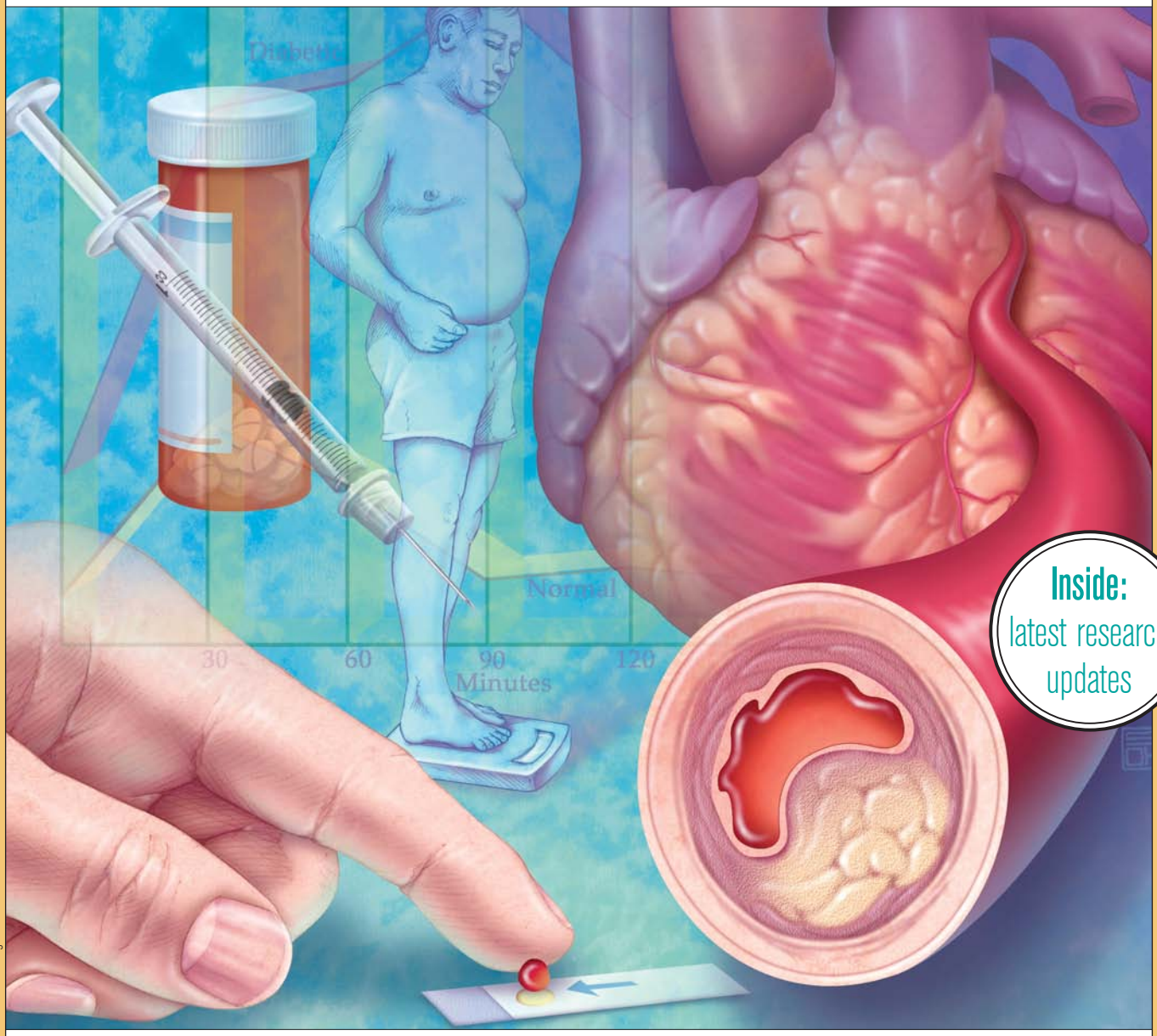
diabetes

a **patient**care clinical practice guide



Inside:
latest research updates

Phototake / Images.com

Diabetes & depression

Exploring the association; diagnostic and treatment challenges

Plus: The role of post-prandial glucose

The role of post-prandial glucose

Disclosure: Dr. J. Robin Conway is involved in a clinical trial sponsored by Merck and has received funding/payments from the company.

by Dr. J. Robin Conway
medical director of the Canadian Centre for Research on Diabetes
staff member, Perth/Smiths Falls (Ont.) District Hospital

Type 2 diabetes mellitus is a pandemic that takes a large toll on the quality of life of those affected, while expending increasing amounts of our health-care dollars. Diabetes is characterized by hyperglycemia, with the definition, diagnosis and classification being based on levels of glycemia. It is the elevated glucose levels that lead to the macrovascular and microvascular complications of the disease. The first glycemic abnormality seen in the person destined to develop type 2 diabetes is a modest elevation in post-meal glucose.

