Clinical Focus:

Advances in the Treatment of Diabetes

CONTRIBUTORS

SPECIALIST OVERVIEW
Phil Hardin, MD, FACP, FRCPC
Assistant Clinical Professor,
Division of Endocrinology
University of Alberta
Edmonton, Alta.

FP REVIEW
J. Robin Conway, MD
Medical Director, The Diabetes Clinic
Smiths Falls, ON

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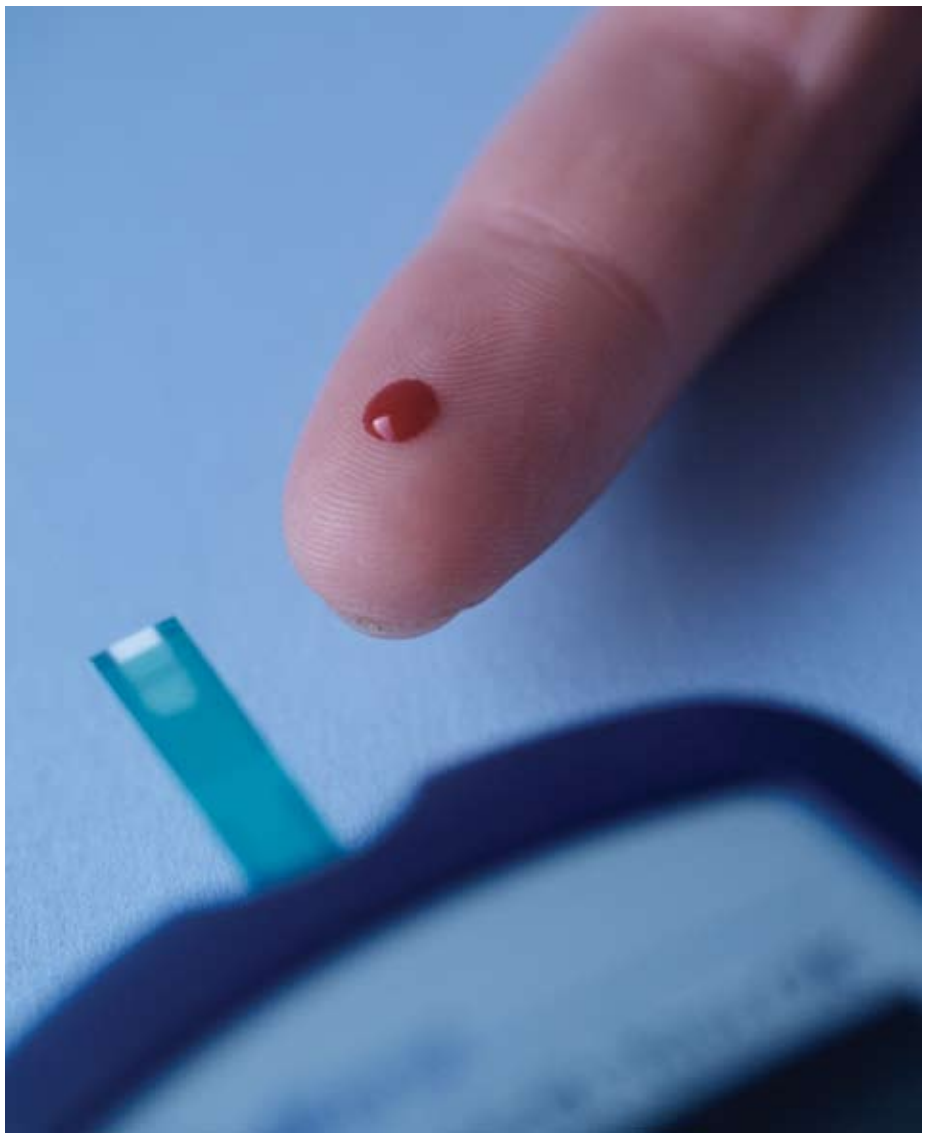

Preventing type 2 diabetes through pretreatment

According to Statistics Canada, 1.3 million Canadians aged 12 years or older report having a confirmed diagnosis of diabetes, representing 5% of that population. This figure skyrockets to 14.6% for those over age 65 — an alarming figure considering the number of additional individuals in that age range who may be living undiagnosed — bringing the total to well over two million people who suffer from the disease. Prevalence rates vary slightly across provinces. Newfoundland and Labrador have the highest rates of diabetes (6.8%), while Alberta has the lowest (3.9%). Data are incomplete for the Northwest Territories and Nunavut. Additionally, there is a large population of Canadians with impaired glucose tolerance (IGT) who supply a steady stream of people into the diabetes population.

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PERSPECTIVE

Taking into account all contributing factors, this diabetic population has been projected to increase by 35% over the next 25 years. That scenario worsens in light of recently published data from a population database in Ontario, which suggests the prevalence of diabetes from 1995 to 2005 actually increased 69%. While this increase may be due in part to declining mortality from diabetes, the study noted an absolute increase in the incidence of diabetes, which was more prominent in the younger age group. Prevalence rates for people aged 50 years or older was found to be 7.1%, while prevalence of diabetes in those aged 20 to 49 years was 3.5%. However, this represented a relative increased prevalence of 94% in the younger age group versus only a 63% increase in the older age group (each compared to 10 years ago).

The Cost of Diabetes

While it is clear that diabetes is a costly disease in terms of healthcare expenditures, there is surprisingly little reliable data available to support an accurate dollar value. The most thorough estimate to date of the economic cost of treating people with diabetes in Canada was based on 1998 data that suggested the government spends an equivalent (at that time) of $5 billion U.S. annually, including direct and indirect costs. It should be noted that although it has generally been emphasized that the cost of renal disease/dialysis is a major cost component of diabetic treatment, it is a mere 1/20th of the cost of cardiovascular disease complications.

Although this figure includes physician and paramedical costs, hospital stays and costs of complications (i.e., costs that the government eventually incurs), it clearly underestimates the true cost of diabetes in this country. Indirect morbidity costs were not included in the estimate, such as those incurred through missed work or school days, or from lower employee productivity. Other costly features of diabetes care are not captured by government costs, not the least of which is capillary glucose testing, which was likely underestimated to be at $115 million annually, based on the average Canadian diabetic testing approximately eight times per week (including type 1 diabetics) and the cost of a strip being $0.60.

The Canadian Diabetes Association alternatively pegs the cost to the Canadian healthcare system at $13.2 billion annually, based on U.S. data, while the Public Health Agency of Canada suggests overall costs of $9 billion, including direct healthcare costs and those arising from lost productivity and premature death. Despite these varying estimates, it remains clear that diabetes exacts a huge toll on the Canadian economy.

DIAGNOSIS

PREDIABETES

Normal glucose can be arbitrarily defined as a glucose level that does not predispose to, or predict, a higher-than-baseline incidence of developing micro- or macrovascular disease. Generally, we consider glucose to be normal if it is less than 6.1 mmol/L fasting, and less than 7.8 mmol/L measured two hours after a glucose challenge.

