Diabetes: Staying Two Steps Ahead

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The prevalence of diabetes is increasing worldwide and will double in the next 25 years.[1] Diabetes affects about 5% to 6% of the Canadian population and is estimated to affect approximately three million Canadians by 2010.[2]

What causes Type 2 diabetes?

U.S. statistics show that approximately half of all diabetics are unaware of the diagnosis. The increasing prevalence has been attributed to an aging population and an increasing prevalence of obesity, both of which contribute to insulin resistance. Insulin resistance affects approximately 90% of patients with Type 2 diabetes, but it is neither necessary nor sufficient for the development of the condition, as it requires some degree of pancreatic islet cell dysfunction. Genetic predisposition to both insulin resistance and pancreatic islet cell dysfunction has been demonstrated, and probably accounts for the strong familial tendency to this condition.

Insulin resistance affects 90% of Type 2 diabetics.

Diabetes is associated with microvascular and macrovascular complications. While microvascular complications resulting in blindness and kidney failure are the major causes of concern for diabetics, in practice, most patients are more likely to be impacted by macrovascular complications (*i.e.,* premature mortality and morbidity). There is now compelling evidence that intense control of glycemia reduces microvascular complication, but the same cannot be said for macrovascular disease.

From the data published to date, it appears that good glycemic control, at least as practised over

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the past two decades, has little impact on coronary artery disease (CAD) or stroke in diabetics. This is not because the accelerated atherosclerosis that occurs in diabetes is irreversible since in very similar populations, lipid lowering and blood pressure lowering medications have dramatic effects on mortality and morbidity related to macrovascular disease. Indeed, in diabetic patients, the benefits from tight blood pressure control or lipid-lowering medication is greater than in non-diabetic patients.

Two possible explanations need to be considered in relation to this conundrum. First, we may need to identify patients with diabetes much earlier and treat to even tighter or possibly different glycemic targets. There is evidence that CAD is already well established at the time of diagnosis in many diabetics and the risk for myocardial ischemic events is increased in patients with mild disturbances in glucose homeostasis, who do not as yet have diabetes, or may never develop diabetes.

Furthermore, there is now emerging evidence that postprandial, rather than fasting hyperglycemia, may be a better predictor of CAD risk. Few diabetics, particularly those with Type 2 diabetes, do postprandial self-blood glucose monitoring and the detection of postprandial hyperglycemia in the non-diabetic population requires a costly and concerted screening effort. The relentless decline in glycemic control that occurs in practice, and also in clinical trials, may be due in part to glucose toxicity, or lipotoxicity which is a consequence of sub-optimally treated diabetes. However, it is important to remember that the very reasons diabetes is more prevalent in older individuals (*i.e.,* the age-related decline in insulin sensitivity and pancreatic islet cell function) also contribute to the declining ability to maintain glycemic control in these patients.

Another factor that may have some impact on glycemic control is the obesity that accompanies most diabetic treatments. It has been suggested that the obesity associated with the use of insulin and sulfonylureas has a negative impact on lipids and blood pressure, and thus contributes to the difficulty in demonstrating a significant benefit of good glycemic control on macrovascular disease.

There is an alternative explanation for the failure of good glycemic control to impact positively on CAD and cerebrovascular disease. It is not that glycemic control itself is unimportant, but rather simply identifies individuals with a metabolic predisposition to macrovascular disease. While we know that up to 60% of patients with documented CAD have disturbed glucose

