ABSTRACT

Options for the medical management of diabetes have increased substantially in recent years. Numerous large clinical trials conducted over the last 2 decades have clearly established that good blood glucose control slows or prevents the progression of diabetic microvascular complications including retinopathy. But while there are now more tools to help control blood glucose, it is still not easy for patients to meet their glycemic targets. Effective diabetes management requires dedicated self-care on the part of the patient and the expert assistance of skilled healthcare professionals. Effective use of self-monitoring of blood glucose levels and hemoglobin A1c can help to assess the progress of glycemic control, but both these modalities are underutilized. A number of new approaches are currently in development for diabetes management, including new agents to manage weight and blood glucose, and new technologies to continuously monitor glucose and administer insulin. These innovations will ultimately make it easier for patients to attain their glycemic targets and reduce the progression of diabetes-related complications.


It is clearly established that glycemic control can prevent or retard the development of diabetic microvascular complications including diabetic retinopathy (DR). Intensive glycemic control in type 1 diabetes was examined in the Diabetes Control and Complications Trial (DCCT), and a contemporaneous Swedish Study. In the DCCT, 1441 patients with type 1 diabetes were divided into a primary prevention cohort (patients with no DR at baseline; n = 726) and a secondary prevention cohort (patients with mild DR at baseline; n = 715) and then randomized to either intensive glucose control or to conventional treatment. Progression of DR was defined as a change of 3 or more steps on a 25-point rating scale developed by the Early Treatment Diabetic Retinopathy Study (ETDRS) investigators. As shown in the Figure, intensive therapy was associated with a significant reduction in the incidence of DR progression in both cohorts over a follow-up period of up to 9 years. The DCCT also demonstrated that progression of nephropathy is slowed by intensive glycemic control in type 1 diabetes.

Glycemic control in type 2 diabetes was examined in the United Kingdom Prospective Diabetes Study (UKPDS), in which 3867 patients with newly diagnosed type 2 diabetes were randomized to either intensive glucose control with a sulfonylurea (later adding metformin) or insulin, or to conventional treatment and diet. Over a median duration of follow-up of 10 years, assignment to the intensive treatment group was associated with a 21% relative reduction in the risk of a 2-step progression of DR, from 48.76% of patients who received conventional therapy to 38.6% of those who received intensive therapy ($P = .015$). A smaller study in Japan had similar findings.

In sum, there is no doubt that good glycemic control is essential for the reduction of diabetic microvascular complications including diabetic retinopathy, diabetic peripheral neuropathy, and diabetic
nephropathy. The question has shifted: how do we achieve good glycemic control?

MANAGING DR

OVERVIEW OF MANAGEMENT

A number of tools are available to help manage diabetes, including nutrition and exercise, oral agents, and insulin. Type 1 diabetes always requires insulin in addition to a solid nutritional plan. For type 2 diabetes, patients are sequenced through increasingly intense management. Some will be well controlled, or well controlled for a while, on nutrition therapy and exercise alone. Those who are not (see discussion below for how to assess adequacy of control) should be treated with oral agents; and those who are not controlled on oral agents should receive insulin.

A major problem in the management of type 2 diabetes is that therapy is often advanced too slowly to provide maximum benefit. The natural history of type 2 diabetes is for progressively less pancreatic insulin secretion and consequent progressively increased need for pharmacologic therapy. Oral agents should be advanced to maximum doses until control is achieved or side effects occur. About 30% of people with type 2 diabetes at any given time require insulin, not necessarily because of poor compliance or poor self-care, but because of the predictable decline in pancreatic insulin secretion.

NUTRITION

The management of diabetes with nutrition and exercise has not changed substantially in recent years (although for billing purposes dietary consultations are now called “Medical Nutrition Therapy”). Evidence-based dietary recommendations developed by the American Diabetes Association still emphasize glycemic control, and close attention to the lipid and lipoprotein profile that reduces the risk of macrovascular disease. Patients should consume a diet low in saturated fat and cholesterol. The precise proportions of carbohydrate, protein, and fat in the daily diet are still somewhat controversial. Intermediary metabolism interconverts nutrients, so it may not in fact matter a great deal whether a patient consumes a relatively high-carbohydrate/low-fat or low-carbohydrate/high-fat diet, so that particular argument (Atkins Diet vs Pritikin Diet) rages on. The emphasis of nutritional plan for type 1 diabetes is often quite different than that of type 2 diabetes.