At the other end of the spectrum is diabetes, which can be defined as the level of glucose at which the incidence of microvascular disease sharply increases (independent of the incidence of macrovascular disease, which increases far earlier in the disease progression). This occurs at a fasting glucose of 7.0 mmol/L, or at a post-challenge glucose of 11.1 mmol/L.

Prediabetes falls between these parameters as impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). IGT is defined as a post-challenge (after drinking a 75 gm glucose load) glucose value of 7.8 to 11.0 mmol/L. According to the guidelines set out by the Canadian Diabetes Association in 2003, IFG is defined by fasting glucose greater than or equal to 6.1, but less than 7.0 mmol/L (see Figure 1). Since this definition was published, the American Diabetes Association lowered their criteria to include fasting glucose values of 5.6 to 6.9 mmol/L. Canadian guidelines will likely follow suit when published in 2008.

Other organizations in the world, specifically the International Diabetes Federation and the World Health Organization, are almost certain not to mirror these guidelines, and will maintain an IFG definition of greater than or equal to 6.1 mmol/L. It should be noted that European organizations tend to shun the terms prediabetes, IFG and IGT altogether, instead using the more general term of "intermediate hyperglycemia."

TREATMENT

PREDIABETES

Should prediabetes be treated?

There has been considerable discussion about whether it is worthwhile to treat prediabetes, or if it makes more sense to simply wait and treat diabetes, and attempt to prevent complications at that

FIGURE 1

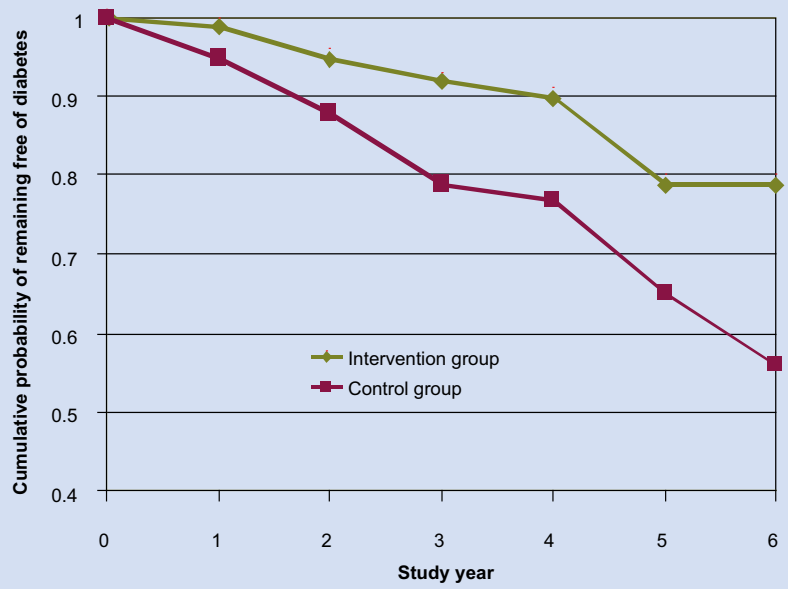
Classification

Classification	Fasting plasma glucose(mmol/L)		2-h plasma glucose 75g OGTT
Normal	<6.1	and	< 7.8
Impaired Fasting Glucose (IFG)	6.1 - 6.9	and	< 7.8
Impaired Glucose Tolerance (IGT)	< 6.1	and	7.8 - 11.0
IFG and IGT	6.1 - 6.9	and	7.8 - 11.0
Diabetes	≥ 7.0	or	≥ 11.1

Adapted from: The Canadian Diabetes Association 2003 Clinical Practice Guidelines.

FIGURE 2

Finnish Diabetes Prevention Study: Proportion of subjects without diabetes during the trial



Adapted from: *NEJM* 344:1343-50, 2001.

FP Review: Perspective

Although we may not realize it, a significant proportion of our practice as family physicians involves patients with diabetes or dysglycemia. The Diascan study (*Diabetes Care* 24:1038-1043, 2001) demonstrated that 23.5% of all patients presenting in the family physician's office for any reason have diabetes, though it may not yet be diagnosed. If we also count the people who have dysglycemia or prediabetes — IFG or IGT — then it is likely that more than half the patients we see have abnormalities in glucose metabolism.

Individuals with abnormal glucose metabolism are at very high risk of cardiovascular (CV) disease, and 80% will die of a CV event. The prediabetic may not experience the microvascular complications of diabetes, but they have almost as high a CV risk as the diabetic. As simple, effective treatments can reduce cardiovascular risk by almost 80%, it is imperative that we recognize this large segment of our practice. With proper screening and treatment, we can have an enormous positive impact on the quality of life of these high-risk patients.

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time. It is this author's opinion that this can be likened to not treating a precancerous lesion because it will not by itself limit lifespan — clearly bad medicine, since if the lesion turns cancerous, lifespan would almost certainly be limited. Put simply, waiting would make no sense. So, too, with prediabetes.

Remember: The only primary prevention in diabetes is to prevent the disease itself from developing.

There is currently no approved oral diabetic treatment agent for prediabetes in Canada.

Progression to diabetes

Once prediabetes has been diagnosed, the incidence of progression to diabetes is high. People are often given standard lifestyle advice to slow the development of diabetes, i.e., to lower fats, lose weight and exercise. In individuals that were enrolled in Diabetes Prevention Program (DPP) studies, those that were given this advice comprised the studies' control groups.

It must be pointed out that the individuals enrolled in prevention trials were motivated to lessen the risk of developing diabetes, or they would not have been enrolled in the studies in the first place. They were, therefore, likely more motivated than the general population to adhere to the lifestyle advice they were given, and it follows that they may have had a higher rate of success with the lifestyle interventions than might be achieved in typical, less-motivated individuals. In other words, the rate of conversion from prediabetes to diabetes may be more than that established in the prevention trials listed below.

The annual rate of development of diabetes in people with IGT seen in the control groups was similar, but there were differences between studies. In both the DPP (Suggested Reading #5), DaQing IGT and Diabetes (Pan XR *et al. Diabetes Care* 1997; 20:537–44) studies, rates of progression to diabetes were 10% to 11% annually. In the Finnish Diabetes Prevention Study (DPS), the annual rate of progression to diabetes was 7%. The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) trial showed a similar result (Suggested Reading #9).

Furthermore, the category of their glucose intolerance is also important. People who had both IFG and IGT developed diabetes at a rate of 14% (DREAM trial) to 22% (DPP) annually. Obviously, the higher their glucose in the specific category also determines risk.

Other factors need to be taken into account to define the risk of developing diabetes. Regardless of the glucose status, a high rate of diabetes development correlates to a higher body mass index (BMI) and waist circumference measurements. Total body fat content also plays an important role in the development of the disease.