The increased level of cardiovascular risk begins in the stage of pre-diabetes, where post-prandial glucose is only modestly elevated. The microvascular complication risk, in contrast, starts much later, when fasting glucose levels exceed 7 mmol/l and post-prandial levels exceed 11 mmol/l.

Diabetes is associated with insulin resistance, especially in the early or pre-diabetic phase, when insulin resistance is the predominant abnormality. At diagnosis of diabetes it is estimated that 50% to 60% of insulin-producing ability has been lost and there is progressive insulin deficiency. As well as insulin deficiency there is associated deficiency of the incretin hormones.

The incretins—glucagon-like peptide-1 (GLP-1) and glucagon insulinotropic peptide (GIP)—are polypeptide hormones secreted by the gut in response to food ingestion. GLP-1 has therapeutic potential in diabetes. The actions of GLP-1 are:

- to increase satiety by central stimulation of the brain appetite centre;
- to slow gastric emptying;
- to inhibit glucagon production from the alpha cells of the pancreas (this in turn decreases hepatic glucose production); and
- to increase glucose-dependent insulin secretion.

The incretin hormones got their name because they increase insulin output; this is called the incretin effect and may be responsible for as much as 60% of insulin production by the pancreatic beta cell. The loss of the incretin effect is largely responsible for the loss of first-phase insulin secretion that occurs early in the course of diabetes. GLP-1 is rapidly broken down and rendered inactive by the enzyme dipeptylpeptidase-4 (DPP-4). The inactivation of GLP-1 is very rapid.

Is glucose control important?

The Diabetes Control and Complications Trial (DCCT) in 1989 showed us that a 1% reduction in HbA1c (glycosylated hemoglobin) led to a 30% to 35% reduction in microvascular complications of retinopathy, nephropathy and neuropathy in people with type 1 diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) in 1993 showed similar reductions in microvascular complications in people with type 2 diabetes, as well as a modest 14% (non-significant) reduction in macrovascular complications. Subsequent trials, including the ADVANCE trial, the ACCORD trial and the VADT (Veterans Affairs Diabetes Trial), all reported in 2008, show consistent reductions in microvascular endpoints at even lower levels of glycemia, as well as consistent but not statistically significant reductions in macrovascular end points. These findings have led to a progressive reduction in glycemic targets in order to reduce the toll of diabetic complications.

Diagnosis and target glucose

Normal fasting glucose levels are from 4 mmol/l to 6 mmol/l, while normal two-hour postprandial glucose levels are from 5 mmol/l to 8 mmol/l. Diabetes is diagnosed when fasting glucose levels exceed 7 mmol/l or

when two-hour postprandial glucose exceeds 11 mmol/l on a 75-gram glucose tolerance test. (In the absence of symptoms a confirmatory test is done.) Above these levels of glycemia, microvascular complications of diabetes start to occur. We term the area between normal and the diabetic threshold as pre-diabetes (impaired glucose tolerance or impaired fasting glucose).

The 2008 Canadian Diabetes Association clinical practice guidelines target a fasting glucose of less than 7 mmol/l and a two-hour post-prandial glucose of less than 10 mmol/l. If the patient is having difficulty achieving the HbA1c target of less than 7%, then aim for a post-prandial glucose of less than 8 mmol/l.