With type 1 diabetes, consistency of dietary intake, especially of carbohydrate, is important. Intake must be matched to insulin usage. This is especially true for patients who use fixed insulin doses and do not adjust the premeal insulin. For type 2 diabetes, weight control is usually the main objective. This requires, above all, a hypocaloric diet together with enhanced physical activity. Again, the arguments for eliminating either carbohydrate or fat pale in importance compared with the significance of simply eating fewer total calories.

Every person with diabetes deserves an individual dietary prescription and instruction to help its implementation. Medical Nutrition Therapy is now generally covered by health insurance.

ORAL AGENTS

In contrast to Medical Nutrition Therapy, the use of oral medications for diabetes treatment has changed significantly during the last several years. There are

Figure. Cumulative Incidence of a Sustained Change in Retinopathy in Patients with Diabetes Receiving Intensive or Conventional Therapy

In the Diabetes Control and Complications Trial (DCCT), progression of retinopathy was defined as a change from baseline of at least 3 steps using the 25-step Early Treatment Diabetic Retinopathy Study (ETDRS) rating scale. For the primary prevention cohort (patients with no retinopathy at baseline; panel A) and the secondary prevention cohort (patients with mild retinopathy at baseline; panel B), assignment to intensive therapy was associated with a significantly lower incidence of retinopathy progression over a 9-year follow-up period. Reprinted with permission from The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-986.
now 3 major classes of oral agents for glycemic control. The sulfonylureas (glibenclamide, glyburide, gliclazide, glipizide, and glimepiride) all act by stimulating insulin release from pancreatic beta cells. They have long been used for the treatment of diabetes and are still a mainstay of diabetes therapy. By far the most common side effect is hypoglycemia, although that is much less common and less severe than is the case with insulin therapy.

Metformin has been used throughout the world for decades and in the United States for about 20 years. Its strengths and weaknesses are very well characterized. Metformin acts, apparently, by reducing hepatic glucose production, for example, sensitizing the liver to endogenous insulin. It can cause gastrointestinal side effects (loose stools, bloating), which may be more common than many clinicians realize. There is also a concern about lactic acidosis, which occurs far more commonly due to a pharmacologically related drug, phenformin (not available in the United States). In order to minimize the risk of lactic acidosis, metformin should be avoided in patients who have conditions that increase the production of lactic acid or decrease its clearance. These contraindications include renal insufficiency (creatinine >1.6 mg/dL), congestive heart failure requiring pharmacological treatment, elective surgery, underperfusion (shock, arterial insufficiency, etc), or acute or chronic metabolic acidosis. Large clinical trials have shown that lactic acidosis is not more common among patients who use metformin in the absence of these contraindications. In other words, used in the properly selected patient, metformin is safe.

Thiazolidinediones (TZDs), which act as insulin sensitizers, have entered clinical practice during the last 3 to 5 years. TZDs may be used as monotherapy or in combination with a sulfonylurea, metformin, or insulin and diet. The downside is that TZDs are associated with dose-related weight gain, especially when used with insulin, and can also cause fluid retention and even induce congestive heart failure. With the removal from the market of troglitazone, the TZDs do not appear to cause serious hepatic toxicity.

How should the oral agents be sequenced? This is more a matter of opinion than of evidence. On the basis of the shorter experience and the adverse event profiles reported, it is reasonable to reserve the use of TZDs for patients who have not responded to other agents. Combining oral agent therapy is often more effective for glucose control than using monotherapy, but when and how to combine the agents optimally is unresolved.

### Insulin

Insulin therapy has also changed markedly in recent years. Animal source (beef/pork) insulin is no longer available, with recombinant DNA insulin now being used universally. The recombinant DNA-produced insulin may be “human,” for example, with the identical structure of human insulin, and prepared in various forms such as neutral protamine Hagedorn (NPH), regular or lente human insulin. Common brand names for all the preparations of human insulins are Humulin® and Novolin®. Several recombinant insulin analogs have been developed recently, meaning small changes in the amino acid sequences that confer significant pharmacokinetic changes. Two fast-acting analogs are insulin lispro and insulin aspart, and a long-acting preparation is insulin glargine. Another long-acting agent, insulin detemir, may soon be approved for clinical use. While some patients believe that they are allergic to the recombinant DNA insulins, the evidence indicates less, not more, allergy to the new insulins. So as a rule, if a patient can take beef/pork insulin, he/she can take recombinant DNA insulin.