Lifestyle approaches

Generally speaking, patients should be advised to see a dietitian and to cut their fat intake to no more than 30% of calories (saturated fats should be less than 10%). They should be placed on a calorie-reduced, nutritionally balanced diet, preferably one that is high in fibre and with a low GI index. These are common recommendations. As there is very little evidence in the literature that suggests any particular diet is more beneficial than another, the actual method used to induce weight loss is usually of little importance. Losing weight can be difficult and patients should be encouraged to pursue whichever healthy method or program suits them, and/or has demonstrated success for them in the past.

Individuals should also be encouraged to exercise for 30 minutes daily, five days per week, achieving a minimum of 150 minutes weekly. Certainly, it may take time to build up to this level. Exercise may consist of walking, but any form of physical exertion that the individual prefers is acceptable.

How long should lifestyle interventions be tried?

The lifestyle interventions used in studies that have demonstrated a marked lowering of diabetes development could best be described as intensive. These have included the following:

- Achieving and maintaining a 7% reduction in body weight using the noted dietary changes (limiting fats and calories);
- Increasing physical activity to at least 30 minutes per day, minimum five days per week;
- Initiating regular access to dietitians, a health club and/or personal trainers; and
- Counselling sessions to reinforce behavioural changes.

Initiating these lifestyle changes on a population basis may not be practical, and many patients lack the motivation required to successfully adopt a healthier lifestyle. Therefore, individual patient circumstances will dictate how long lifestyle interventions should be employed before resorting to pharmacologic measures in the prevention of diabetes. Generally speaking, if an individual is less obese and does not have combined IGT and IFG — and in the absence of other risk factors — lifestyle measures might be trialled for six months or more. Individuals who are obese, with IFG in the upper range (6.5 to 6.9 mmol/L) and with two-hour post-challenge (oral glucose tolerance test or OGTT) glucose readings in the upper range (9.5 to 11.0 mmol/L), are at very high risk of developing diabetes in a short period of time. These patients should be given a shorter period of up to three months to see if lifestyle changes can be effective independent of medication.

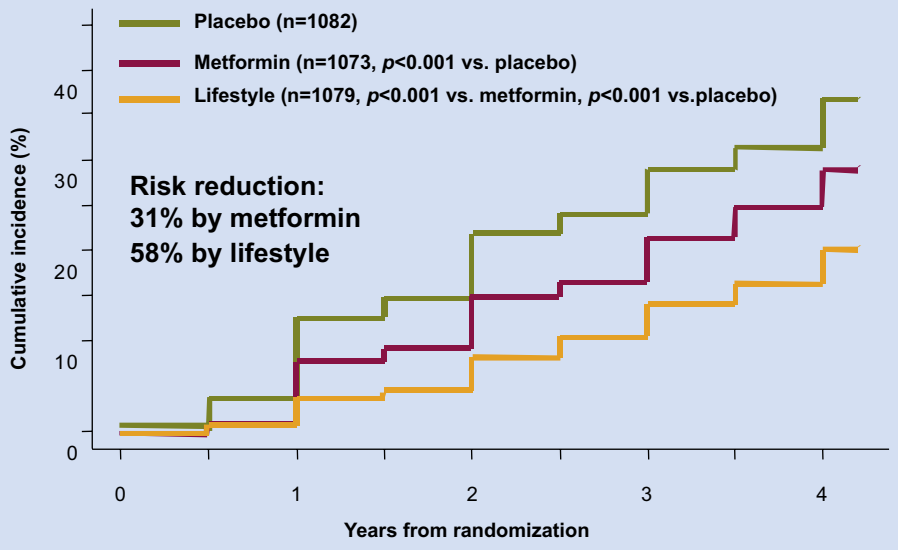
Useful measures to monitor the success of lifestyle intervention include tracking overall history, identifying both dietary and activity levels, documenting waist circumference (a loss of 2 cm over the first three months is a reasonable target) and, to a certain extent, weight loss (although this may be a somewhat deceiving parameter in an individual who is exercising more).

How effective can lifestyle changes be?

In the Finnish Diabetes Prevention Study (Suggested Reading #4), the risk of developing diabetes was reduced by 58% in patients using the intensive interventions discussed above (see Figure 2, page 2). Not coincidentally, the same risk reduction was also seen in the DPP studies (Suggested Reading #5).

FIGURE 3

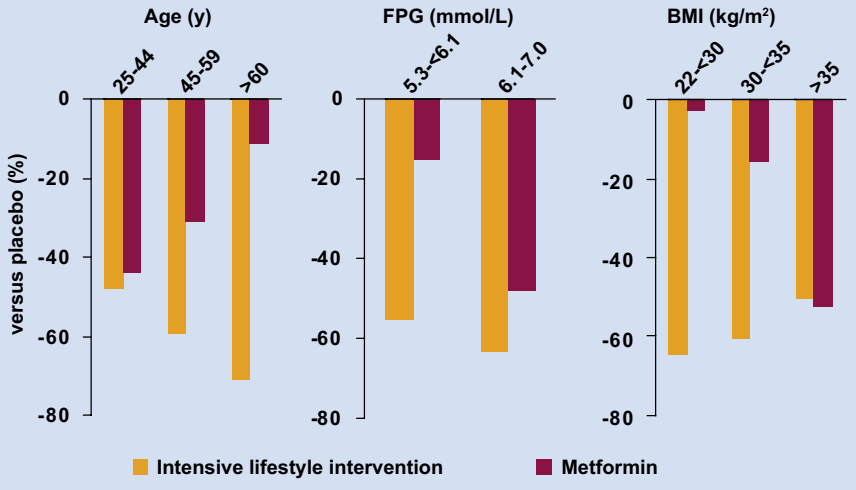
The DPP: Incidence of diabetes



Adapted from: The DPP Research Group, *NEJM* 346:393-403, 2002.

FIGURE 4

Subgroup analysis in the DPP



Adapted from: The DPP Research Group, *NEJM* 346:393-403, 2002.

There has been considerable discussion about whether it is worthwhile to treat prediabetes… It is this author's opinion that this can be likened to not treating a precancerous lesion because it will not by itself limit lifespan.

~Dr. Phil Hardin

While it may not be realistic to believe people will adopt healthier lifestyles that achieve results similar to these clinical studies — it can, after all, be difficult to motivate change even in patients who are diagnosed with diabetes — lifestyle interventions are worth trying in prediabetes, however slim the odds of success.

Pharmacologic interventions

There are now a number of studies that demonstrate the benefits of employing pharmacologic therapy in preventing progression to diabetes in individuals with IGT.

The DPP showed metformin at a dose of 850 mg twice daily resulted in a 31% overall reduction of the incidence of developing diabetes (see Figure 3, page 3). Certain subgroups taking metformin reported results almost as good, or even slightly better than those derived from lifestyle changes alone (see Figure 4, page 3). Predictors of improved risk reduction were a younger age (< 44 years) and a BMI > 35 (reduction in incidence of developing diabetes: 53%).

