



Focus on CME at the
University of Alberta

Tips for Type 2: *Treating* *Diabetes Mellitus*

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How should I approach Type 2 diabetes?

The approach to Type 2 diabetes encompasses the use of diet/exercise, oral hypoglycemic agents (OHAs), and insulin in a concerted effort to control glycemia and prevent diabetes complications. Figure 1 shows different mechanisms which elevate blood glucose in Type 2 diabetes and the sites OHAs primarily affect.



Patty's Presentation

Patty, 74, has had Type 2 diabetes for eight years. She has some congestive heart failure and previously had a myocardial infarction. Patty lives alone, and feels fairly well.

Tests show:

- glucose 12.4 mmol/L,
- random glucose 15.5 mmol/L,
- hemoglobin A1c (HbA1c) 9.3 %, and
- weight 69 kg.

Patty has no known diabetes complications as yet, but her creatinine is 155 μ mol/L. She was previously treated with just diet and exercise which are considered reasonable treatment modalities.

Neither the HbA1c, nor the glucose are well controlled.

For more on Patty, go to page 106.

Table 1

Expected changes in glucose or HbA1c with OHAs

	Fasting (mM)	Postprandial glucose (mM)	HbA1c (%)
Glucosidase inhibitor	0.7	4.5	0.9
Metformin	3.2	4.8	0.5-1.5
Sulphonylureas	2.9	3.5	1.9
Meglitinides	1.7	2.6	0.7
Thiazolidinediones	3.0	3.1	0.5-1.3

HbA1c: Hemoglobin A1c

Table 2

Improvement with oral hypoglycemic agents (OHAs)

Acarbose

- Decreases glucose absorption
- Minimal effect on the fasting glucose level
- Major side-effects are flatulence and diarrhea

Metformin

- Decreases hepatic glucose production
- Major side-effect is gastrointestinal upset, especially diarrhea
- Rare, but serious side-effect is lactic acidosis, which is more likely when used in the presence of significant renal, liver, or heart disease

Sulfonylureas

- Stimulate beta cells to make more insulin, regardless of what the ambient blood glucose
- Major side-effect is hypoglycemia

Meglitinides

- Repaglinide, nateglinide
- Short-acting agents that bind to the sulfonylurea receptor
- Can also cause hypoglycemia

Thiazolidinediones

- Enhance insulin sensitivity
- Major side-effect is edema
- Severe hepatotoxicity associated with troglitazone does not appear to be a problem with rosiglitazone or pioglitazone

Diabetes is, however, a progressive disease; although patients may have control over their weight and exercise to enhance insulin sensitivity, if pancreatic secretion is destined to decline over time, the diabetes will deteriorate accordingly. Therefore, many patients can expect to

progress from nutrition therapy alone to oral hypoglycemic agents to insulin. They need to be aware that this is not necessarily a failure of compliance, but rather that of their pancreas. Aside from glucose control, attention to lipids, hypertension, and smoking cessation are equally important in preventing macrovascular disease.

Can diet and exercise really help?

Diet and exercise do work in Type 2 diabetes. A meta-analysis of 14 studies showed that in the exercise group, the hemoglobin A1c (HbA1c) was 0.7% lower despite no change in overall weight.¹ Likewise, a review of six randomized, control trials confirmed that medical nutrition therapy is advantageous.²

Unfortunately, OHAs are also required as diet and exercise are rarely sufficient to control glycemia in the long-term.

What's the word on OHAs?

Improvement in HbA1c is similar with the major OHAs (Table 1). Metformin is the drug of choice in obese subjects with Type 2 diabetes. It is preferred to start at a low dose and work up to the maximum dose of 2.5 g/day. Glyburide or glimiperide are the first-line drugs in lean patients who may have more insulin deficiency. In seniors, glimeglitinide has an advantage with a shorter half-life and less problems occur with hypoglycemia. Meglitinides are excellent for coping with postprandial hyperglycemia or an erratic eating schedule, as subjects can just take them before meals. Acarbose is better suited to milder cases of diabetes, where the fasting glucose is not elevated. The dose should be started at a low level and increased slowly. Thiazolidinediones have a natural advantage when insulin resistance is prominent (usually when obesity is present).

What about insulin?

Insulin therapy in Type 2 diabetes is geared to provide background insulin rather than replace endogenous insulin secretion completely. It is reasonable to start with bedtime neutral protamine Hagedorn (NPH) at a dose of 10 units and work up gradually. Dose requirements of one unit per kg or more of insulin are not unusual in Type 2 diabetes.

