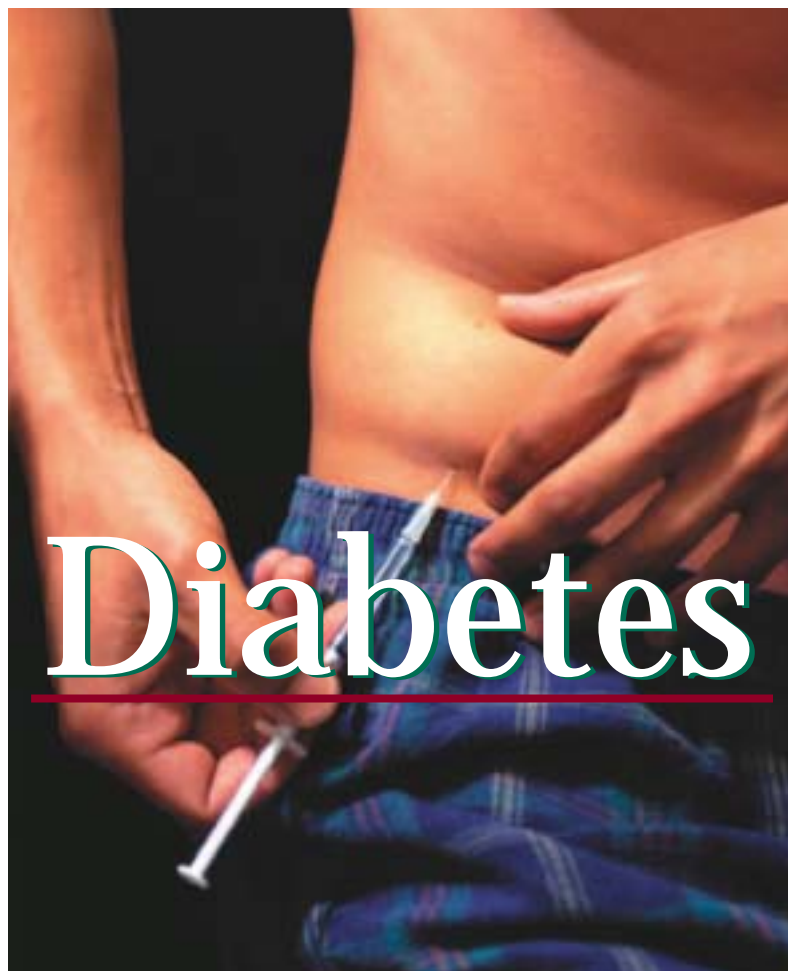




What's New in Diabetes



By Sarah Capes, MD, FRCPC

Presented at
McMaster University,
Hamilton, Ontario, October 2001.

Diabetes is becoming more common. By the year 2025, diabetes is expected to affect more than 5% of the population worldwide and

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more than 7.5% of people in the developed world.¹ Fortunately, new therapies and new approaches to prevention in diabetes are improving the outlook for people with the disease. This article will provide an overview of four areas of diabetes research in which important advances have been made over the past few years:

- New drugs for Type 2 diabetes;
- New therapies for Type 1 diabetes;
- New evidence for cardiovascular disease (CVD) prevention in diabetes; and
- New approaches to preventing diabetes.

Diabetes

New Drugs for Type 2 Diabetes

Sulfonylureas (glyburide) and biguanides (metformin) have long been the mainstay of therapy for Type 2 diabetes. In the past few years, however, three new classes of oral hypoglycemic agents have become available in Canada: α -glucosidase inhibitors (acarbose); meglitinides (repaglinide) and thiazolidinediones (TZDs) (rosiglitazone and pioglitazone).

α -glucosidase inhibitors (acarbose). Acarbose is the only drug in this class available in Canada. It works by inhibiting the α -glucosidase enzyme in the gastrointestinal (GI) tract, which inhibits the breakdown of complex carbohydrates and delays the absorption of glucose. As a result, this drug tends to reduce postprandial peaks in blood glucose in people with Type 2 diabetes. It can be used alone or in combination with sulfonylureas or metformin, and generally reduces HbA1c by about 0.5%. It works best in patients on a high-carbohydrate diet (> 50% carbohydrates). When used alone, it does not cause hypoglycemia. Hypoglycemia can occur when acarbose is combined with other oral hypoglycemic agents and such patients should be treated with glucose gel or tablets. Complex carbohydrates may not be effective because of reduced absorption with acarbose. GI side effects (*i.e.*, bloating, flatulence, diarrhea and abdominal pain) are common and dose-dependent. These GI side effects can be minimized by starting acarbose at a low dose (50 mg once per day) and gradually titrating upwards (to a maximum of 100 mg three times daily [tid]).¹ In practice, GI side effects often limit the use of this drug.