In the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP NIDDM) study (Suggested Reading #8), acarbose achieved a relative risk reduction of 36% in the development of diabetes (see Figure 5). All subgroups showed similar risk reductions, with no particular benefit in one versus another.

Finally, rosiglitazone in the recently completed DREAM study showed a 62% risk reduction in the development of diabetes (see Figure 6, page 5). Indeed, people at highest risk, i.e., people with the highest BMI, seemed to experience the greatest relative risk reduction.

DIABETES

The overall aim in treating diabetes is to prevent devastating complications. Most people with diabetes (75% or more) will die a vascular death, and thus it remains our primary goal to prevent macrovascular disease. Furthermore, we need to improve diabetics' quality of life by preventing microvascular complications, including renal disease, retinopathy, neuropathy and amputation. The more we can maintain beta-cell function, the better we are able to optimize glucose control and thereby achieve these goals. Therefore, maintaining beta-cell function must be an aim in its own right.

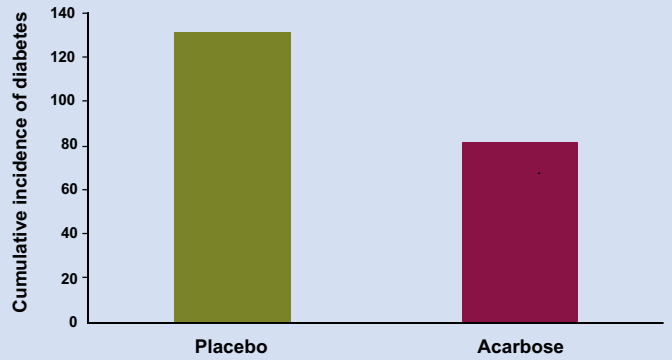
How common are complications?

With respect to microvascular disease, diabetes is the most common cause of blindness in working-age adults, and is by far the commonest cause of end-stage renal disease requiring dialysis. With its associated neuropathy, diabetes is also the leading cause of non-traumatic amputations of the lower extremity.

Its contribution to macrovascular disease is enormous, and is almost universally underappreciated and underestimated. In one study looking at people who present to hospital with myocardial infarction (MI), it was shown that one-third of all people post-MI had diabetes, and that a further third had IGT. When OGTTs were repeated three months later to exclude the effect of "stress hyperglycemia," the results

FIGURE 5

The effect of acarbose on the cumulative incidence of diabetes in subjects with IGT based on 2 OGTTs



HR = 0.64 (0.49 - 0.85); *p*=0.0018 Relative risk = 36%; Absolute risk = 7%

Adapted from: Chiasson, J.-L. *et al. Lancet* 359:2072-2077, 2002.

FP Review

Diagnosis and Treatment of Prediabetes

It is imperative that all patients over 40 years of age have their fasting blood glucose tested every three years, with more frequent testing for high-risk individuals. If properly screened, patients with prediabetes can be diagnosed and treated in time to prevent the progression to diabetes.

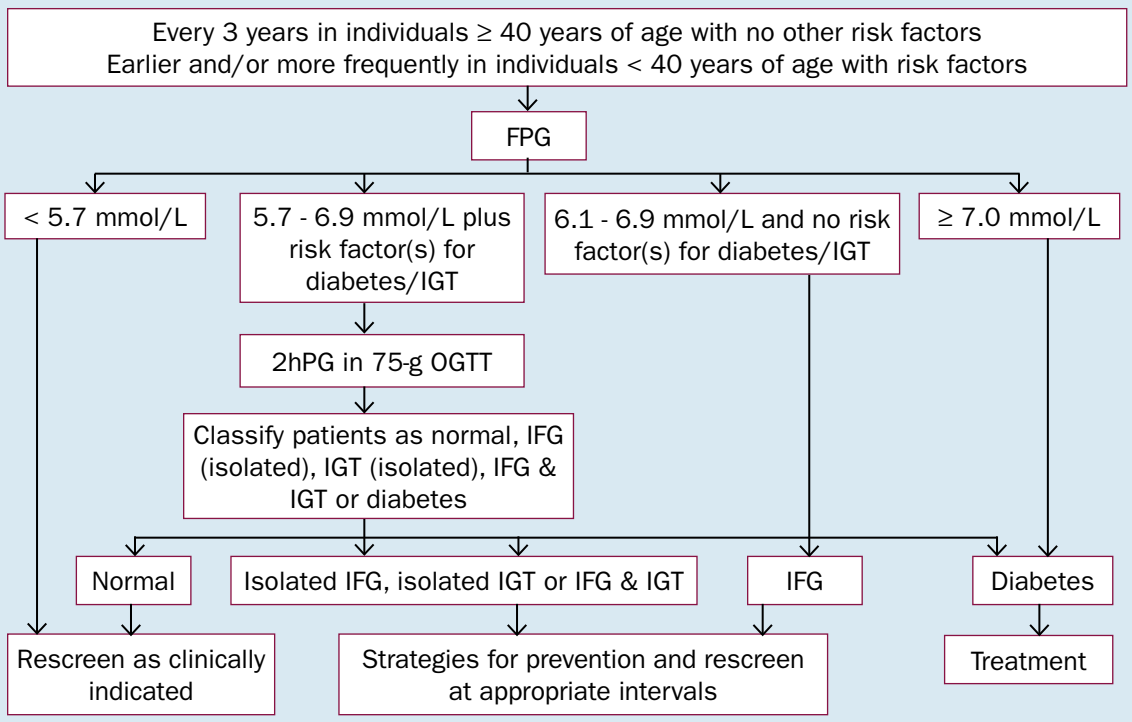
Those who have a fasting glucose greater than 5.7 but less than 6.9 mmol/L should have a two-hour, 75 gm glucose tolerance test to rule out IGT. Those with fasting glucose between 6.1 and 7.0 mmol/L have IFG, a prediabetic condition. A fasting glucose of > 7.0 mmol/L or a random glucose of greater than 11 mmol/L in the presence of symptoms indicates diabetes. If there are no symptoms, such as polyuria, polydipsia or fatigue, then confirmatory tests should be done (see Figure below).

According to the DPP, diet and exercise in prediabetics can reduce conversion to diabetes by up to 58%. The barriers to success here are that weight loss of 7% of total body weight is required, as well as vigorous exercise for at least 30 minutes each day.

In those individuals who cannot maintain the extensive lifestyle changes required to prevent diabetes, pharmacotherapy must be considered. Acarbose, metformin and rosiglitazone have all shown benefit in prevention of diabetes. The DREAM trial demonstrated that 8 mg of rosiglitazone a day resulted in a 62% reduction in conversion to diabetes in individuals with prediabetes, making it an effective agent according to available evidence.

Additionally, we can reduce the risks of cardiovascular disease by using simple vascular protection strategies offered with ACE inhibitors, ASA and statins.