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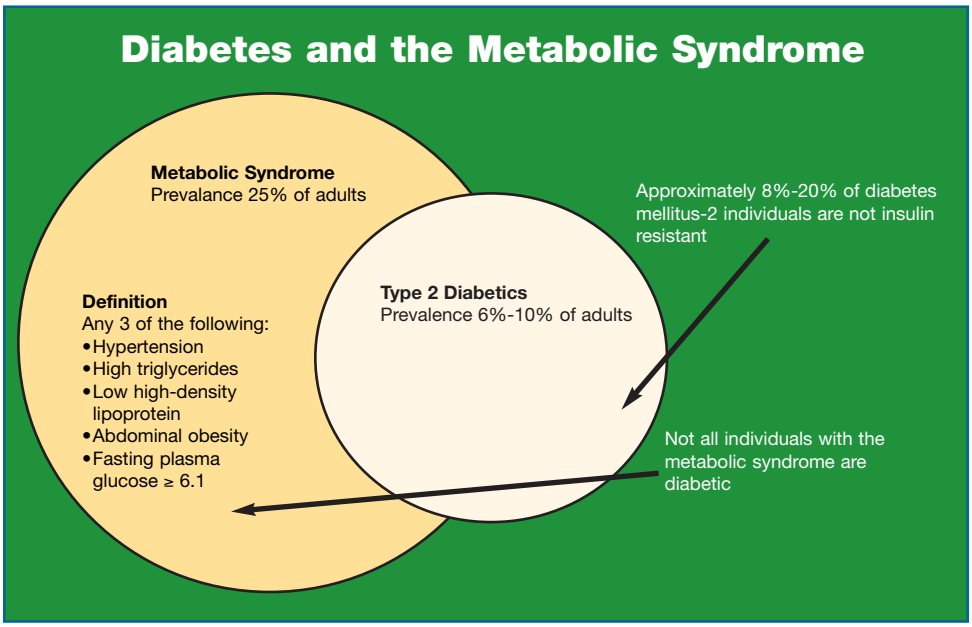

Figure 1. Diabetes and the metabolic syndrome.

homeostasis, and that diabetes increases the risk of CAD (twofold to fivefold), a significant proportion of patients with CAD do not have any disturbance in glucose homeostasis. In this regard it is important to remember that not all individuals with the metabolic syndrome as defined by the National Cholesterol Education Program Adult Treatment Panel III definition, have diabetes. Neither diabetes, nor any disturbance in glucose homeostasis, is required by this currently accepted definition of the metabolic syndrome (Figure 1). Recent surveys suggest that the metabolic syndrome affects up to 25% of the adult American population, whereas, at best, the prevalence of diabetes is less than half of this amount. Thus, more than half of adults with the metabolic syndrome and presumably insulin resistance, do not have diabetes.

In fact, 10% of individuals with the metabolic syndrome have perfectly normal glucose homeostasis, but are probably still at risk for macrovascular disease. Furthermore, approxi-

Table 1
Recommendations for diabetes screening

1. **Fasting plasma glucose testing should be done every three years in people 45 years or older.**
2. **More frequent or early testing should be done under the following circumstances:**
   - a first-degree relative with diabetes
   - obesity
   - high-risk ethnic background like Hispanics, Asians, Aboriginals, and Africans
   - low high density lipoprotein (> 0.9 mmol/L) or elevated fasting triglycerides (> 2.8 mmol/L)
3. **Annual testing should be considered if there is:**
   - a history of impaired glucose tolerance or impaired fasting glucose
   - a history of gestational diabetes mellitus or baby with birth weight over 4 kg
   - presence of hypertension
   - presence of coronary artery disease

mately 10% of patients with Type 2 diabetes are not insulin resistant and do not have the metabolic syndrome (Figure 1).

Irrespective of whether hyperglycemia itself is important in macrovascular disease, or whether diabetes simply identifies individuals at risk for CAD, early identification is important, since prompt and aggressive treatment of hyperlipidemia and hypertension has dramatic effects on reducing myocardial infarction and stroke. Thus, there is a need for some form of population screening if the burden of CAD and cerebrovascular disease is to be reduced.

Table 2
The diagnosis of diabetes

Diabetes is present if any one of the following criteria is met:

- symptoms of diabetes plus a random glucose value of > 11.1 mmol/L
- fasting plasma glucose of ≥ 7.0 mmol/L on two or more occasions
- a plasma glucose value in the two hour sample of the oral glucose tolerance test ≥ 11.1 mmol/L (after 75 g of glucose load)

Who should be screened for diabetes?

Approximately 3% to 5% of the general adult population has undiagnosed Type 2 diabetes.[3] Identification of these individuals is important. The Canadian Diabetes Association 1998 clinical practice guidelines recommend against mass screening of the population, but suggest targeted screening (Table 1).

How is diabetes diagnosed?