Meglitinides (repaglinide). Repaglinide is the only agent of this class available in Canada. Meglitinides are non-sulfonylurea insulin secretagogues that work by closing adenosine triphosphate (ATP)-dependent potassium channels in the

pancreatic beta cell. This leads to calcium influx into the cell and a subsequent release of insulin. Repaglinide is rapidly absorbed, fast-acting and causes less hypoglycemia than sulfonylureas. It lowers HbA1c up to 1.5% and can be used alone or in combination with metformin in doses ranging from 0.5 mg to 4 mg before meals (maximum 16 mg per day).²

TZDs: Rosiglitazone and pioglitazone. These drugs are part of a novel class of agents believed to lower blood glucose by reducing insulin resistance. They work by activating peroxisome proliferator-activated protein receptor (PPAR- γ). PPAR- γ is an intranuclear receptor found in skeletal muscle, adipocytes and the liver. It regulates genes that control key metabolic activities, including adipocyte differentiation and the synthesis of glucose transporters. These drugs can be used alone or in combination with metformin or sulfonylureas. The starting dose of rosiglitazone is 4 mg once per day or 2 mg twice daily (bid). The dose may be increased up to 4 mg bid. The starting dose of pioglitazone is 15 mg once daily, and may be increased up to 45 mg daily. In general, up to six weeks is needed for these medications to achieve their full effect. When used alone, they do not cause hypoglycemia. They are not metabolized by the kidney and are safe in renal insufficiency.

Common side effects include fluid retention and weight gain. Weight gain may be due to either an increase in subcutaneous adipose tissue or to fluid retention. As a result, these drugs are contraindicated in patients with New York Heart Association (NYHA) class III or IV heart failure. Heart failure may be exacerbated when these drugs are combined with insulin. In Canada, TZDs are not approved for use in combination with insulin.

Although the two TZDs available in Canada have not been shown to cause significant liver damage, a related drug (troglitazone) was taken off

the market in the US due to liver toxicity. It is, therefore, recommended that liver enzymes be checked at baseline and every two months for the first year of treatment with these drugs and periodically thereafter (Table 1).³

New Therapies for Type 1 Diabetes

Islet cell transplantation. Few advances in diabetes research have generated as much excitement as a report on successful islet cell transplantation, published in the *New England Journal of Medicine* in 2000.⁴ The study reported on seven Type 1 diabetic patients who underwent islet cell transplantation at the University of Alberta, using a novel, low-dose, steroid-free immunosuppressant regimen, called the Edmonton Protocol. This study was the first to show consistent independence from insulin for more than one year following islet cell transplantation.⁴

An update from the University of Alberta reported that as of January 2001, 12 patients with Type 1 diabetes mellitus (DM) had undergone islet cell transplantation.⁵ Before transplantation, all

patients had at least one of the following major indications for transplantation, despite optimal diabetes management:

- Markedly reduced or absent awareness of hypoglycemia;
- Labile glycemetic control; or
- Severe and progressive complications of diabetes.

The mean age of these patients was 40 ± 2.7 years, and the mean duration of diabetes was 29 ± 3.2 years. After a median follow-up of 12.2 months, nine of the 12 recipients remained independent of insulin. Those few patients who required insulin were on much lower doses than before transplantation. All transplant recipients had significantly better glycemetic control after transplantation, regardless of whether or not they were using insulin. Side effects of the transplantation, including bleeding and portal vein thrombosis, were infrequent and easily treated, and the immunosuppressant regimen was well tolerated. Further studies of islet cell transplantation using the Edmonton Protocol are planned worldwide.