Screening for type 2 diabetes, IFG and IGT



Adapted from: *Can J Diab*, December 2006.

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changed very little; there were slightly fewer diabetics, but a few more patients with IGT. Still, two-thirds of the post-MI population had some abnormality of glucose tolerance. Furthermore, the sizable Nurses Health Study demonstrated that the risk of having a coronary event in those destined to have diabetes started rising even before the onset of the disease.

Maintenance of beta-cell function

There are no studies that suggest that once an individual has diabetes (and by definition, significantly impaired beta-cell function), any degree of lifestyle intervention will prevent worsening of beta-cell function. This is not to say that aggressive lifestyle improvement won't contribute significantly to controlling blood glucose, which it likely does by improving insulin sensitivity.

The question remains whether this is possible with oral hypoglycemic agents. We learned from the UK Prospective Diabetes Study (UKPDS) study that insulin therapy, metformin or sulfonylurea therapy cannot maintain beta-cell function and that there is a progressive loss of function with time. In UKPDS, this loss of beta-cell function occurred whether hypoglycemic therapy was used or not, and at an equivalent rate (see Figure 7).

There are a considerable number of animal models of diabetes in which thiazolidinedione (TZD) drugs have been shown to prevent the onset of diabetes, while maintaining normal islet-cell architecture. The recently released A Diabetes Outcome Progression Trial (ADOPT) was designed to evaluate the durability of glycemic control in patients receiving monotherapy, either rosiglitazone, metformin or glyburide. The study showed progressive loss of beta-cell function in the glyburide and metformin groups. There was some loss of beta-cell function in the rosiglitazone group as well, but the rate of loss was slower, and target glucose levels were maintained for longer periods of time. This equated to better maintained glucose and HbA1c over time, as well.

It must be emphasized that although the loss of beta-cell function over time was minimized with rosiglitazone, it still occurred. This may be a function of starting the drug too late in the course of the decline of the beta cell, or it may simply reflect how little can be achieved with monotherapy. It is possible that initial dual therapy, even with HbA1c of less than 7%, may do an even better job of preventing beta-cell deterioration. There is substantial theoretical reason to believe that the combination of metformin and rosiglitazone may be better at preventing beta-cell loss. Both glucotoxicity and lipotoxicity (each thought to play a role in beta-cell deterioration) can be minimized with early combination therapy of a TZD and metformin. We need to address the beta cells as early as possible in the course of diabetes, while there is still considerable function left to preserve. Although there are no specific published studies looking at early initial combination therapy in type 2 diabetes, some insights may be available with upcoming release of the CAnadian Normoglycemia Outcomes Evaluation (CANOE) and Avandia + Amaryl or Avandamet Compared With Metformin (AVALANCHE) studies.

Why is achieving and sustaining glycemic control important?

All studies looking at the incidence of microvascular disease and glucose control suggest that the better the glucose control and A1c, the lesser the incidence of microvascular complications of diabetes, including retinopathy and nephropathy.

There are a large number of epidemiological studies that identify a reduction in the incidence of cardiovascular events with improved glucose control. However, there is a lack of intervention studies that corroborate this finding; this question will likely not be resolved until the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is released. Acknowledging that it is unethical in an intervention trial to study a group of diabetics with deliberate poor glucose control, we will have to wait for the outcome of "perfect" versus "good" control.

Early aggressive therapy

We increasingly stress "early aggressive therapy" in the treatment of diabetes. This involves aggressively trying to achieve glucose control, aiming for a normal HbA1c. This will reduce the incidence of microvascular complications, and there is reason to believe it will also lessen the incidence of macrovascular disease, as well.

According to the most recent Clinical Practice Guidelines for the Management of Diabetes in Canada, metformin is the first-line antihyperglycemic agent for almost all patients with diabetes. This is based on the fact that it is effective and that the incidence of hypoglycemia is low with its use. There is evidence to suggest metformin is more effective at reducing macrovascular disease in obese individuals compared with sulfonylureas or insulin.

However, the guidelines may in fact overstate the clinical evidence for this latter claim, which was based on results in a fairly small number of obese people in the UKPDS study. Nevertheless, there is biological plausibility to support this belief, as metformin therapy in UKPDS (and numerous other studies) resulted in less weight gain (more obese patients may have had more CV disease on that basis), and because it achieved equivalent glucose control in the absence of hyperinsulinemia (which both sulfonylureas and insulin clearly created).

There is another variable in the equation. The ADOPT study suggests that there is a difference in the functional deterioration of beta cells, and that rosiglitazone can stall this process. In the interest of preserving the ability to maintain good glycemic control over a long interval, we should perhaps be using this class of drugs as first-line treatment. It may make sense to combine metformin and a TZD early, for potential benefit in glucose control, resulting in a larger number of individuals achieving target HbA1c with minimal hypoglycemia, and for better beta-cell preservation. There is also an additive lowering of the state of hyperinsulinemia, which may result in a subsequent lowering of vascular events.

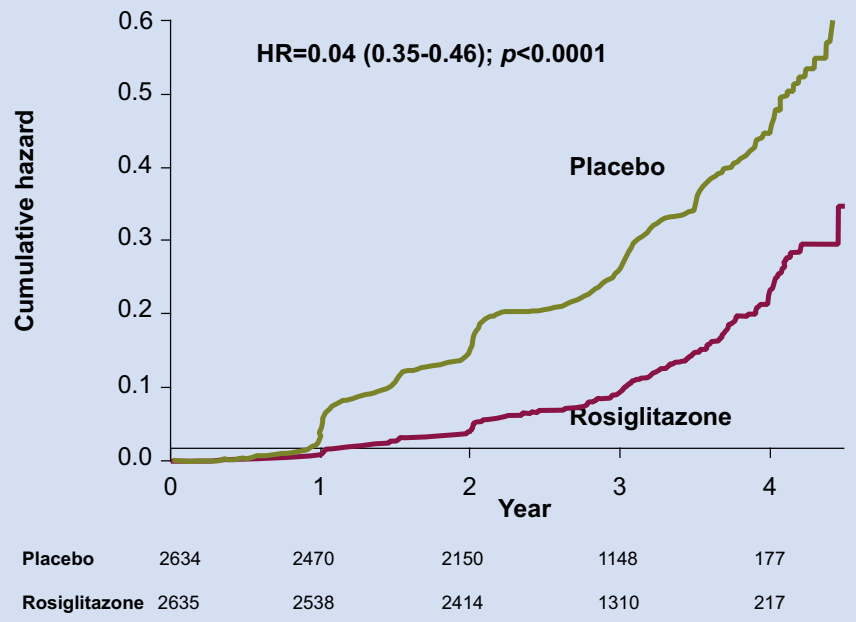
Aggressive treatment does not stop here. As noted, the aim in treating the individual with diabetes is to prevent complications, and aggressive therapy entails achieving all target values, including those for lipids and blood pressure. We must also be fanatical about bringing blood pressure levels to < 130/80 mmHg, bringing LDL cholesterol levels to < 2.0 mmol/L and bringing total cholesterol/HDL levels to < 4.

