, blood pressure, urinary albumin excretion, C-reactive protein, plasminogen activator inhibitor, and endothelium are being elucidated, their use is likely to increase in the future. They may even have a role in the prevention of Type 2 diabetes in individuals at risk. Rosiglitazone has been demonstrated to increase the amount of insulin in the beta cells of diabetic rats, thus suggesting a beta cell sparing effect. Troglitazone has been demonstrated to reduce the development of Type 2 diabetes by about 50% in high-risk patients. With the current interest in preventing or delaying the onset of Type 2 diabetes in high-risk individuals, studies, such as the Diabetes Reduction Assessing Medications (DREAM) study, are in progress, which will likely provide answers to these questions. Dx

Suggested Readings
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4. Khan MA, St. Peter JV, Xue JL: A prospective randomized comparison of the metabolic effects of pioglitazone or rosiglitazone in patients with type 2 diabetes who were previously treated with troglitazone. Diab Care 2002; 25(4): 798-11.
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