Clinical Focus:

The Future of Diabetes Management

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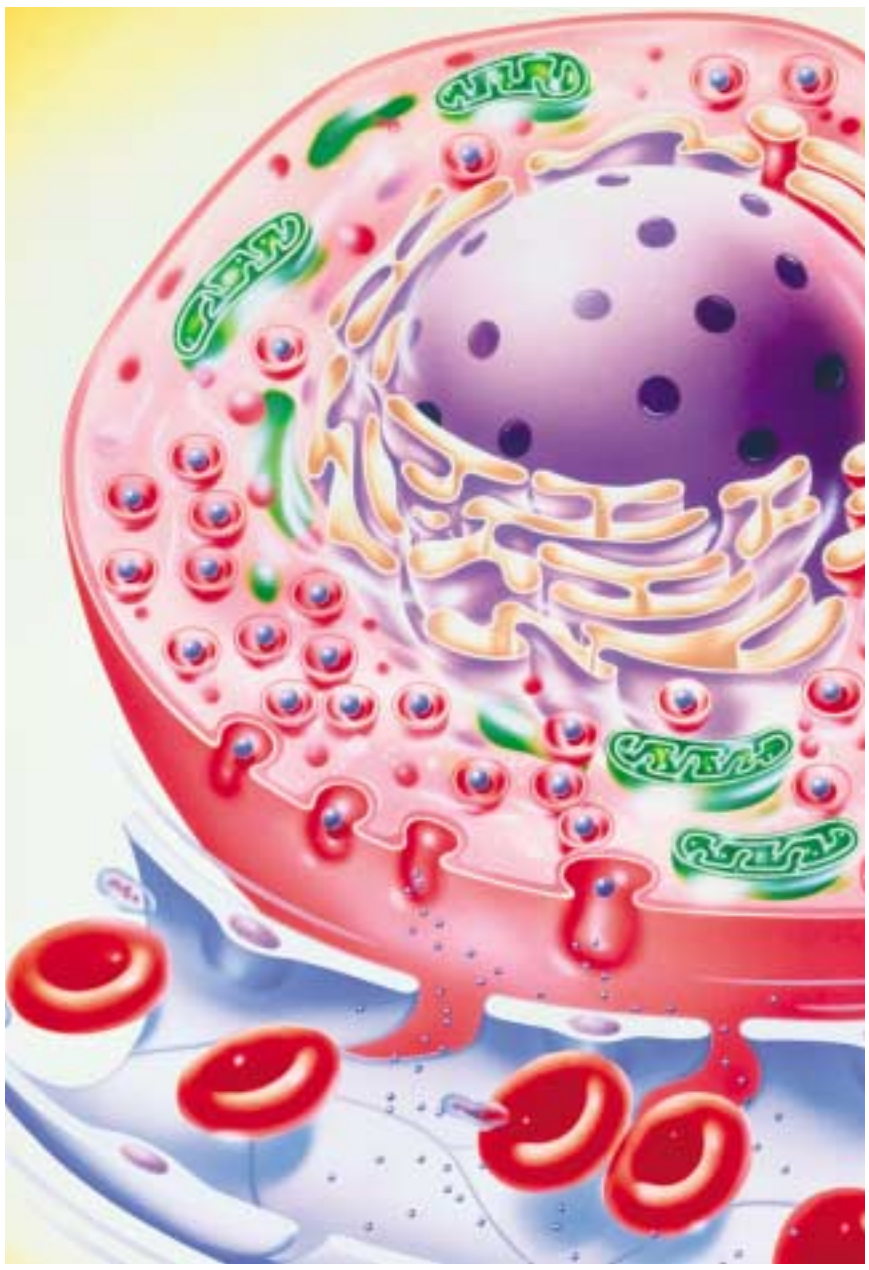


Insulin granules released into the blood.

New Research Opens Door for Advanced Treatments

Despite the fact that insulin was discovered in Canada in 1922, and that oral antidiabetic agents have been available since the 1950s, diabetes is the leading cause of end-stage renal disease, blindness and nontraumatic amputations. Individuals with diabetes have a two- to fourfold increase in cardiovascular disease compared to their nondiabetic counterparts. According to the Canadian Diabetes Association (CDA), the cost of treating diabetes and its complications in Canada is estimated to be at least $14 billion annually. Future treatments must try to help alleviate this epidemic.

The last full set of *Clinical Practice Guidelines for the Management of Diabetes in Canada* was released in 1998. The next set of guidelines will be released in 2003 and will incorporate the new studies and agents that have become available since that time.

Supported by an educational grant from GlaxoSmithKline

This article will update the trends in the understanding and management of type 2 diabetes (T2D) and discuss possible future therapies.

PERSPECTIVE

EPIDEMIOLOGY

The prevalence of diagnosed diabetes is increasing worldwide and is expected to affect 5.4% of the population by 2025. In Canada, an estimated 1.6 million individuals have diagnosed diabetes. However, an estimated 40% to 50% of individuals with diabetes remain undiagnosed. The prevalence of diabetes increases with age. Diabetes affects 12% of the population between the ages of 40 and 75, and 19% of the population older than 75. T2D represents about 90% of diabetes, and type 1 diabetes (T1D) represents most of the remainder. Incidence of T2D is increasing in younger age groups as well. First Nations peoples, South Asians, Africans and Hispanics are at particularly high risk for the disease.

With an increasing prevalence of diabetes comes an increase in diabetes-related complications. Over the next 15 years, the annual rate of cardiovascular hospitalizations will increase two- to three-fold. The number of new patients on renal dialysis will almost double, and lower-limb amputations are expected to almost triple.