Unless a type 2 diabetes patient's lipids are near perfect at the outset, treatment with a statin is often necessary and, in a significant percentage of patients, combination therapy with ezetimibe (and/or a fibrate and/or niacin) may be warranted.

Arguably, all people with type 2 diabetes should be on an ACE inhibitor for vascular protection if it can be tolerated. All doses of ACE inhibitors that have been shown in studies to offer a reduction in vascular events have been relatively large. This would translate

FIGURE 6

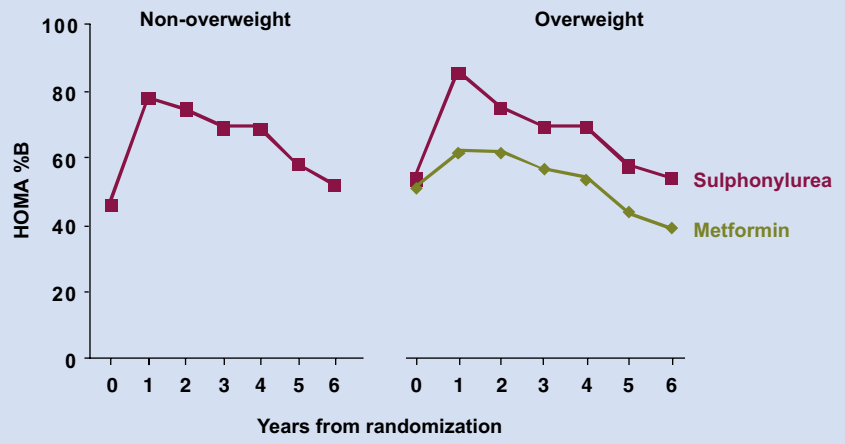
DREAM primary outcome



Adapted from: *Lancet* Vol 368, 2006; 1096-1105.

FIGURE 7

Beta-cell function is decreased and declines progressively



Adapted from: UKPDS 16. *Diabetes* 1995; 44:1249-58.

to a ramipril dosage of 10 mg, at least 8 mg for perindopril, 20 mg for enalapril and 5 mg for cilazopril.

We also must prevent renal disease and treat microalbuminuria aggressively, with the addition of angiotensin receptor blockers (ARBs) when necessary.

Maintaining target blood pressure is of the utmost importance in preventing renal and macrovascular disease. The addition of diuretics and calcium channel blockers is often needed; in fact, it is often necessary for diabetics to be on three or four medications to control blood pressure at target.

Most studies (in diabetics or otherwise) tend to analyze impacts on one risk factor at a time. There is, however, some information in diabetics on treating multiple risk factors, and looking at the outcome when all are aggressively treated.

There is recently published data from the UKPDS study that looks at rates of myocardial infarction at different HbA1c levels and blood pressures. It demonstrates that having blood pressure of 150 mmHg compared to < 130 mmHg, and having an A1c of 8% versus < 6%, will increase the rate of MI at least five-fold, at least in that particular study.

The Steno-2 Diabetes Trial (Suggested Reading #14) looked at a small number of diabetic individuals in clinic, and targeted systolic and diastolic blood pressure, total cholesterol and triglycerides and A1c. Target levels were not achieved in all individuals, but the act of targeting is by itself useful. The results demonstrated a 50% reduction in CV events over eight years.

We await the ACCORD trial data, which is similar to Steno-2, but on a much larger scale. It will look at very tight glucose control versus good control, statin alone versus statin plus fibrate and tight blood pressure control versus more relaxed control.

ROSIGLITAZONE & CARDIOVASCULAR SAFETY

There has been concern regarding the cardiovascular safety of rosiglitazone following a recent meta-analysis in *The New England Journal of Medicine* (*NEJM* 2007;356, June14, Nissen SE, Wolski K).

However, we should reserve judgment until the RECORD trial (Rosiglitazone Evaluation for Cardiac Outcomes and Regulation of glycemia in Diabetes) is published. The trial, which is looking at the incidence of vascular disease with TZDs, is a prospective, randomized, open-label, controlled trial conducted over a prolonged period of time. Results will not be available until 2009, but it is reassuring that the FDA is monitoring interim results, as is the study's Safety Monitoring Committee. Also, the DREAM and ADOPT trials show no significant increase in risk of MI with rosiglitazone.

Statements from the Canadian Diabetes Association, the FDA, The Endocrine Society and the American Diabetes Association (in a joint statement with the American Heart Association and American College of Cardiology) agree that we need more information and that we should not unduly stop a medication that is beneficial for some patients.

PROGNOSIS

In summary, early aggressive therapy involves the initiation of at least one or two antihyperglycemic agents, a statin, +/- another lipid agent, an ACE inhibitor and perhaps one or two other antihypertensives, plus ASA. Continued emphasis on lifestyle adjustments must also be made.

Diabetes is a devastating disease with multiple complications, and while it cannot be reliably ascertained how many years a diabetic individual's life may be shortened, it is nevertheless clear that their lifespan is negatively impacted. Effective screening of our at-risk patients for prediabetes, along with early, aggressive treatment, can go a long way towards reducing the physical, psychosocial and economic consequences of this disease. ●

FP Review

Treatment

We know that increasing insulin resistance may precede diabetes by 10 to 15 years, but that insulin deficiency is required to become diabetic. In the early stages of the disease, it is primarily a disease of insulin resistance, but with progressive beta-cell failure, insulin deficiency becomes the predominant defect.

In most cases, our initial therapy should be directed toward decreasing insulin resistance. The UKPDS trial has shown that the progressive increase in glucose levels of diabetes is caused by a progressive loss of insulin production by the failing beta cell. Until recently, the progressive beta-cell failure continued no matter what treatment we used. I try to get a glitazone into the therapeutic regimen as soon as possible. Although CDA Guidelines (which were published before these trials were reported) do not generally suggest a glitazone as initial treatment, the preservation of beta-cell function, as well as the decrease in insulin resistance, should be a major consideration.

BARRIERS TO TREATMENT

Lifestyle measures, while extremely important, have been traditionally very difficult to maintain. In the diabetes prevention studies that demonstrated the potential benefit of the lifestyle modifications, it was a costly and labour-intensive program that may be difficult to duplicate outside of a study environment.

Optimal care also involves the use of many medications (see Table 1, page 7). Frequently, our patients are reluctant to take multiple prescriptions, particularly if they are feeling well. Employing long-acting or combination medications can reduce the number of pills that must be taken daily, and a careful explanation of the role of each pill can highlight their importance in the overall treatment strategy. Compliance is always an issue with multiple medications that are sometimes dosed many times a day, and so it is wise to make medication regimens as simple as possible — some studies suggest dosing more than twice a day significantly limits adherence.