The diagnosis of Type 2 diabetes has recently changed, and there is no worldwide consensus on how diabetes should be diagnosed. In 1997, the American Diabetes Association (ADA) changed its diagnostic criteria. It decreased fasting plasma glucose (FPG) threshold from 7.8 mmol/L to ≥ 7.0 mmol/L. In addition, the ADA no longer recommends using an oral glucose tolerance test (OGTT) for the diagnosis of diabetes, although individuals with two-hour post load value of > 11.1 mmol/L are classified as diabetics, as are individuals with random plasma glucose in this range. The 1998 Clinical Practice guidelines published by the

Canadian Diabetes Association (CDA) established the Canadian recommendations for the diagnosis of diabetes (Table 2).[3] Both the ADA and the CDA recommendations recognise two new categories of disturbed glucose homeostasis or pre-diabetes (Figure 2). Impaired fasting glucose (IFG) occurs when the fasting plasma glucose is between 6.1 mmol/L to 6.9 mmol/L, while impaired glucose tolerance (IGT) occurs when the two-hour plasma glucose value in an OGTT is between 7.8 mmol/L to 11.0 mmol/L. It is important to note that random post-prandial plasma glucose determinations are not necessarily equivalent to glucose determinations after a standardised glucose challenge. Thus, the diagnosis of IGT requires an OGTT.

Practice Pointer

The DECODE study was conducted to evaluate the prevalence of diabetes and risk of death in older European men and women, aged between 60 and 79 years at baseline, using the new ADA diagnostic criteria.

The study showed that about one third of older subjects with diabetes were diagnosed using isolated post-challenge hyperglycemia and would have otherwise remained undiagnosed using the new criteria.

This group has an elevated risk of mortality similar to patients with diabetes diagnosed with the new criteria. The study recommended that patients with IFG (6.1 mmol/L to 6.9 mmol/L) should have OGTT to screen for these subjects.

The DECODE Study Group. Consequences of the New Diagnostic Criteria for Diabetes in older men and Women, Diabetes Care 1999; 22: 1667-1672.

What's the impact?

With a decreased threshold for FPG, the prevalence of diabetes has generally increased and may have even doubled, although this is not true for all populations.[4] As reported by the DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) study, old criteria was more likely to diagnose diabetes in lean older subjects while new criteria is more likely to diagnose it in middle-age obese subjects.[5]

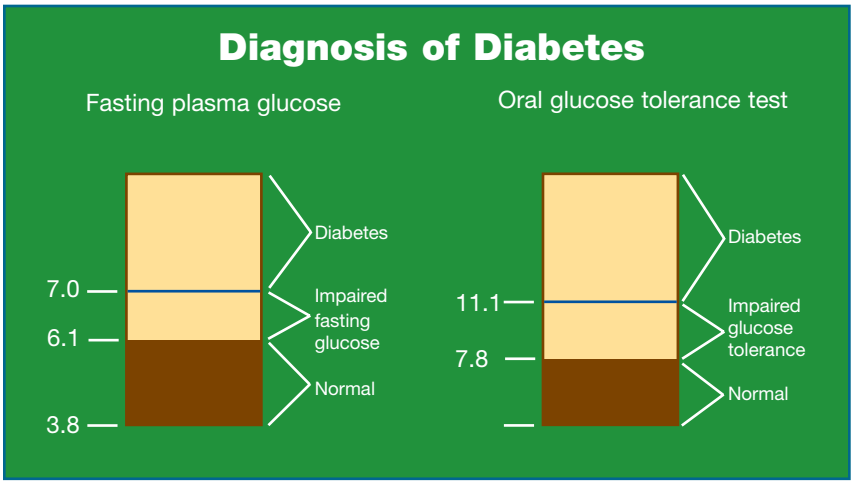

Figure 2. Diagnosis of diabetes.

There is increasing evidence that the old criteria (where higher fasting plasma glucose was required and more reliance was placed on the OGTT) resulted in better prediction of cardiovascular risk and mortality. In a study of 4,515 patients aged 65 and older, the new criteria were found to be less sensitive than the old criteria in predicting cardiovascular disease (CVD) mortality.[6] This is due to the fact that individuals with IFG and IGT are at an increased risk of developing diabetes and macrovascular complications, even when they do not develop diabetes and the latter group (*i.e.,* those with IGT) are more likely to be older, male, less obese and generally are not diagnosable unless an OGTT is ordered. The OGTT adds to the cost and is inconvenient in diagnosing diabetes and prediabetic states.

What are the benefits of early diagnosis?