Intensive insulin regimens are now widely used. These often consist of 3 to 4 injections daily of combinations of long- and fast-acting insulins, with variable doses according to need at the time. It is reasonable for all patients with type 1 diabetes to use these intensified regimens. The fast-acting insulins (lispro and aspart) have very rapid absorption and shorter duration of action than conventional regular human insulin. These agents are therefore best injected immediately before meals.

Glargine and detemir have been developed as “basal” insulins, providing a 24-hour effect, with less variability in level throughout the day and a reduced likelihood of nocturnal hypoglycemia. Glargine insulin, however, cannot be mixed in the same syringe with short-acting insulin. There is still a major role for regular and NPH insulins in many patients, so the options have expanded considerably, providing better opportunity for fine management of glycemia.

Another recent trend has been the more widespread use of external insulin pumps, especially among patients with type 1 diabetes. They can be programmed to deliver insulin at a continuous rate, with an increased rate or extra bolus doses at mealtimes or during the early morning hours. Pumps have become easier to program and operate, and are increasingly common for both type 1 and unstable type 2 diabetes.
ASSESSING DIABETES

With any type of diabetes, it is absolutely essential to assess the status of glycemia. There are 2 broad methods: self-monitoring of blood glucose and glycosylated hemoglobin (HbA1c). These approaches are complementary. Self-monitoring tests the immediate, momentary blood glucose at a particular time, while HbA1c assesses the average blood glucose over a period of 2 to 3 months. Self-monitoring, at least used infrequently, does not provide much information about the overall, day-to-day or week-to-week averages; HbA1c does not elucidate diurnal patterns of glycemia or explain immediate symptoms.

All patients with diabetes should perform regular self-monitoring of blood glucose. The frequency and timing of self-monitoring will vary from person to person and will depend on the stability of the diabetes. Patients should be encouraged to self-monitor because it allows them to assess their glycemic control hour to hour, and most people find this very helpful once they get in the habit. Among the barriers to increasing self-monitoring, probably the most significant is simple denial: patients are worried about the results, or do not believe they can do anything about poor control. Physicians often do not encourage or promote self-monitoring and do not use a Certified Diabetes Educator to teach self-monitoring, and may discourage its use by failing to show interest in the results or by failing to translate results into a change in the patient's treatment. There is also some inconvenience involved, although newer monitoring systems are simple and quick. The most obvious objection—that it hurts—is in fact not the most common. In practice, most people quickly adapt to the discomfort.

HbA1c should be considered the “gold standard” for assessing glycemic control in all patients with diabetes. It should be performed every 3 to 6 months, and patients should know their HbA1c values. As a general guide to the results, a value under 6% is normal, 6% to 7% is excellent glycemic control, 7% to 9% signals a need for improvement, and over 9% indicates poor glycemic control.

The progression of DR, a direct result of poor glycemic control, is generally very slow for patients who maintain their HbA1c values at 7% or less. In the DCCT, only about 3% of patients with HbA1c values below 7% had a 3-step progression of retinopathy over a 9-year period. Thus, although HbA1c of 7% is not normal, it is an achievable goal that is effective for reducing the risk of microvascular events.

THE FUTURE OF DIABETES TREATMENT

Future advances in diabetes care should result in improved clinical outcomes, and allow a far better quality of life for people with diabetes. One emerging trend is the development of new pharmaceuticals that directly address the underlying causes of diabetic complications. For example, the recent research suggests that the activation of protein kinase C (PKC) is central to the physiological processes that produce DR and diabetic macular edema. (The role of PKC in diabetic microvascular complications is described by Lloyd P. Aiello, MD, PhD, elsewhere in this monograph; the effects of PKC inhibition on the progression of DR are described in the article by Thomas Gardner, MD, MS.)

New drugs for the treatment of obesity could become available. The development of a medication that would help patients with diabetes to maintain a healthy weight without serious side effects would represent a significant clinical advance, especially since some diabetes therapies (eg, insulin, sulfonylureas, TZDs) may also promote weight gain.