Although this research is very promising, the long-term safety and effectiveness of islet cell transplantation needs to be studied in many more patients

Summary

What's New in Diabetes

- Sulfonylureas (glyburide) and biguanides (metformin) have long been the mainstay of therapy for Type 2 diabetes. In the past few years, however, three new classes of oral hypoglycemic agents have become available in Canada: α -glucosidase inhibitors (acarbose); meglitinides (repaglinide); thiazolidinediones (rosiglitazone and pioglitazone).
- Cardiovascular disease (CVD) is the most common cause of death in people with diabetes. American population-based surveys have reported almost half of Caucasian adults with diabetes have coronary artery disease, as compared to about one-quarter of those without diabetes.
- Several interventions may reduce or prevent CVD in people with diabetes, including blood pressure (BP) lowering, lipid lowering and angiotensin-converting enzyme (ACE) inhibitors.

Diabetes

Table 1

Medications for Type 2 Diabetes

Class name	Examples	Mechanism of Action
Sulfonylureas	Glyburide, gliclazide.	Stimulates the pancreas to secrete insulin.
Biguanides	Metformin.	Reduces liver production of glucose. May help the muscle use insulin more efficiently.
α -glucosidase inhibitors	Acarbose.	Reduces absorption of sugars in the small bowel.
Thiazolidinediones	Rosiglitazone. Pioglitazone.	Helps muscle use insulin more efficiently.
Meglitinides	Repaglinide.	Stimulates the pancreas to make insulin.
Insulin	Humulin R, N, U; Humalog; Novolin Toronto, NPH; Ultralente.	Stimulates muscle to take up glucose from the blood. Reduces glucose production by the liver.

before it can be considered a routine treatment for Type 1 diabetes. Another challenge is that the number of organ donors is limited. The University of Alberta team estimates that at the current rate of organ donation in Canada, no more than 40 islet cell transplantations can be performed per year.⁶

For more information about the Edmonton Islet Transplantation program, contact:

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Edmonton, Alberta, Canada, T6G 2C8

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Web site (including Physician Referral Form):
www.med.ualberta.ca/islet/

Table 1 Cont'd

Medications for Type 2 Diabetes Cont'd

Potential Advantages	Common Side Effects	Contra-indications
Useful if marked hyperglycemia (> 10).	Low blood glucose.	Advanced renal dysfunction.
May promote weight loss. Lower risk of hypoglycemia than sulphonylureas; useful if marked hyperglycemia (> 10).	Diarrhea, nausea, metallic taste.	Renal or liver dysfunction; congestive heart failure.
Minimal weight gain.	Bloating, gas, diarrhea.	GI tract disease.
Not metabolized by the kidney. Safe in renal insufficiency.	Leg swelling, mild weight gain.	Class III or IV heart failure; liver dysfunction.
Shorter-acting, may cause less hypoglycemia than sulphonylureas.	Low blood glucose.	Advanced liver dysfunction.
Can be combined with oral agents.	Low blood glucose.	None.

New Evidence for CVD Prevention in Diabetes

Cardiovascular disease (CVD) is the most common cause of death in people with diabetes. American population-based surveys have reported almost half of Caucasian adults with diabetes have coronary artery disease, as compared to about one-quarter of those without diabetes.⁷ Several

interventions may reduce or prevent CVD in people with diabetes, including blood pressure (BP) lowering, lipid lowering and angiotensin-converting enzyme (ACE) inhibitors. While not discussed in detail here, use of acetylsalicylic acid (ASA) and smoking cessation are also effective strategies known to prevent CVD, and should be encouraged in people with diabetes (Table 2). Increasing evidence suggests good glycemic control may also

Diabetes

Table 2

Preventing CVD in diabetes

Strategy	Target
Control hypertension	BP < 130/80 mmHg
Control hyperlipidemia	LDL < 2.6 mmol/L TG < 2 mmol/L
ACE inhibitors	Prescribe for middle-aged diabetic patients with ≥ 1 CV risk factor
ASA	81 mg to 325 mg per day for diabetic patients over age 30
Smoking cessation	Encourage in all diabetic patients

reduce CVD, but further study is required.