Early diagnosis and tight glycemic control is essential for preventing diabetes-related microvascular complications. Diabetes is a major cause of blindness in adults. Diabetic retinopathy is already present in about 21% of Type 2 diabetics at the time of diagnosis. Diabetic nephropathy is the number one cause of end stage renal disease (ESRD) in Canada and elsewhere. Intensive glycemic control has been shown to have dramatic and highly significant effects on the development of microalbuminuria and the progression of microalbuminuria to overt proteinuria.[7] Since microalbuminuria affects up to 80% of all diabetics but the lifetime risk of ESRD in diabetics (Type 1 or 2) is only about 12%, microalbuminuria is, at best, a poor surrogate marker of ESRD risk. It is, however, a much stronger predictor of cardiovascular risk in Type 2 diabetics and diabetic patients with ESRD have increased morbidity and mortality due to CVD and most die of CAD. CVD is a major cause of morbidity and mortality in diabetics.

In the DPP study, the incidence of diabetes was reduced by 58% in the intensive lifestyle group and by 31% in the metformin group.

The risk of CVD and stroke is increased twofold in male diabetics and threefold to fourfold in female diabetics. Silent ischemia and myocardial infarction are more common and the outcome of myocardial infarction is worse as compared to non-diabetics. Although it has yet to be convincingly demonstrated that intensive glycemic control reduces CVD, many endocri-

nologists believe that early aggressive intervention may reduce CVD and clearly there are other benefits in terms of microvascular disease that justifies intensive glycemic control.

Neuropathy develops within 10 years of diagnosis in 40% to 50% of patients with Type 2 diabetes. Intensive glycemic control has been shown to decrease the prevalence of neuropathy and more importantly to reduce lower limb amputations.

Is diabetes preventable?

Screening and early intervention in individuals with disturbed glucose homeostasis, such as IFG and IGT, is important since there is evidence that it is possible to at least delay the onset of diabetes. In many elderly individuals, delaying the onset of Type 2 diabetes may be equivalent to preventing diabetes. Longitudinal studies in high-risk groups, such as women with a history of gestational diabetes or Pima Indians, suggest that most individuals who develop diabetes pass through a phase of IGT. Resistance to insulin progressively increases as someone progresses from normal to impaired glucose tolerance to diabetes.[8] Based on such observations it is likely that any intervention in the IGT phase that improves insulin resistance, or protects beta cells, or both, should prevent or delay the progression to diabetes.[9]

Several studies have shown benefits with intensive lifestyle modifications, as well as various oral hypoglycemic drugs. In the Acarbose for the Prevention of Type 2 Diabetes (STOP NIDDM) Trial, patients with IGT were randomised to either acarbose arm or placebo.[9] At the end of the study, the acarbose arm had a 25% reduction in the risk of progression to diabetes. This effect was shown irrespective of age, sex, and body mass index (BMI), and while the mechanism is unclear, it may be related to improved postprandial hyperglycemia and reduced glucose toxicity. In the Diabetes Prevention Program (DPP) study, the goal was to demonstrate if it is possible to delay or prevent Type 2 diabetes through lifestyle changes.[10] Patients with BMI greater than 24 and impaired glucose tolerance were enrolled and randomised to three groups. One group made intensive lifestyle modifications with goals of achieving and main-

taining a weight reduction of at least 7% of the presenting body weight by following a low-fat, low-calorie diet and supervised exercise. The second group was treated with metformin, while the third group received standard medical advice regarding healthy lifestyle, including diet and exercise. The DPP study showed that the incidence of diabetes was reduced by 58% in the intensive lifestyle group and by 31% in the metformin group. Clearly in clinical practice, the cost of intensive lifestyle intervention as instigated in this trial would be prohibitive. CME

Take-home message

- Diabetes is a serious disease with devastating complications. Despite the widespread nature of the disease, the diagnosis is delayed, and most patients already have the complications at the time of diagnosis.
- There is now emerging evidence that treating individuals in the pre-diabetic stage, that is when they have IGT, is well worthwhile. Since the diagnosis of IGT requires an OGTT, the challenge is to target screening for this condition to situations where this is likely to be cost-effective.
- Efforts should be made to screen the high-risk population and diagnose diabetes and pre-diabetic states early.
- Once the diagnosis is made the goal should be to maintain tight glycemic control.
- It is not clear yet whether treating individuals with IFG with lifestyle intervention or with medication such as metformin or acarbose reduces the risk of diabetes.

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