DIAGNOSIS

A diagnosis of diabetes is made if there are symptoms of diabetes plus a casual plasma glucose >11.1 mmol/L. Alternatively, a diagnosis of diabetes can be made if the fasting plasma glucose is >7.0 mmol/L or a two-hour value of the oral glucose tolerance test (OGTT) >11.1 mmol/L. A validation test must be done on another day in all cases, in the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation. It is recommended that testing for diabetes using a fasting plasma glucose test should be performed every three years in people over the age of 45. More frequent or earlier testing should be considered in those with additional risk factors for diabetes, such as having a first-degree relative with diabetes, being a member of a high-risk population, obesity, and having a low level of high-density lipoprotein cholesterol (HDL-C) or an elevated fasting triglyceride (TG) level.

Perspective

FP Review

Through history and until the last century, the only known treatment for diabetes was diet. In the last 20 years more people have started using blood glucose level as a gauge to determine the condition of each individual's blood glucose control. The use of a glucometer for checking blood sugar levels has been one of the most important inventions in the management of diabetic patients.

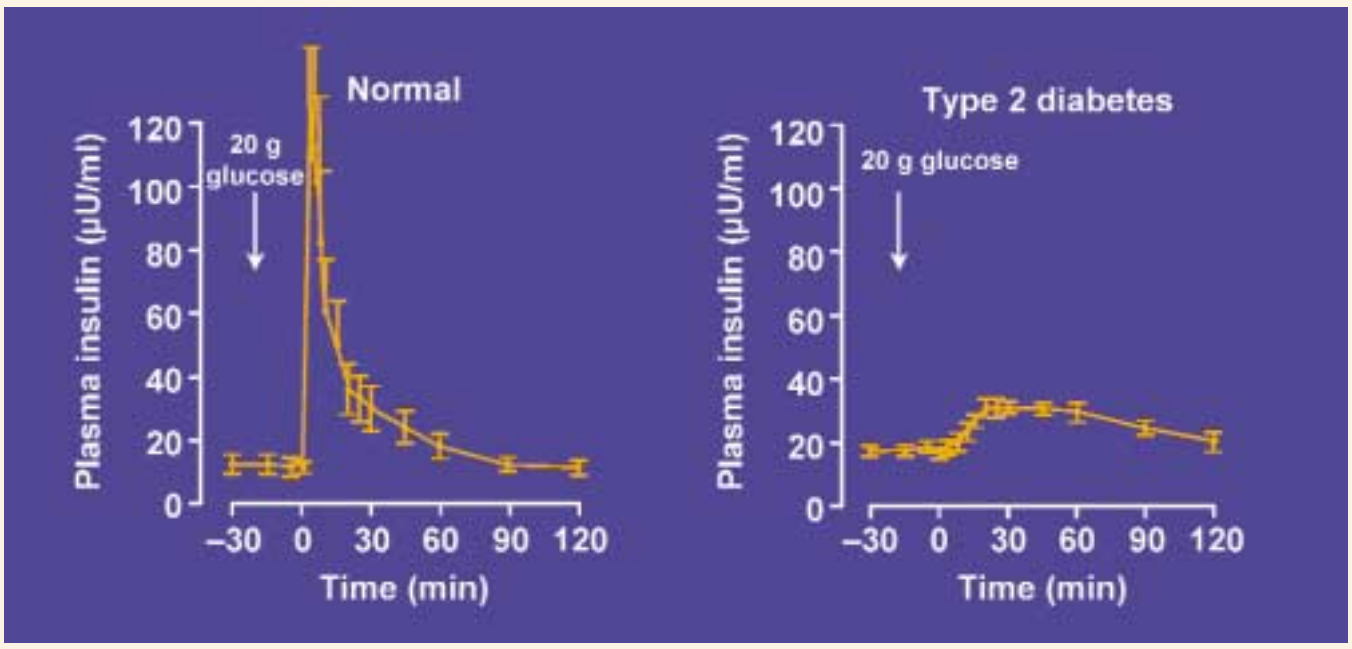
Past and current clinical trials reveal that T2D is caused by multiple factors and requires a multifactorial approach to control the blood glucose level, and to normalize the metabolic parameters as well as overcome and control the insulin resistance syndrome.

Studies have shown that microvascular complications may start at the onset of hyperglycemia and the macrovascular diseases or complications may begin during the prediabetic phase. Sometimes it may be up to 20 years before T2D is diagnosed. In addition, the aggressive control of fasting and postprandial blood glucose will decrease and slow the development of microvascular and macrovascular diseases. Studies also show the use of angiotensin-converting enzyme inhibitor (ACE I) and/or angiotensin II-converting enzyme-receptor blocker (AT II blocker) not only will control blood pressure but also will slow down or prevent the progression of nephropathy with evidence of decreasing microalbuminuria.

The economic burden of T2D will continue to rise in Canada, where up to three million people will be diagnosed with diabetes while about two million will remain undiagnosed in the next decade. Family physicians will have to be well equipped to face the increasing number of patients with diabetes. Whether we like it or not, these cases are coming to us in amazingly fast and increasing numbers.

FIGURE 1

Loss of Early-phase Insulin Secretion is a Typical Finding in Type 2 Diabetes



Source: Ward WK *et al. Diabetes Care* 1984; 7:491–502.