Antiobesity agents such as orlistat and sibutramine have produced only modest weight loss in placebo-controlled clinical trials, but some studies have suggested that even limited weight reduction with these agents may significantly improve health outcomes in patients with diabetes. Sibutramine is a norepinephrine and serotonin reuptake inhibitor that is thought to primarily affect satiety, whereas orlistat impairs the absorption of dietary fat. To be sure, neither is without its limitations, and neither is routinely used in the treatment of type 2 diabetes. A new weight-loss agent, rimonabant, is being evaluated in clinical trials.
Rimonabant is a cannabinoid receptor antagonist that is thought to reduce appetite.\textsuperscript{16}

New medications are also being developed that are intended to affect insulin resistance and dyslipidemia, including new agents that act at peroxisome proliferated activated receptors (PPAR). The PPAR family of nuclear receptor molecules modify DNA transcription in response to varying levels of substances that are important in metabolic homeostasis, such as fatty acids.\textsuperscript{18} One PPAR isotype (PPAR\textsubscript{\alpha}) binds to members of the fibrate class of lipid-lowering medications, whereas a second isotype (PPAR\textsubscript{\gamma}) binds to TZDs. Thus, it has been proposed that dual activators of both PPAR\textsubscript{\alpha} and PPAR\textsubscript{\gamma} may improve both lipid profile and insulin sensitization, which may be beneficial in patients with diabetes or the metabolic syndrome.\textsuperscript{18}

Data from animal models and from initial clinical studies suggest that PPAR\textsubscript{\alpha}/\gamma activators improve dyslipidemia and insulin resistance in a dose-dependent manner.\textsuperscript{19,20}

Other agents are in development that may improve signaling between the intestine and the pancreas (eg, amylin analogs). Amylin (islet amyloid polypeptide) is a peptide hormone that is stored and secreted by the pancreas in parallel with insulin.\textsuperscript{21} Amylin is lost, along with insulin, as a consequence of the elimination of pancreatic beta cells in diabetes.\textsuperscript{21} Amylin analogs (eg, pramlintide) are thought to inhibit excessive glucagon secretion and delay gastric emptying.\textsuperscript{21} In a 52-week double-blind clinical trial of 651 patients with type 1 diabetes, the adjunctive use of pramlintide in combination with insulin produced a mean reduction of HbA\textsubscript{1c} values of 0.34\% from baseline, compared with a mean reduction of 0.04\% with placebo (\(P < 0.001\)), and also significantly decreased body weight.\textsuperscript{21} While not a major change in glycemic control, these studies point to the potential for amylin analogs.

New developments are also expected for glucose monitoring. The use of new external devices will permit continuous glucose monitoring, including a subcutaneous 3-day monitor and a 15-hour wristwatch monitor. These are not yet available for widespread clinical use, and the available devices have significant shortcomings at present. Implanted glucose sensors are also being evaluated. These include an implanted subcutaneous glucose sensor and a long-term intravenous glucose sensor that is being developed for use for patients in intensive care. These systems could become widely used within the next 5 years.\textsuperscript{23,24}

Advances in insulin pump technology are also expected during the next few years. Implanted insulin pumps are being developed, and improvements in pump design and in insulin formulation may soon permit more efficient long-term glucose control with an implanted insulin pump.\textsuperscript{25} One of the most significant challenges that is posed by current glucose monitoring and insulin pump technology is the development of an insulin pump that can adjust insulin release automatically in response to changes in blood glucose levels. The available pumps do not monitor blood glucose, cannot adapt automatically to changing insulin demands, and must be signaled by the user in response to glucose testing results. With continuing improvement in both glucose sensing and insulin delivery technologies, it may be possible in the future to develop “closed loop” pumps that automatically adjust insulin release as needed.\textsuperscript{25} This could represent a significant advance in diabetes care by permitting long-term, accurate blood glucose control with a relatively simple minor surgical procedure.

**SUMMARY AND CONCLUSIONS**

The evidence is now incontrovertible that tight blood glucose control significantly reduces the incidence of the diabetic microvascular complications including DR, both in patients with type 1 and type 2 diabetes. Dietary approaches to the management of hyperglycemia have not changed substantially in recent years, but pharmacologic therapy for diabetes has evolved considerably with the introduction of new oral agents, new fast-acting and long-acting human insulin analogs, and other glucose-lowering agents. Self-monitoring of blood glucose should be an important part of diabetes care for all patients with diabetes. A number of novel approaches to diabetes treatment are currently being evaluated in clinical trials, including new medications that could address the underlying causes of diabetic complications, agents that could assist in weight control, and agents that could affect secretion of endogenous insulin or glucagon. As advances are being made to improve glucose monitoring and insulin delivery, this forward momentum in diabetes care will allow easier, more effective glycemic control, and ultimately could relegate diabetic complications to medical history.
REFERENCES