Drug cost may also be a barrier, and so we need to be aware of alternatives. In most cases, combination medications cost less, but there are still a few instances in which the combination actually costs more than its individual components. Significant savings can result from prescribing medications at twice the strength required, and cutting the tablets in half. Lack of coverage for patients on provincial drug plans is also an issue. The provincial plans frequently do not pay for the drugs or the treatment order recommended by CDA Guidelines, and consequently people on these plans may receive substandard care with pancreatic deterioration that may have been avoided with appropriate treatment. There are often mechanisms by which we can gain special access to these medications, and we need to be familiar with how they work (and we must be willing to assume the resulting paperwork burden).

CDA Guidelines support metformin as initial treatment. Metformin decreases the excess glucose production by the liver, which is an integral aspect of diabetes. While it improves insulin sensitivity and decreases glucose levels, it does not prolong the inevitable beta-cell decline. Metformin is available in 500 mg and 850 mg tabs, as well as 500 mg sustained-release tablets (Glumetza). In the generic form, it is inexpensive. Dosage is from 500 to 2000 mg/day — doses in excess of 2000 mg may lead to decreased efficacy. The pharmacokinetics of metformin are such that there is no advantage in dosing more than twice a day. I generally titrate up to 1000 mg, twice a day. Insulin sensitizers (glitazones) are indicated where control cannot be achieved with metformin monotherapy.

The ADOPT study has shown that the most persistent control with monotherapy comes with a glitazone (rosiglitazone). My tendency is therefore to start a glitazone early, either as monotherapy or in combination with metformin. Formulations of a glitazone with metformin are available (e.g., Avandamet), and these may make adherence easier for the diabetic.

Where glycemic targets cannot be maintained with metformin and a glitazone in full therapeutic doses, we need to consider the other fundamental defect of diabetes: insulin deficiency. Here, we need to increase insulin levels with either an insulin secretagogue or with insulin. If A1c is > 9%, then two classes of agents with a complementary mechanism of action should be started together, since each will only give a 1% to 1.5% A1c reduction.

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TABLE 1

Antihyperglycemic agents for use in type 2 diabetes

Class	Expected decrease in A1C with monotherapy	Therapeutic considerations
Alpha-glucosidase inhibitor acarbose	0.5 - 0.8	• Not recommended as initial therapy in people with severe hyperglycemia (A1C ≥ 9.0%) • Mostly used in combination with other oral antihyperglycemic agents • Gastrointestinal side-effects • Treat hypoglycemia with dextrose tablets, milk or honey
Biguanide metformin	1.0 - 1.5	• Contraindicated in patients with renal or hepatic dysfunction, or cardiac failure • Use Cockcroft-Gault formula to calculate creatinine clearance (< 60 mL/min indicates caution or contraindicates the use of metformin) • Associated with less weight gain than sulfonylureas and does not cause hypoglycemia • Gastrointestinal side-effects
Insulin	Depends on regimen	• When initiating insulin, consider adding bedtime intermediate-acting insulin, long-acting insulin or extended long-acting insulin analogue to daytime oral antihyperglycemic agents (although other regimens can be used) • Intensive insulin therapy regimen recommended if above fails to attain glycemic targets • Causes greatest reduction in A1C and has no maximal dose • Increased risk of weight gain relative to sulfonylureas and metformin
Insulin secretagogues **Sulfonylureas:** gliclazide, glimepiride, glyburide (note: chlorpropamide and tolbutamide are still available in Canada, but rarely used) **nonsulfonylureas:** nateglinide, repaglinide	1.0 - 1.5 0.5 (for nateglinide)	• All insulin secretagogues reduce overall glycemia similarly (except nateglinide) • Postprandial glycemia is especially reduced by nateglinide and repaglinide • Hypoglycemia and weight gain are especially common with glyburide • Consider using other class(es) of antihyperglycemic agents first in patients at high risk of hypoglycemia (e.g., the elderly) • If a sulfonylurea must be used in such individuals, gliclazide and glimepiride are associated with less hypoglycemia than glyburide • Nateglinide and repaglinide are associated with less hypoglycemia in the context of missed meals
Insulin sensitizers (TZDs) pioglitazone, rosiglitazone	1.0 - 1.5	• Contraindicated in patients with hepatic dysfunction or significant cardiac failure • Between 6 and 12 weeks required to achieve full blood glucose lowering effect • Triple therapy: addition of TZD to metformin plus sulfonylurea is acceptable (Editor's note: this usage is not currently approved by Health Canada) • May induce mild edema, fluid retention • When used in combination with insulin, may increase risk of edema and CHF The combination of a TZD plus insulin is currently not an approved indication in Canada
Combined formulation of rosiglitazone and metformin	1.0 - 1.5	• See rosiglitazone and metformin
Antiobesity agent orlistat	0.5	• Associated with weight loss • Gastrointestinal side-effects

Adapted from: The Canadian Diabetes Association 2003 Clinical Practice Guidelines.

RESOURCES

CANADIAN DIABETES ASSOCIATION
The website of the Canadian Diabetes Association has evidence-based Clinical Practice Guidelines for the diagnosis and treatment of diabetes in Canada.
www.diabetes.ca

DIABETES CLINIC
A non-commercial Canadian website dedicated to educating diabetics and healthcare professionals.
www.diabetesclinic.ca

TYPE 2 DIABETES,A HEALTH PROFESSIONAL'S GUIDE
Published by the Canadian Centre for Research on Diabetes, this is a short (36-page), simple guide designed to assist health professionals in treating type 2 diabetes to CDA standards. Can be obtained free of charge in English or French by sending an email request to
diabetes@igs.net

PREVENTION AND MANAGEMENT OFTYPE 2 DIABETES IN ADULTS
by Stewart B. Harris, MD; Elsevier Canada, 2007.

Suggested Reading

1. Statistics Canada. Smoking and Diabetes Care: Results from the CCHS Cycle 3.1 (2005). www.statcan.ca/english/research/82-621-XIE/82-621-XIE2006002.pdf
2. *Lancet* Vol. 369, 2007;750–56. Trends in Diabetes prevalence, incidence and mortality in Ontario, Canada 1995–2005: a population-based study.
3. *Diabetes Care* 24,2002:1303–07. The economic cost of diabetes in Canada 1998.
4. *NEJM* Vol. 344, 2001; 1343–50. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with Impaired Glucose Tolerance.
5. *NEJM* Vol. 346, No. 6, 2002; 393–403. Reduction in the incidence of type 2 diabetes with lifestyle intervention or Metformin.
6. *Diabetes* Vol. 54, 2005; 1150–56. Prevention of type 2 diabetes with Troglitazone in the Diabetes Prevention Program.
7. *Canadian Journal of Diabetes* 27, 2003, suppl 2. Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada.
8. *Lancet* Vol. 359, 2002; 2072–77. Acarbose for the prevention of type 2 diabetes mellitus. The STOP-NIDDM randomized trial.
9. *Lancet* Vol 368, 2006; 1096–1105. The effect of Rosiglitazone on the frequency of diabetes in patients with Impaired Glucose Tolerance or Impaired Fasting Glucose: a randomized controlled trial.
10. *NEJM* Vol. 355, 2006; 2427–43. Glycemic durability of Rosiglitazone, Metformin or Glyburide monotherapy.
11. *Lancet* Vol. 352, 1998; 837–53. Intensive blood glucose control with Sulfonylurea or insulin with conventional therapy and risk of complications in patients with type 2 diabetes mellitus (UKPDS33).
12. *Lancet* Vol. 352, 1998; 854–65. Effect of intensive blood glucose control with Metformin on complications in overweight patients with type 2 diabetes (UKPDS34).
13. *Diabetologia* Vol. 49, 2006; 1761–9. Additive effect of glycemia and blood pressure exposure on risk of complications in type 2 diabetics: a prospective observational study (UKPDS75).
14. *NEJM* Vol. 348, 2003; 383–93. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes.