In most major studies the barrier to lowering HbA1c has been the increased incidence of hypoglycemia. Since the landmark studies such as the DCCT and the UKPDS, there have been significant improvements in the tools available to treat diabetes. Rational medication choices today, including the use of analogue insulins and combinations of oral agents less likely to cause hypoglycemia, have resulted in much lower risk of both minor and major hypoglycemia. In the ADVANCE trial, reported in 2008, HbA1c levels of 6.5% were accomplished with no major hypoglycemia and only a 3% incidence of minor hypoglycemia. Appropriate treatment of both fasting and post-prandial glycemia leads to much lower rates of hypoglycemia. Oral medications such as metformin, incretin therapies and glitazones alone or in combination rarely cause hypoglycemia. Glyburide has a high incidence of hypoglycemia but the more selective sulphonylureas and the short-acting secretagogues (meglitinides) are associated with much less hypoglycemia. The long-acting insulin analogues cause less hypoglycemia than NPH (isophane insulin) and because of better matching of insulin needs to supply, the short-acting insulin analogues cause less hypoglycemia than regular insulin.

Patient adherence to effective treatments and lifestyle changes, as well as cost of medications, have always been a challenge in achieving glycemic control. About half of Canadians have their medications paid for by public drug plans. Lack of access to the newer, more effective insulins and oral medications via drug plans has made it very difficult for many people to achieve glycemic targets and avoid vascular complications.

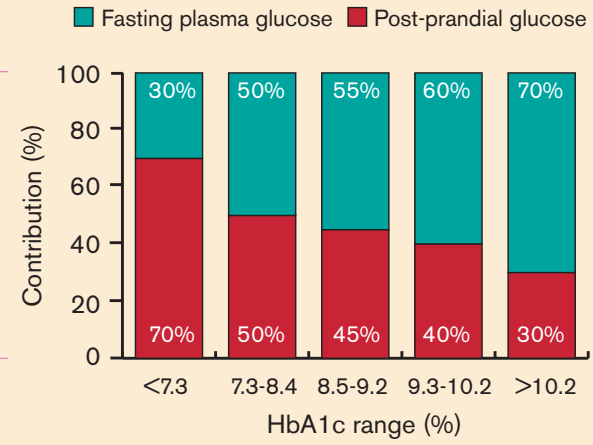
Heart and stroke risks

The glycemic threshold for development of macrovascular complications is lower than that for microvascular complications. The increased risk for heart disease and stroke starts earlier in the course of the disease, when there is only a modest increase in post-prandial glucose levels. The reason for the increased macrovascular risk may be because elevated post-prandial glucose increases plasma levels of triglycerides, chylomicrons and free fatty acids. These acute glucose fluctuations increase oxidative stress more than sustained hyperglycemia, leading to endothelial dysfunction. The DECODE prospective study of 25,000 subjects in Europe over seven-plus years demonstrated that increased cardiovascular mortality risk was much more closely associated with two-hour post-prandial glucose levels than with fasting plasma glucose. The increased risk of post-prandial glucose over fasting glucose on cardiovascular outcomes was also found in the Honolulu Heart Study, the Diabetes Intervention Study and the Whitehall study of British male civil servants, which showed post-meal glucose levels of greater than 5.2 mmol/l were associated with doubling of mortality from cardiovascular disease.

Post-prandial glucose elevations activate protein kinase C (PK-C), the enzyme that may link hyperglycemia to microvascular complications. The activity of PK-C impairs contraction of pericytes, increases production of basement membrane materials, enhances cell proliferation and capillary permeability, leading to microvascular complications. This activation of PK-C occurs at higher glucose levels than the changes that lead to macrovascular complications. Thus, while an increase in macrovascular risk is seen with PPG levels greater than 5.2 mmol/l, microvascular changes are typically seen only when post prandial glucose levels exceed 8 mmol/l.

To achieve the Canadian Diabetes Association target HbA1c of less than 7%, we have to control both fasting and post-prandial hyperglycemia. When HbA1c levels are high (greater than 8.5%), the largest component of the HbA1c is the fasting glucose; therefore, we emphasize fasting glucose monitoring and treatment with basal agents such as metformin, glitazones, long-acting sulphonylureas or

Post-prandial contributions to glucose load



Adapted from Monnier L, et al. Diabetes Care 2003;26:881

long-acting insulins. As we approach our glycemic target of HbA1c <7%, a greater component of the HbA1c is post-prandial glucose, so we need to target our therapies to lower it without inducing hypoglycemia. Studies have shown that post-prandial hyperglycemia is a major risk factor for both macro- and microvascular complications, and that lowering post-prandial glucose excursions reduces risk. The price of post-prandial glucose lowering has traditionally been an increase in risk of post-prandial hypoglycemia but the use of the more modern selective medications has allowed improved control without increased risk.