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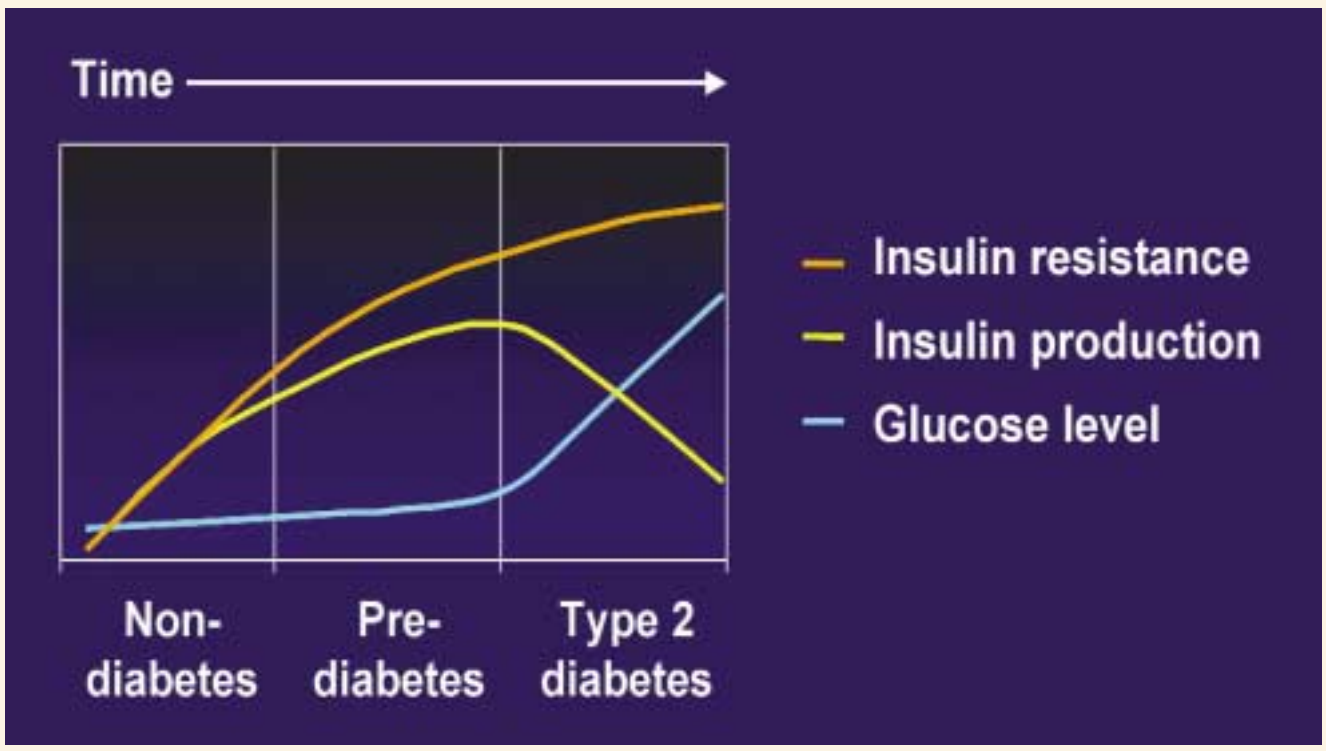
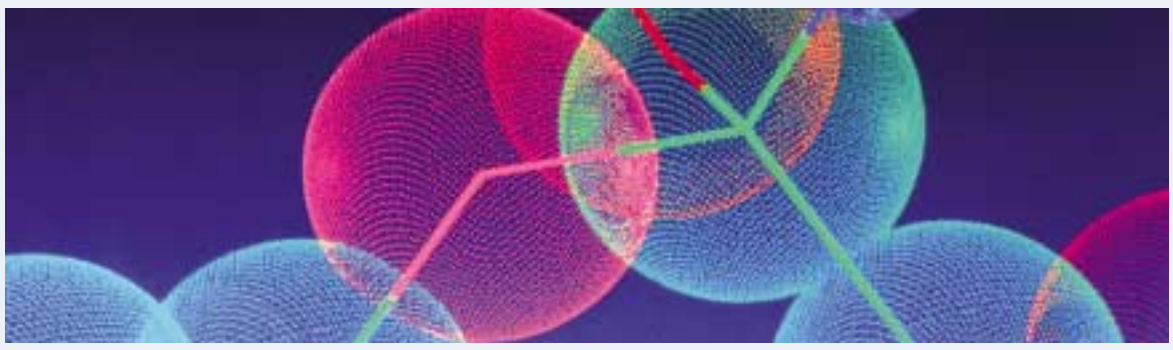
FIGURE 2

Progression of Insulin Resistance



Source: Rickheim *et al*. Type 2 Diabetes BASICS, International Diabetes Center, 2000.



FP Review

Diagnosis

As family physicians, we are at the front-line screening and defining diabetic cases and detecting the impaired fasting glucose or the impaired glucose tolerance cases in the earliest stages. We do this with the goal of preventing the possible damage done to our patients caused by abnormally high glucose levels. We should be familiar with the risk factors that may increase the chances of developing T2D such as persons aged 45 or over, lack of excercise, known family history of diabetes, obesity, susceptible races, known history of hyperlipidemia or hypertriglyceridemia, gestational diabetes, mothers of abnormally large newborns, history of hypertension, cardiovascular heart diseases and impotency. As well, in the near future, the age factor will likely be lower than the previously mentioned 45 years old, as younger individuals develop T2D.

Besides the conventional blood sugar tests (e.g. the venous blood and finger prick tests, and other methods), many other innovative technologies are currently being developed. However, none of these innovations are readily available in Canada. We can only imagine what kind of practical, convenient, noninvasive and portable blood-sugar tests the future will bring.

Relying just on the fasting plasma glucose as the main criteria for the diagnosis of diabetes in clinical practice has been questioned. The DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) study group showed that almost one-third of patients who were considered diabetic according to a two-hour plasma glucose value after an OGTT were considered normal if only a fasting level was used.

PATHOPHYSIOLOGY

T2D results from two main abnormalities: insulin resistance and beta-cell dysfunction. Insulin resistance is a core defect in T2D: 92% of patients with T2D have it. Insulin resistance is an impaired response to the physiological effects of insulin, including the effects on glucose, lipid and protein metabolism, as well as effects on vascular endothelial function. Peripheral insulin resistance occurs in muscle and adipose tissue and is combined with an increase in hepatic glucose output.

The increased insulin resistance is linked to beta-cell dysfunction. In many patients with T2D, the early phase of insulin secretion, which normally limits the post-prandial rise in glycemia, is attenuated (see Figure 1, page 2). Beta-cell dysfunction continues to deteriorate the longer an individual has diabetes.