Blood pressure lowering. Several large, randomized controlled trials have recently confirmed the importance of good control of hypertension to prevent CVD. In the United Kingdom Prospective Diabetes Study (UKPDS), patients with Type 2 diabetes who were randomized to tight control of hypertension with captopril or atenolol (mean achieved BP 144/82 mmHg) had a 21% lower risk of myocardial infarction (MI) and 44% lower risk of stroke over nine years, as compared to those randomized to standard treatment (mean achieved BP 154/87 mmHg).⁸ The risk of fatal or non-fatal MI decreased by 12% for each 10 mmHg decrease in systolic blood pressure and the risk of fatal or non-fatal stroke fell by 19% for every 10 mmHg reduction in systolic blood pressure.⁹

Among diabetic patients in the Hypertension Optimal Treatment (HOT) Trial, those treated intensively with felodipine (mean BP 140/81 mmHg) had a 52% lower risk of CV events or stroke than conventionally treated patients (mean BP 144/85 mmHg).¹⁰

The Systolic Hypertension in the Elderly Program (SHEP) found that, in older diabetic adults with isolated systolic hypertension, lowering blood pressure with chlorthalidone and atenolol (BP 145/70 mmHg in treatment group *versus* 155/70 mmHg in controls) resulted in a 56% lower risk of CV events and a 22% reduction in stroke.¹¹

The best choice of anti-hypertensive agents to prevent CVD in diabetic adults is under study. Several large trials, however, have suggested that ACE inhibitors are

preferable to calcium channel blockers. There is also some evidence from the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) that alpha-blockers should not be used as first-line therapy for hypertension in people with diabetes, because they led to a 20% higher risk of CV events, as compared to diuretics.¹² The American Diabetes Association currently recommends a target BP < 130/80 mmHg for most adults with diabetes.¹³

Lipid lowering. Subgroup analyses of several large studies have shown that patients with diabetes and moderately elevated low density lipoprotein (LDL)-cholesterol benefit as much or more from LDL-lowering with statin drugs as those without diabetes. On average, the risk of CV events is reduced by 20% to 30%. It has been observed that people with diabetes without prior myocardial infarction (MI) have a similar risk of future CV events as people without diabetes who have had prior MI. This has led some authorities to recommend a similar target level of LDL-cholesterol in both groups (LDL < 2.6 mmol/L).¹⁴ Indeed, 2002 guidelines from the American Diabetes Association

recommend a target LDL-cholesterol < 2.6 mmol/L in adults with diabetes, using statins if LDL-cholesterol is > 3.35 mmol/L or if dietary management fails to reduce LDL-cholesterol to target.¹⁵

ACE inhibitors. The HOPE study, which randomized 9,541 people aged 55 or older to the addition of ramipril 10 mg per day or placebo, included 3,654 people with diabetes and either pre-existing CVD or ≥ 1 cardiac risk factor. After 4.5 years, diabetic patients treated with ramipril had a 25% lower risk of the combined outcome of MI, stroke or CV death, as compared to controls.¹⁶ This study shows that treatment with ACE inhibitors is indicated to prevent CV events in middle-aged diabetic people at risk for CVD.

New Approaches to Preventing Diabetes

Healthy eating and exercise are hardly new, but preliminary, unpublished results from the Diabetes Prevention Program Trial show that healthy lifestyle changes can prevent diabetes (publication of these results was expected in February 2002, but were not available at press time). This study randomized 3,234 overweight Americans aged 25 to 85, with impaired glucose tolerance (IGT), to either lifestyle modification or conventional management. Those people who received the lifestyle intervention were encouraged to exercise about 30 minutes per day (most chose walking), eat a balanced, low-fat diet and lose weight (7% of total body weight, on average about 6.8 kg [15 lbs]). After three years follow-up, people who received the lifestyle intervention developed diabetes at less than half the rate of the control group. In another arm of the study, metformin 850 mg bid also was effective at preventing diabetes, but less so than the lifestyle interven-

tion.¹⁷ A smaller study conducted in Finland showed that a similar modest lifestyle intervention reduced the incidence of diabetes by 58% in overweight individuals with IGT.¹⁸

Ongoing research is evaluating the ability of medications to prevent diabetes in people at risk. These include acarbose (in the Study to Prevent Non-insulin-dependent Diabetes Mellitus [STOP-NIDDM] Trial), ramipril and rosiglitazone (in the Diabetes Reduction Assessment with Ramipril and Rosiglitazone medications [DREAM] Trial).^{19,20}

Conclusion

Diabetes is on the rise in North America. However, we now know more about how to manage the disease, prevent complications and even prevent diabetes than ever before. The future promises to bring more advances that will improve the outcome for people with diabetes and those at risk. CME

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