If nocturnal hypoglycemia is a problem, glargine insulin will have an advantage when it becomes available in Canada. If fasting glucose is not controlled with evening NPH, twice daily NPH, with premixed insulin in the

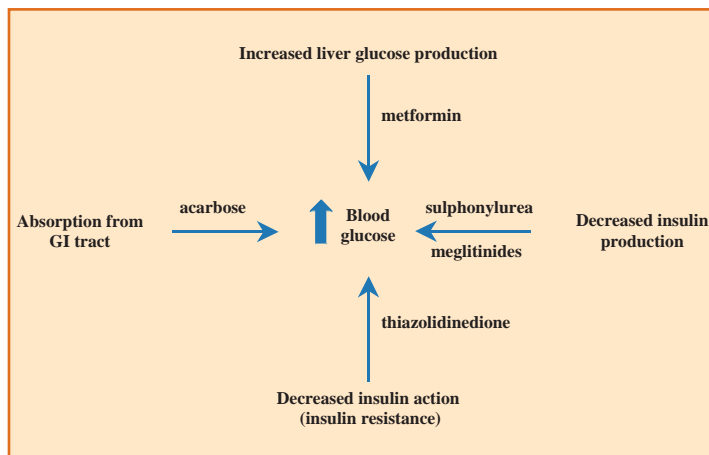
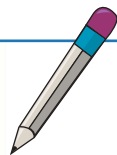


Figure 1. Different mechanisms by which the blood glucose may become elevated and the primary sites where OHAs exert their affect.

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Take-home message



- Increasing rates of obesity and lack of physical exercise are contributing to an epidemic of Type 2 diabetes.
- First-line therapy should focus on nutrition, counselling, and exercise.
- OHAs can be used as single or combined therapy.
- Good glycemic control, and controlling hyperlipidemia, blood pressure, and smoking cessation can decrease diabetes complications and improve longevity.

morning and at supper-time, if needed, are the natural next steps. Some patients progress to significant insulin insufficiency; for these patients, more intensive insulin therapy similar to Type 1 diabetes is indicated.

Treating Patty

Given the fasting glucose (12.4 mmol/L), acarbose would be inadequate. The creatinine and cardiac situation preclude the use of metformin. Thiazolidinediones would likely aggravate the congestive cardiac failure.

Given her age and that she lives alone, glyburide would carry a risk of profound hypoglycemia; the best drug for Patty would be glimepiride or meglitinides.

If her diet was erratic, in terms of eating times, a meglitinide is advantageous.

What do the new guidelines say?

The new guidelines from the Canadian Diabetes Association recommend lifestyle changes (exercise and medical nutrition therapy) and an earlier introduction of OHAs than previously suggested.³ It is important to have a nutritional assessment, as some patients who are polyuric drink an excess of sweetened beverages and simply eliminating this may correct a significant degree of hyperglycemia.

In practice, it is wise to start with exercise and medical nutrition therapy. If success is not achieved or if the hyperglycemia is severe and unlikely to be rapidly responsive to

nutrition therapy, oral agents are added to the care plan. If monotherapy is not successful, an alternative hypoglycemic agent is added.

In patients who have failed sulphonylurea therapy, both metformin and pioglitazone performed equally well as the additional oral agent when studied.⁴

What about triple therapy?

When patients are on two oral hypoglycemic agents, the choice is to either go to insulin or proceed to triple oral hypoglycemic therapy. The advantage of triple therapy is the different mechanisms of the OHAs can be used and the patient avoids insulin injections. The disadvantages are the increased cost and problems with adverse events.

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Triple therapy or pre-mixed insulin and metformin showed similar efficacy in patients whose glucose was uncontrolled on two OHAs.

In a study that examined patients whose glucose was not controlled on two OHAs, use of either triple therapy or pre-mixed insulin and metformin demonstrated similar efficacy, but a higher cost was associated with the triple therapy.⁵ At this stage of failure on two OHAs, the patient must be engaged in the discussion as to whether to go with insulin or triple oral hypoglycemic therapy.

What about OHAs in pregnancy?

In general, although metformin is used in polycystic ovarian disease and is likely safe in the first trimester, pregnant patients with Type 2 diabetes on OHAs are best switched to insulin. Insulin requirements will generally rise in pregnancy and the OHAs are unlikely to be able to contain the situation. The safety of thiazolidinediones in the first trimester is unknown and are, therefore, not recommended in this setting. CME

References

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Further references available—contact *The Canadian Journal of CME* at cme@sta.ca.