With long-term studies such as the United Kingdom Prospective Diabetes Study (UKPDS), the natural history of diabetes is better known. Prior to developing T2D, the increased insulin resistance leads to compensatory increases in circulating insulin levels. This prevents an increase in glucose levels. As time passes, insulin resistance continues to increase, but the beta cell at some point will begin to dysfunction and fail (see Figure 2). Impaired glucose tolerance (IGT) occurs before T2D. Depending on the population studied, it is estimated that between 4% and 14% of IGT patients per year will develop T2D.

TREATMENT

It is now well recognized that the treatment of diabetes is not just about glycemic control. It is vitally important to target lipid levels, blood pressure, smoking cessation and other treatments to prevent the microvascular and macrovascular complications of diabetes. To achieve these goals, a multidisciplinary team approach is required.

The target levels for $HbA1_c$ are currently under debate. The Diabetes Control and Complications Trial (DCCT) with people with T1D, and the UKPDS with patients with T2D, have helped define target levels. Currently, the American Diabetes Association (ADA) and the CDA have targeted an $HbA1_c$ level ≤7.0% or lower as 'optimal' control. The European Association of Diabetes and the American Association of Clinical Endocrinologists have targeted a lower level of $HbA1_c$, which is 6.5%.

There is emerging evidence that elevated post-prandial glucose levels are associated with an increased risk of cardiovascular events. The DECODE study evaluated fasting glucose levels and two-hour levels after a 75g oral glucose tolerance test. A total of 15,388 men and 7,126 women between the ages of 30 and 89 were studied with a mean followup of 8.8 years. The two-hour glucose levels were significantly better predictors of all-cause mortality and cardiovascular disease than the fasting glucose level.

Because of the association between post-prandial hyperglycemia and cardiovascular risk, agents that improve these glucose levels are being evaluated.

The prevalence of diagnosed diabetes is increasing worldwide and is expected to affect 5.4% of the population by 2025.

ORAL ANTIHYPERGLYCEMIC AGENTS

Sulfonylureas have been available in Canada for decades. Recently, newer sulfonylurea agents have been released, including glimepiride and gliclazide modified-release. The fact that these are both once-daily medications may help some patients who have compliance problems. In some studies comparing these agents to glyburide, patients had less weight gain and less hypoglycemia. Glimperide and gliclazide are contraindicated in patients with severe liver or renal impairment.

The thiazolidinediones (TZDs) currently available are rosiglitazone and pioglitazone. Classified as insulin sensitizers, they decrease insulin resistance in muscle and adipose tissue and decrease hepatic glucose output. The mechanism-of-action for the TZDs is through the peroxisome proliferator-activated protein receptor gamma (PPAR-gamma). The PPAR-gamma is an intranuclear receptor found in muscle, adipose tissue and the liver. It regulates genes that increase the sensitivity to insulin. The TZD rosiglitazone's indications are in monotherapy, with use in combination with metformin or with use in combination with sulfonylurea. The TZD pioglitazone's indication is in monotherapy only.

Caution should be used when combining the TZDs with insulin, and they are contraindicated in patients with class III or IV heart failure.

The TZD rosiglitazone also has other beneficial properties beyond glycemic control, including a lower incidence of microalbuminuria compared to glyburide. Larger studies are ongoing. As well, there is an improvement in the lipid profile, with a greater increase in HDL-C than with glyburide, TGs and the total cholesterol:HDL-C ratio is also improved. Diastolic blood pressure is lowered, and when compared to glyburide, there is a 3 mmHg to 4 mmHg difference in reported trials. Long-term efficacy and preservation of beta-cell function is also being studied. Researchers working on A Diabetes Outcome Progression Trial (ADOPT) will study rosiglitazone, glyburide and metformin as monotherapy and ascertain the time to secondary failure. When used in monotherapy, TZDs have a low incidence of hypoglycemia similar to metformin. It is recommended that an alanine aminotransferase (ALT) level be performed prior to initiating therapy, and then every two months for the first year while the patient is on therapy. The medication should not be initiated if the level is 2.5 times higher than normal. During treatment, if there is a rise of the ALT to three times above the upper limit of normal, the medication should be discontinued. Dosing does not have to be changed in the elderly or with mild-to-moderate renal impairment.

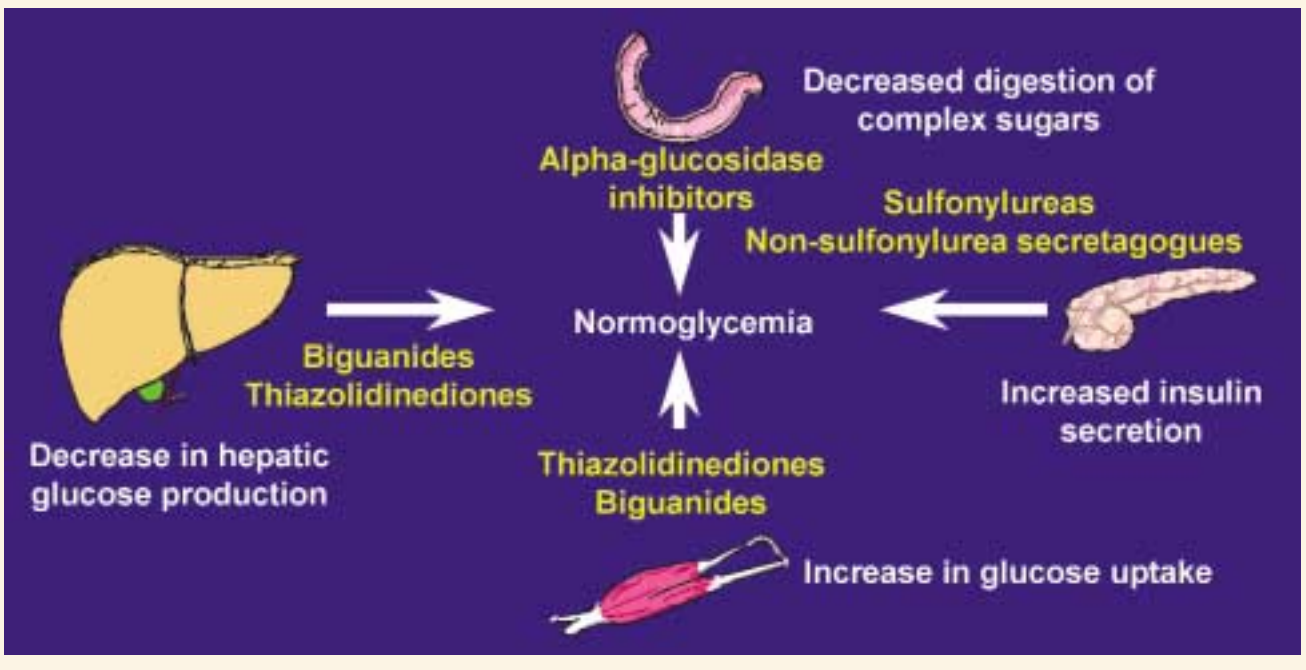
Metformin is an oral antihyperglycemic agent that has been available in Canada for decades. It should be considered as initial therapy for obese patients. It is associated with less weight gain and less hypoglycemia than the sulfonylureas. Gastrointestinal side-effects may be a limiting factor, and metformin is contraindicated in the presence of significant renal, cardiac or hepatic dysfunction, since it may cause lactic acidosis. Metformin can be combined with other oral agents.

