Taking on Type 2 Diabetes

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Both insulin resistance and defective insulin secretion are important in the pathogenesis of Type 2 diabetes. Insulin resistance is characterized by an inefficient cellular response to endogenous or exogenous insulin. The exact cause of insulin resistance is unknown, but post-receptor defects in signaling are most likely involved. Insulin resistance occurs at multiple sites, such as the skeletal muscle, adipocytes, and liver. The defects in insulin sensitivity and insulin resistance are demonstrable several years before the onset of overt hyperglycemia, and it is postulated that at the time of diagnosis, both insulin sensitivity and insulin secretion are reduced by as much as 50%. Insulin resistance is not specific for Type 2 diabetes, but has demonstrated to be present in:

- polycystic ovary syndrome (PCOS),
- obesity,
- metabolic syndrome,
- hypertension; and
- normoglycemic relatives of patients with Type 2 diabetes.

Although an oversimplification, insulin resistance may be viewed as the primary pathophysiologic/mechanistic defect in overweight/obese diabetic patients, whereas insulin deficiency appears to be the predominant defect in lean patients with Type

Janice's diabetes

You are caring for Janice, 50, who is caucasian and was diagnosed with Type 2 diabetes 10 years ago. Janice also has a history of hypertension and dyslipidemia.

After lifestyle modifications failed, metformin was added three years after the diagnosis. Her hemoglobin $A1_c$ level ranged between 6-8% over the next four years, but subsequently increased despite maximal doses of metformin. You added glyburide to the regimen five years after the diagnosis.

The doses of metformin and glyburide have been progressively increased, and at this time Janice is on 2 g/day of metformin and 20 mg/day of glyburide. She is also on an angiotensin-converting enzyme inhibitor and a statin. Her last three hemoglobin $A1_c$ readings over a one-year period have ranged between 8-9.5%. She is compliant with her diet and exercise. Her family history is remarkable for Type 2 diabetes in her father and one maternal uncle.

Janice wishes to improve her glycemic control, but is reluctant to start insulin therapy.

For Janice's examination, see page 59.

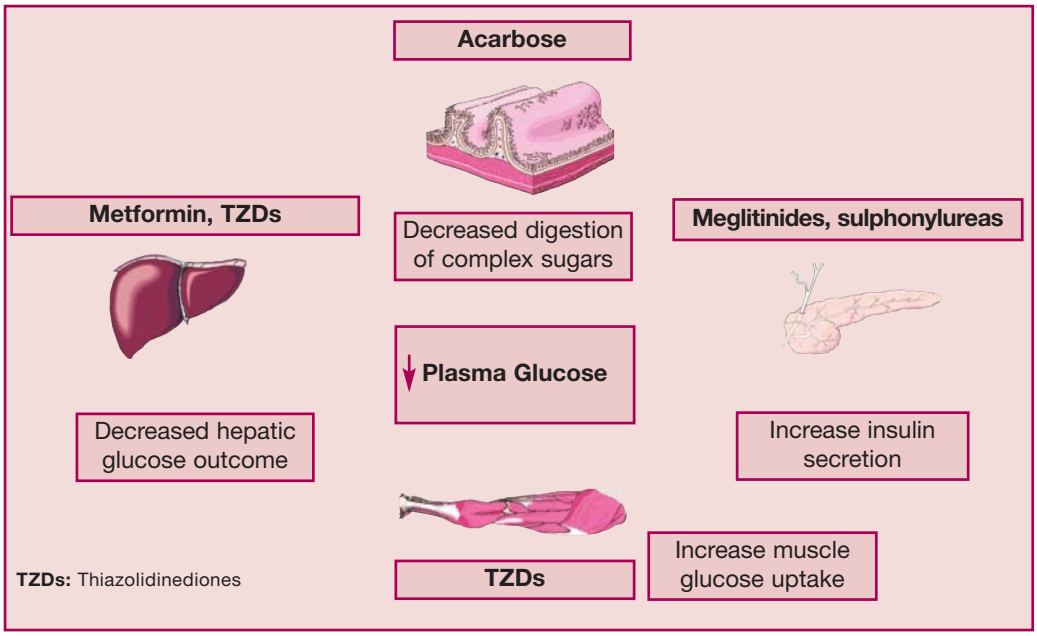

Figure 1. Sites of action of the oral hypoglycemic agents (OHAs).