Treatments

There are a number of different drug classes that affect glucose levels. It may be helpful when selecting the medications to treat high glucose to think of them in terms of their ability to effect either fasting or post-prandial glucose levels in the same way as we classify insulins as having predominantly basal or bolus (prandial) effect.

Basal drugs affect predominantly fasting glucose levels. These include metformin, glitazones (pioglitazone and rosiglitazone), long-acting sulphonylureas (glyburide), NPH insulin and longacting insulin analogues (detemir and glargine).

Bolus drugs affect predominantly post-prandial glucose levels, and include acarbose, repaglinide, nateglinide, DPP-4 inhibitors (sitagliptin), GLP-1 analogues or mimetics (not yet available in Canada) and short-acting insulin analogues (aspart, glulisine or lispro insulin).

Combination drugs affect both fasting and post-prandial glucose levels. These include the analogue premix insulins (biphasic insulin aspart and biphasic insulin lispro).

As HbA1c levels fall below 8.5%, the major component becomes post-prandial glycemia, so we need to use medications that target this area.

Acarbose is an alpha glucosidase inhibitor that slows the breakdown of disaccharides and polysaccharides into monosacharides that can be absorbed. It is dosed as 50 mg to 100 mg, to be taken with the first bite of each meal. Side-effects of gastrointestinal distress are common and the expected HbA1c reduction is only 0.5%.

Meglitinides, including nateglinide 125 mg or repaglinide 0.5 mg to 4 mg, are taken with each meal. They increase post-prandial insulin production, thus lowering post-prandial glucose. Nateglinide is associated with a somewhat lower HbA1c lowering potential than the 1% reduction seen with repaglinide. Hypoglycemia is the major side-effect.

Incretin therapies: GLP-1 cannot be given orally as the polypeptide would be broken down by digestive enzymes; it has to be given by injection. Since GLP-1 is very rapidly inactivated by DPP-4, to be effective it would have to be given by continuous infusion and this would be impractical. There are compounds that mimic the effect of GLP-1 and are not broken down by the DPP-4 enzyme, such as exenatide. It is given twice a day by injection but is not yet available in Canada. Another possibility is a GLP-1 analogue, such as liraglutide, which is conjugated to a fatty acid to slow breakdown and has to be injected once a day. It also is not yet available in Canada.

An alternative to enhancing GLP-1 levels is to slow the breakdown of GLP-1 by inhibiting the DPP-4 enzyme. This can be done by taking an oral DPP-4 inhibitor, which is the basis of action of a new class of incretin therapies. The first of this new class, sitagliptin (marketed as Januvia), is now available in Canada. There are minimal adverse events or drug-drug interactions but since it is cleared by the kidney, it should not be given in renal failure. Because of the mechanism of action in increasing glucose-dependent insulin secretion, the DPP-4 inhibitors affect predominantly post-prandial glucose. Since the major component of HbA1c is the post-prandial component as we get closer to the 7% target, this is when we use the DPP-4 inhibitors; in this range the HbA1c-lowering effect is modest, usually about 0.7%. The drug requires a functioning beta cell with the ability to produce insulin so it can enhance insulin production. It is not indicated in type 1 diabetes or for type 2 diabetes when the beta cell function is extremely poor (>10 years after diagnosis), when insulin deficiency is predominant. DPP-4 inhibitors cannot on their own cause hypoglycemia, neither will they cause hypoglycemia when given with thiazolidenediones or metformin. In Canada, sitaglipitin is indicated in association with metformin and this combination appears to enhance the incretin effect. The improvement in GLP-1 levels does increase satiety somewhat and slightly slow gastric emptying, resulting sometimes in weight loss but usually these drugs are weight-neutral. The GLP-1 analogues or mimetics have a more robust GLP-1 effect and may result in HbA1c improvements of up to 1.5% and significant weight loss. These drugs are not yet licensed in Canada.

Short-acting insulin analogues: Insulin aspart, glulisine or lispro are all short-acting insulin analogues. By substitution of some of the amino acids on the human insulin molecule, these analogues prevent the formation of the stable hexamer that is a hallmark of human insulin and retards its effect. The actions of the insulin analogues are essentially identical, as they all act rapidly as monomeric insulin. Onset of action is within a few minutes, with peak activity in about one hour and a half life of about two hours. The major side-effect is hypoglycemia.

References are available in the online version of this article at www.medicalpost.com.