Repaglinide is an oral antidiabetic agent. A carbamoylmethyl benzoic acid derivative, it is a short-acting insulin secretagogue. This medication is taken with each meal. Compared to glyburide, it has a lower risk of severe hypoglycemia and weight gain and can be used in patients with mild renal or liver impairment. It may be particularly useful in patients who eat at irregular times.

Nateglinide, which was released in Canada in March 2002, is also an oral antidiabetic agent. Nateglinide is a D-phenylalanine derivative, which can be classified as an insulin secretagogue. Although it has a different chemical structure than the sulfonylureas and repaglinide, it should not be combined with these agents. The medication is usually taken three times a day with meals, and it improves fasting and post-prandial blood glucose levels. Compared to glyburide, there are lower post-prandial glucose excursions, less weight gain and fewer episodes of hypoglycemia. Nateglinide is metabolized by the liver

FIGURE 3

Sites/Mechanism-of-action of Antihyperglycemic Agent



Source: Krenz et al. Drug Safety 1994;11:223–241; Bloomgarden. *Clinical Therapeutics* 1998;20:216–231. Spiegleman. *Diabetes* 1998;47:507–514; Saltiel et al. *Diabetes* 1998;445:1661–1669. American Diabetes Association. *Diabetes Care* 1995;18:1510–1518.

It is now well recognized that the treatment of diabetes is not just about glycemic control.

and also excreted, unchanged, by the kidney. It may be used in patients with mild renal or hepatic impairment.

Orlistat is an anti-obesity agent that recently received an additional indication for use in combination with antidiabetic agents, to improve blood glucose control in overweight or obese T2D patients.

The medication blocks about 30% of ingested fat from being absorbed. It should be used with a multivitamin. Gastrointestinal side-effects such as diarrhea are limiting for some patients. Another weight-loss agent that has been released in Canada is sibutramine, which is a serotonin and norepinephrine re-uptake inhibitor. Heart rate and blood pressure have to be monitored closely with this medication. It is contraindicated in patients with active coronary artery disease.

The stepwise approach for initiating oral agents is also being updated. Sequential therapy at the beginning or very early may have advantages, such as a more rapid achievement of glycemic goals and the use of submaximal doses of agents, which may reduce side-effects. Because many of these agents have different mechanisms-of-action, we are in an era when triple and quadruple oral agent therapy can be effective. (Sites and mechanism-of-action of antihyperglycemic agents are illustrated in Figure 3 on page 4.)

INSULIN THERAPY

Insulin therapy for patients with T2D is often initiated only after diet, exercise and oral agents have failed to help them reach target glycemic goals. A combination of insulin and oral agents is often effective to control glucose levels. When insulin therapy is added to oral agents, a single injection of intermediate or long-acting insulin may be added at bedtime.

Neutral protamine hagedorn (NPH) or Lente insulin is the insulin most often used at bedtime, but there is a risk of overnight hypoglycemia with these insulins. A newer long-acting insulin, insulin glargine, will soon become available in Canada. Studies have shown fewer episodes of overnight hypoglycemia with glargine insulin.

Short-acting insulins may be required at mealtimes, especially if post-prandial hyperglycemia is targeted. Lispro insulin and insulin aspart are short-acting insulins that are absorbed more quickly than regular insulin. When taken with dinner, these can decrease the rate of overnight hypoglycemia compared to regular insulin.

HYPOGLYCEMIA

Hypoglycemia from insulin secretagogues and/or insulin is a major obstacle

Treatment

FP Review

A multifactorial approach is imperative for treating T2D. Studies show that lifestyle changes with active exercise reduce the risk of developing T2D by 58%. Lifestyle intervention including a healthy, balanced, calorie-restricted diet, has proved to be beneficial to both impaired glucose tolerance and overt diabetic cases.

The patient's metabolic parameters should be improved by aggressively treating and controlling blood sugar, blood pressure and blood lipid levels by whatever appropriate means, including lifestyle modifications and medications.

Insulin resistance is the core defect for underlying long-term complications of T2D, and must be overcome, controlled and treated. Experience shows us that all diabetic cases, at some point in time, will develop insulin resistance. The patients at risk of insulin resistance are: those over the age of 40; a hyperglycemia FBG > 7 mmol/L; those with a hypertension BP > 140/90 mmHg; low HDL-cholesterol of < 1.16 in females and < 0.91 in males; obesity, (BMI ≥ 27.3 kg/m^2 in females and >27.8 kg/m^2 in males); elevated waist/hip ratio (WHR > 0.9 in females and > 1.0 in males); waist circumference of > 80 cm in females and > 94 cm in males; physical inactivity; family history of diabetes; history of gestational diabetes; and polycystic ovary syndrome.