2 diabetes. This pathophysiologic/mechanistic distinction may be important in choosing the appropriate therapeutic agent.

What's new with oral hypoglycemic agents?

A number of new oral hypoglycemic agents (OHAs) have become available in the last few years; newer, once-a-day slow-release formulations of sulphonyureas, such as gliclazide MR and glymeperide, are available. They provide 24-hour glycemic control with, perhaps, a lesser risk of hypoglycemia and weight gain. Non-sulphonylurea insulin secretagogues, such as repaglinide and nateglinide (specifically to target postprandial hyperglycemia), and insulin sensitizers, such as rosiglitazone and pioglitazone, are also available. 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-effect profile, and nonglycemic effects that can be exploited to suit the individual patient (Figure 1).

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How do TZDs work?

Thiazolidinediones (TZDs) are an attractive option to treat patients with Type 2 diabetes, either as monotherapy, or in combination with other OHAs. They have a unique mechanism of action, and are generally safe and well tolerated. TZDs act as agonists on the perioxysome proliferator activated receptors (PPAR). They act primarily at the PPARg 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, adiposite 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 and fatal hepatotoxicity. Rosiglitazone and pioglitazone were the next TZDs available. They are similar in many respects, however, differences between these agents have emerged, primarily with respect to their non-glycemic effects. These differences may be due to activation of other PPAR receptors (a, ß) and activation/inhibition of different genes. As far as their hypoglycemic 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.

How effective are TZDs?

Both rosiglitazone and pioglitazone are comparable in terms of their hypoglycemic effects and a 1.5% to 2% reduction in $HbA1_c$ in drug naïve patients, and 1% to 1.5% reduction in previously treated patients can be expected. The non-glycemic effects of TZDs, particularly the effects on blood pressure reduction, urinary albuminum excretion, endothelial dysfunction, and lipids have been a focus of recent interest. Whether these nonglycemic effects are clinically relevant or not is a matter of debate.

What are the side-effects?

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. These agents should be used cautiously, if at all, in patients with or at risk of chronic heart failure (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.

Janice's examination

On examination, pertinent findings include:

- Blood pressure of 128/76 mmHg
- Body mass index of 31
- Background retinopathy on fundoscopy
- Presence of intact sensation to 10-gram monofilament

Recent laboratory investigations show:

- Normal electrolytes, renal function, and liver enzymes
- Fasting glucose is 8.6 mmol/L
- $HbA1_c$ is 8.5%
- Lipid profile shows total cholesterol of 5.85 mmol/L
- Triglycerides 3.76 mmol/L
- Low-density lipoprotein 2.87 mmol/L
- High-density lipoprotein 1.15 mmol/L
- Urine microalbumin is 22 g/L (0-19)

Weight gain is another major side-effect seen with TZDs. An average of 2kg to 4 kg of weight increase is seen with both the agents.

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.