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1 Case Study: Presentation

MR. D. M., A CAUCASIAN MALE, 44 YEARS OLD, PRESENTS FOR ROUTINE FOLLOW-UP OF HYPERTENSION DIAGNOSED TWO YEARS PRIOR. HE WAS TREATED WITH ACE INHIBITOR. HE HAS A SEDENTARY LIFESTYLE AND HAS NOTED A 5 KG WEIGHT GAIN OVER THE LAST YEAR. THERE IS A FAMILY HISTORY OF TYPE 2 DIABETES (FATHER) AND CAD (MOTHER, MI AT AGE 53).

Physical examination:

- WC = 106 cm, weight 98 kg, BMI = 31.0
- BP = 134/82 mmHg
- Remainder of physical exam is unremarkable

Laboratory investigations:

- FPG = 6.5 mmol/L
- TC = 4.17 mmol/L, LDL-C = 2.2 mmol/L, HDL-C = 0.87 mmol/L, TG = 2.4 mmol/L, TC/HDL ratio = 4.8

Mr. D. M. has the criteria for a diagnosis of metabolic syndrome, with treated hypertension (still not at goal), high waist circumference, low HDL, high triglycerides and a fasting glucose of 6.5.

These results identify an increased risk for cardiovascular events and also define an increased risk of developing diabetes. Established treatment of metabolic syndrome consists of weight management and treatment of separate CV risk factors. The former will also lessen the risk of diabetes. However, a glucose tolerance test should be done to further define this risk.

When this was performed, his repeat fasting glucose was 6.4, and a two-hour post-challenge glucose was 10.3 — suggesting IGT in addition to his IFG. His risk of developing diabetes would be expected to be 15% or more within a year.

FOLLOW-UP

He was given "lifestyle" management advice and seen again in three months. At this time, he had not increased activity levels. He tried to "diet," but admits his downfall is watching TV in the evening and snacking. He feels that he may have lost a few pounds, but the scale does not confirm any change in his weight. There is no change in his waist circumference.

At this point, he would benefit from pharmacologic intervention, and there is evidence supporting the use of rosiglitazone, metformin or acarbose. More benefit has been demonstrated with rosiglitazone. This was explained to Mr. D.M., but he did not like the chances of gaining weight on the medication, deciding on metformin instead. This was not an unreasonable choice, in view of the fact that he fell into two of the categories that would be anticipated to respond well to metformin, i.e., IFG plus IGT and age 44. This was prescribed with directions to increase the dose over the next three weeks to achieve 850 mg twice daily. Unfortunately, he was lost to follow-up. ●

Senior Vice-President: JOHN MILNE
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Assistant Art Director: SANDRA EVERSON
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2 Case Study: Presentation

MR. D.M., CAUCASIAN MALE, IS NOW 47 YEARS OLD AND PRESENTS AGAIN FOR ROUTINE FOLLOW-UP OF HYPERTENSION. HE HAS NOT BEEN IN THE OFFICE FOR THE PAST THREE YEARS. HE DID NOT CARRY THROUGH WITH THE METFORMIN. HE HAD SOME GI UPSET WHEN HE GOT TO A DOSE OF 850 MG TWICE DAILY, WITH DIARRHEA, AND STOPPED TAKING THE MEDICATION. HE DID NOT BOTHER TO INFORM HIS HEALTHCARE TEAM. HE HAS MAINTAINED HIS ACE INHIBITOR, WITH REFILLS GIVEN BY ANOTHER PHYSICIAN.

Physical examination:

- WC = 109 cm, Weight is 102 kg, BMI = 32.2
- BP = 140/84 mmHg
- Remainder of physical exam is unremarkable

Laboratory investigations:

- FPG = 8.5 mmol/L
- TC = 4.70 mmol/L, LDL-C = 2.6 mmol/L, HDL-C = 0.83 mmol/L, TG = 2.8 mmol/L, TC/HDL ratio = 5.7
  An A1c is subsequently obtained and was found to be 7.2%

Since he was last seen, he has gained weight, making his metabolic parameters even worse. He now has criteria for diabetes, and does not require a further glucose tolerance test. Furthermore, his lipids have also worsened.

It would be reasonable to get more baseline readings, including creatinine, electrolytes, urine albumin/creatinine ratio, ECG and chest X-ray. Particular attention should be paid during this physical exam — and at subsequent visits — to his vascular and neurological status, and the condition of his feet. He should have a yearly ophthalmologic exam (unless otherwise indicated by his ophthalmologist).

Aggressive early therapy must now come into play. If we want to minimize CV risk as much as possible, we must strive to achieve and maintain all target levels, including an A1c of < 6.1% if possible, BP < 130/80 mmHg, LDL < 2.0 mmol/L and TC/HDL ratio < 4.0.

He did not tolerate metformin at 850 mg twice daily, but it is too useful a drug to give up on at this juncture. One should try again, starting at 250 mg twice daily, increasing to 500 mg twice daily. We should also start a TZD and rosiglitazone initiated at 8 mg daily. This should work very well in combination with the metformin, and is very likely to achieve target glucose control. Furthermore, the evidence suggests that it is an efficacious agent to maintain beta-cell function, thus allowing us to continue maintaining glucose control for a longer period of time.

His ACE inhibitor is currently ramipril 5 mg daily; this is doubled to 5 mg twice daily and a diuretic is added in the form of hydrochlorothiazide 12.5 mg daily. BP comes down nicely to 126/74 mmHg.

Finally, a statin is started in the form of rosuvastatin 10 mg daily, and his lipid targets are achieved with total cholesterol of 3.2, HDL of .84, LDL of 1.5 and triglycerides of 1.9. Total cholesterol/HDL ratio is 3.8.

The absolute importance and value of weight loss continues to be reinforced, as is increasing physical activity.

Taken in total, we would expect these manoeuvres to lessen the risk of a cardiovascular event by at least 50%. For this very high-risk individual, we should accept no less. ●