Insulin resistance is possibly caused by a prolonged increase of blood glucose in our body due to an unhealthy lifestyle, constant intake of high caloric foods, emotional stress and genetic factors. Treating insulin resistance and regaining insulin sensitivity will result in improved blood glucose levels in patients with diabetes as well as delay the progression of diabetes and prevent the development of complications due to uncontrolled diabetes.

Pharmacological treatments should be approached in a stepwise fashion, in order to achieve goal levels of $HbA1_C$ within three months. Any agent should be started at a lower dose and either titrated to half maximal dose or to full maximal dose, and then combined with a second agent as needed.

The three main goals of diabetes treatment are: to stop the progression of the disease; to prevent macrovascular and microvascular complications; and to preserve the pancreatic β-cell function. The TZDs (either used as monotherapy or combined with other oral agents) seem to be able to achieve all of these goals, improving multiple factors pertinent to the pathology of diabetes. ASA therapy of coated 81 mg per day should be given to all patients with diabetes unless there are contraindications to its use for risk modification.

The recent new guidelines from the Canadian Diabetes Association include recommendations about avoiding drug-induced hypoglycemia in patients with T1D and T2D. The guidelines recommend the use of an alpha-glucosidase inhibitor, a biguanide, an insulin secretagogue or a thiazolidinedione for initial anti-hyperglycemic therapy.

Effective and comprehensive treatment for T2D deserves multifactorial management. It is paramount that the patient's health-care team (family practitioners, nurses, dietitians and pharmacists) collaborate in public education and group therapy in order to battle this epidemic.

in achieving glycemic targets. Severe hypoglycemia is characterized by a decrease in cognitive function or consciousness, to the point that help is required for reversal of the condition. Because of the risk of hypoglycemia, there is a reluctance by some to intensify therapy. Factors that predispose to hypoglycemia include age, impaired renal or liver function, gastrointestinal disease, lack of education on hypoglycemia, and lifestyle factors such as alcohol, exercise and missed meals. The risk of hypoglycemia increases exponentially with age. For the elderly, if an insulin secretagogue is used, glyburide should be avoided, and an agent such as gliclazide, glimepiride, repaglinide or nateglinide should be considered.

In the UKPDS, the proportion of patients experiencing a severe hypoglycemic episode in a year was higher in the intensively treated group compared to the coventionally treated group, particularly in patients treated with insulin. About 3% had a severe episode of hypoglycemia, and 40% had a hypoglycemic event.

GLUCOSE MONITORING

Self-monitoring of blood glucose is clearly important and has revolutionized the management of diabetes. However, many individuals with diabetes do not monitor as frequently as they should, partly for reasons such as pain and cost. Newer technologies are promising and less invasive or less painful.

The GlucoWatch Biographer is a wrist-worn device that monitors interstitial glucose levels in a noninvasive way. This device provides glucose readings every 20 minutes after a warm-up period. The glucose reading has a 20-minute lag period. It may cause minor skin irritation at the site of use, and is therefore rotated from arm to arm and to various locations on the arms. Studies have shown good correlation with conventional blood glucose monitoring. The GlucoWatch is not yet available in Canada.

The Continuous Glucose Monitoring System measures interstitial glucose levels. It is meant for use by diabetes care professionals and their patients to record comprehensive glucose profiles, usually over a 72-hour span. It is not meant for everyday use, but for occasional use. The system is similar to a holter monitor in how it is worn by patients. A glucose sensor is placed subcutaneously, and readings are taken every five minutes. The monitor records the values. It is then downloaded onto a personal computer.

Alternate-site testing devices are now available, which obtain blood from areas that are less sensitive than the fingertips (usually the forearm). As well, there is a laser-lancing device that the manufacturer claims is less painful than traditional lancing devices. Other meters have combined uses, such as an insulin delivery device with a glucose monitor. There are meters which measure $HbA1_c$ or fructosamine using fingertip blood samples.

Companies are trying to develop true noninvasive devices using infrared spectoscopy or other optical glucose-monitoring technologies. These devices may, in the future, allow patients to use the earlobe, eye, finger cuticle or other body parts to measure glucose levels.

LIPIDS

Lipid guidelines have been developed for diabetes patients over the age of 30. These individuals are classified as very high risk. The target LDL-C level is <2.5 mmol/L. As well, the target for the total cholesterol: HDL-C ratio is <4 mmol/L and the TGs target is <2.0 mmol/L.

The Medical Research Council/British Heart Foundation Heart Protection Study results were presented at the American Heart Association Scientific Sessions in November 2001. The results are scheduled to be published shortly. The 5,963 diabetes patients represented 29% of the study population. The results showed that, for individuals at high risk for cardiovascular disease, simvastatin 40 mg decreased all-cause mortality by 12% and cardiovascular events by 24%. This was significant in the diabetes subgroup and among other subgroups irrespective of age, sex and baseline cholesterol levels. Newer guidelines will have to seriously consider this study.

HYPERTENSION

Guidelines for blood pressure targets continue to evolve, as a number of important studies have been reported. Currently, a target blood pressure of 130/80 mmHg or less is recommended. If there is proteinuria, the target blood pressure is 125/75 mmHg. Most often, multiple agents will be required.

The UKPDS showed that the intensively treated group (mean blood pressure: 144/82) using captopril or atenolol decreased myocardial infarction by 21% and stroke by 44% compared to the conventional group (mean blood pressure: 154/87). Diabetic subgroups in the Hypertension Optimal Treatment (HOT) trial, Systolic Hypertension in the Elderly Program (SHEP) and Systolic Hypertension in Europe (SYST-Eur) trial have all helped confirm that lower blood pressure targets are beneficial.