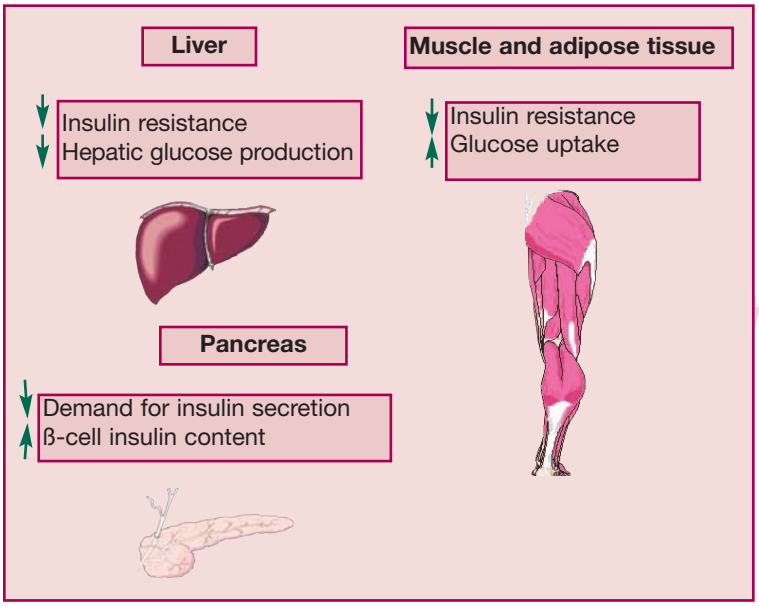

Figure 2. Effects/mechanism of action of thiazolidinediones.

What are the indications for TZDs?

Both rosiglitazone and pioglitazone are approved for treatment of Type 2 diabetes as monotherapy, and in combination therapy with sulfonylureas and metformin. They are not approved for use in conjunction with insulin in Canada. Due to concerns with fluid retention and the precipitation of CHF in susceptible individuals, the combination of TZDs and insulin should be used with caution. The initial dose of rosiglitazone is 4 mg once a day while the initial dose of pioglitazone is 15 mg once a day. The maximum effective dose of rosiglitazone is 8 mg/day, and that of pioglitazone is 45 mg/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. Recently, combination of metformin and rosiglitazone has become available in various dose combinations, and offers the advantage of improving compliance in patients on polytherapy.

How important are TZDs?

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. Their use is likely to increase in the future, due to their non-glycemic effects being elucidated.

Janice's followup

A TZD would be a good choice in Janice's case. Either rosiglitazone, 4 mg/day or pioglitazone, 15 mg/day can be added to Janice's metformin and glyburide. The key is to add, rather than substitute.

A referral to an endocrinologist should also be considered, for assistance with Janice who requires several OHAs. Another option would be to discontinue the metformin and start Janice on a combination of metformin/rosiglitazone, starting at 2 mg/500 mg twice a day and increasing to 4 mg/500 mg twice a day. In an attempt to improve compliance, discontinuing the glyburide and starting a once-a-day long-acting sulphonylurea may also be reasonable. Lifestyle modifications, weight loss and aggressive management of hypertension and dyslipidemia are also essential.

Net Readings

1. Anosos: www.anosos.com/WL/Pod/diabetes.aspx?vmcid=1&vmpid=11&vmkid=417
2. Quest Diagnostics: www.questdiagnostics.com/kbase/topic/detail/drug/hw133689/detail.htm

www.stacommunications.com

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What lies ahead for TZDs?

TZDs may also play a role in delaying the onset of diabetes in individuals at risk. By improving insulin sensitivity and, thereby, decreasing the demand on the beta cells, they may have the potential to decrease progressive beta cell failure and thus delay the risk of developing diabetes. These agents have also been used in patients with PCOS and have been shown to reduce androgen levels, improve menstrual regularity and ovulation-conception rates. However, these agents are not approved for these indications, and we will need to wait for more evidence from ongoing studies. CME

Suggested readings

1. American Diabetes Association: Clinical practice recommendations 2002. Diab Care 2002;25(1)S1-148.
2. DeFronzo RA: Pharmacologic therapy for type 2 diabetes mellitus. Ann Int Med 1999; 131(4)281-303.
3. Inzucchi SE: Oral antihyperglycemic therapy for type 2 diabetes. JAMA 2002;287(3)360-72.
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)708-11.
5. Meltzer S, Leiter L, Daneman D, et al: 1998 clinical practice guidelines for the management of diabetes in Canada. CMAJ 1998;159(8)S1-29.

Take-home message

Facts about oral hypoglycemic agents and thiazolidineiones, concerning Type 2 diabetes:

- A number of new oral hypoglycemic agents (OHAs) have become available in the last few years
- One class of OHA is not necessarily better or more potent than the other. However, there are significant differences can be exploited to suit the individual patient
- Thiazolidinediones (TZDs) are an attractive option in the treatment of patients with Type 2 diabetes, either as monotherapy, or in combination with other OHAs
- The main side-effects of TZDs seen in clinical practice are those related to fluid retention and weight gain.