FP Review

Prognosis

A healthy lifestyle is essential in achieving good prognosis for T2D. $HbA1_C$ is the indicator that reflects the entire past three months of glucose levels. Home glucose monitoring is currently the most practical, convenient and effective method of monitoring blood glucose levels.

Microalbuminuria contributes to endothelial dysfunction, the base of cardiovascular diseases. The presence of microalbuminuria indicates the development or occurrence of nephropathy. In this case, blood pressure should be controlled at less than 120/70 mmHg. The results of recent studies demonstrate the benefits of ACE I (Angiotensin converting enzyme inhibitor) or AT II blocker (Angiotensin II Converting Enzyme Receptor Blocker) for patients with or without nephropathy. These should be added to protect the endothelial function and renal function, and to prevent cardiovascular diseases in middle-aged adults with diabetes. The use of calcium channel blockers in patients with diabetes may increase the protein loss. Endothelial function may be compromised without added ACE I.

Ongoing research such as the Diabetes Reduction Approaches with ramipril and rosiglitazone Medications (DREAM) study may show prevention of T2D in high-risk patients is possible. The thiazolidinedione rosiglitazone has also shown promise in possibly regenerating β-cells in the pancreas. If the study results come out as expected, we as physicians will have a formidable tool to work with in preventing and controlling T2D.

Future treatments will be directed toward protecting endothelial function, preventing nephropathy (by using the ACE I or/and AT II blockers), protecting the pancreas, and preserving the pancreatic β-cell function (by using TZDs such as rosiglitazone, which has favourable and wide-ranging metabolic effects). Many other treatments at the trial stage are: pancreas or β-cell transplants; Dr. Lawrence Rosenberg's discovery of a protein that triggers the creation of insulin-producing cells or islets; vaccination; or gene therapy. Although many of these trials focus on T1D, their results may also apply to T2D.

With concerted effort, family physicians — as well as other members of the health-care team — should be able to achieve our ultimate goals in treating, controlling and containing T2D.

The Heart Outcomes Prevention Evaluation (HOPE) study randomized 9,541 patients over age 55 to ramipril 10 mg or placebo. The diabetic subgroup showed a 25% decreased risk in combined cardiovascular events compared to placebo. Therefore, it is recommended that angiotensin-converting enzyme (ACE) inhibitors be used to prevent cardiovascular disease in all middle-aged adults who have diabetes.

The Irbesartan Microalbuminuria Type 2 (IRMA 2) study compared the angiotensin-receptor blocker irbesartan to usual care (i.e. not using ACE inhibitors) in T2D patients with hypertension and microalbuminuria. There was a 70% reduction in progression to diabetic nephropathy using irbesartan 300 mg versus usual care.

The Irbesartan in Diabetic Nephropathy Trial (IDNT) compared irbesartan to amlodipine and placebo in T2D patients with hypertension and diabetic nephropathy. The primary composite endpoint was the doubling of serum creatinine, end-stage renal disease or death. There was risk reduction of 33% in patients using irbesartan versus placebo, and of 37% for patients using irbesartan versus amlodipine. The Reduction in Endpoints in Patients with Non–insulin-dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial also involved hypertensive T2D patients with nephropathy, using losartan. The losartan group had a 16% risk reduction in the primary composite endpoint. Neither trial used ACE inhibitors.

PROGNOSIS

In the Diabetes Prevention Program in the U.S., 3,234 nondiabetic participants with elevated fasting and postload plasma glucose concentrations were assigned to placebo, metformin or lifestyle modification. The goals were at least a 7% weight reduction and 150 minutes of physical activity a week. The average age of the participants was 51, and the average body mass index was 34. Women comprised 68% of the study group. Members of minority groups comprised 45%. The results after an average followup of 2.8 years revealed that lifestyle intervention reduced the incidence of diabetes by 58%, and metformin reduced the incidence by 31% compared to placebo.

Another recent lifestyle intervention study was reported from Finland involving 522 participants with impaired glucose tolerance (IGT). The average age in this study was 55, and the average body mass index was 31. Lifestyle interventions included dietary changes, physical activity and individualized counselling aimed at reducing weight. The duration of the study was 3.2 years. Results showed that the risk of developing diabetes was reduced by 58% in the intervention group.

The six-year Da Qing study reported from China revealed that the rates of conversion to diabetes were significantly reduced in both lean and overweight IGT subjects with diet (47%), exercise (45%) or both (44%), compared to controls.

The Study To Prevent Non–Insulin-Dependent Diabetes Mellitus (STOP-NIDDM), which used acarbose in IGT patients, showed a 33% reduction in the incidence of T2D. This study was presented in 2001 and has not yet been published.

Ongoing research for the prevention of T2D using pharmacological agents includes the Diabetes Reduction Approaches with Ramipril and Rosiglitazone Medications (DREAM), and Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trials. ■

With concerted effort, family physicians — as well as other members of the health-care team — should be able to achieve our ultimate goals in treating, controlling and containing T2D.

RESOURCES

ARTICLES

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WEB SITE

- OnMedica's Diabetes Clinical Network: Online medical information services programs for health-care professionals, including diabetes-specific news, courses and an on-line forum for users to interact on diabetes-related topics. Diabetes is one of the 12 therapy areas that will be covered in the site's clinical network section. Visit: **www.onmedica.net**.

1 Case Study: Presentation

A 55-YEAR-OLD WOMAN WAS DIAGNOSED WITH T2D THREE MONTHS AGO AFTER HER ANNUAL EXAMINATION. AT THAT TIME HER FASTING GLUCOSE LEVEL WAS 9.4 AND 9.1 MMOL/L, ON TWO READINGS ONE WEEK APART. SHE WAS MOTIVATED TO MAKE LIFESTYLE CHANGES AND ATTENDED THE DIABETES EDUCATION CENTRE.

Over the next three months, the patient was able to lose 1 kg and started walking for 30 minutes, five times per week. Fasting blood sugar fell to <9.0 mmol/L by self-glucose monitoring. Over the next three months, however, no further weight loss occurred, even though she maintained her walking regimen. Glucose levels did not decrease further.

Other past medical history is unremarkable. She is a smoker but has cut down from a half a pack per day to four or five cigarettes per day, and she does not smoke at work now. She works as a manager for a retail chain clothing store. She does not consume alcohol. There is no history of gestational diabetes or macrosomia in her previous pregnancies. Family history is unremarkable for diabetes or cardiovascular disease.

EXAMINATION

The patient is 165 cm tall. Her calculated body mass index is 28 kg/m^2 and her waist circumference is 84 cm. Blood pressure is 130/80 mmHg. The rest of the examination is unremarkable. The current lab tests show:

Fasting blood glucose	8.8 mmol/L
$HbA1_c$	8.1%
Total cholesterol	4.6 mmol/L
HDL-C	1.1 mmol/L
LDL-C	2.8 mmol/L
Urinalysis	Normal
Creatinine	Normal

TREATMENT

This patient has already made some significant lifestyle changes. She has cut down on smoking, but must be encouraged to quit. It remains to be seen whether she can lose more weight or do more exercise.

An oral antihyperglycemic agent is required at this time. Most practitioners would start metformin slowly to help with the gastrointestinal side-effects. There is little or no weight gain with this therapy and the risk of hypoglycemia is low. If metformin cannot be used, or is limited because of side-effects, other agents should be considered. Insulin secretagogues (e.g. the sulfonylureas, or repaglinide or nateglinide) could be considered. Because of her busy lifestyle, the patient may wish to use a newer sulfonylurea, such as gliclazide modified-release, or glimepiride. Both are once daily and result in less weight gain than glyburide. Glyburide is, however, less expensive. Repaglinide and nateglinide can also be used with busy lifestyles and irregular meal patterns. The TZDs (e.g. rosiglitazone and pioglitazone) decrease insulin resistance without causing hypoglycemia, but weight gain and edema are side-effects to consider.

Prevention of heart disease must be started early, in the form of ASA. Even though the patient's blood pressure is at goal, an ACE inhibitor at high dose is indicated because of the HOPE study. Her lipid profile is close to guidelines, but the recent Heart Protection Study demonstrated benefits even in patients whose low-density lipoprotein cholesterol (LDL-C) was <2.6 mmol/L. In light of that, a dose of a statin similar to simvastatin 40 mg/day is indicated.

It is recommended that a dilated eye examination be performed at the time of diagnosis, and urine must be checked for microalbuminuria. This is done by ordering an albumin: creatinine ratio on a random urine sample. ●

2 Case Study: Presentation

THE PATIENT IS A 52-YEAR-OLD MALE MECHANICAL ENGINEER WHO WAS DIAGNOSED WITH T2D FIVE YEARS AGO. OTHER HISTORY INCLUDES HYPERTENSION AND OA OF THE KNEES. HE IS A NONSMOKER WHO CONSUMES ALCOHOL OCCASIONALLY. HIS FATHER HAD T2D AND RECENTLY DIED OF HEART DISEASE AT AGE 75.

The patient attended diabetes education classes two years ago. He admits that he is not always compliant with his eating and has been unsuccessful in losing weight. He does no regular physical activity and states that exercise is difficult because of his arthritis. He has his eyes checked regularly. Other review of systems is unremarkable.

His current medications are glyburide 10 mg bid, metformin 1000 mg bid, simvastatin 10 mg, ramipril 2.5 mg, hydrochlorthiazide 12.5 mg and ASA.

EXAMINATION

The physical exam reveals that the patient has central obesity. His weight is 102 kg, and his calculated body mass index is 30 kg/m^2. His waist circumference is 96 cm. Blood pressure is 140/72 mmHg. Cardiovascular and respiratory examination is unremarkable. Peripheral examination reveals absent ankle jerks and a slight decrease in vibratory sensation. The current lab tests show:

Fasting glucose	8.8 mmol/L
$HbA1_c$	7.6%
Total cholesterol	4.8 mmol/L
HDL-C	1.0 mmol/L
LDL-C	2.8 mmol/L
Triglycerides	2.2 mmol/L
Urine for microalbuminuria	Positive
Alanine aminotransferase (ALT)	Normal

TREATMENT

This patient needs to make lifestyle changes. Because his father died recently, he may be motivated to do so. Weight loss and exercise can significantly improve his glycemic control, blood pressure and lipid profile. Unfortunately, he is also battling the natural history of diabetes, ongoing insulin resistance and further beta-cell dysfunction. The glycemic goal would be to try to achieve an $HbA1_c$ of 7% or less. An additional oral agent could be added, such as a TZD (e.g. rosiglitazone or pioglitazone). ALT levels should be checked every two months, and the patient should be warned about possible edema.

Alternatively, acarbose could be used and should be started at a low dose and titrated up to try to alleviate the gastrointestinal side-effects that often limit its effectiveness. One could also consider bedtime NPH insulin and slowly increase the dose to a target fasting glucose level between 4 mmol/L and 7 mmol/L. The patient would have to be warned about possible nocturnal hypoglycemia.

As glycemic control improves, he will have to increase self-monitoring of his glucose levels. The goals are: pre-meal glucose levels between 4 mmol/L and 7 mmol/L, and post-prandial glucose levels <11 mmol/L. Meeting with a dietician may help him greatly in this regard.

The patient's lipid profile should also be improved: LDL-C should aim for <2.5 mmol/L, TGs should be <2.0 mmol/L and a total cholesterol HDL-C ratio of less than 4. Based on the recent Heart Protection Study, his simvastatin should be increased to 40 mg/day.

The patient's blood pressure should be optimized, especially in the setting of microalbuminuria. His ramipril should be increased to 10 mg/day. If this does not improve his blood pressure to <130/80, then another agent should be added. Possible agents to add could be an angiotensin receptor blocker, a beta-blocker or a calcium channel blocker. ●

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