Current Strategies for Evaluating, Monitoring, and Treating Type 2 Diabetes Mellitus

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ABSTRACT

Diabetes mellitus is a chronic progressive disease that has profound consequences for individuals, families, and society. Despite clear glycemic control targets articulated by the major medical societies, patients and physicians still struggle to meet and maintain these goals, leading to shortfalls in delivery of care. Recent advances in the treatment of type 2 diabetes seek to address these shortfalls: Modern oral hypoglycemic agents may be used with or in place of traditional therapies. Analogue insulins, whose pharmacokinetic and pharmacodynamic properties allow patients improved lifestyle flexibility compared with regular insulins, have done much to improve glycemic control. Using these new classes of therapy, physicians should strive to help patients understand and reach the targets for control that we know to be beneficial for the majority of individuals. Such targets include those for glycosylated hemoglobin (HbA1c), but increasingly we also realize the central importance of maintaining post-prandial glucose levels within recommended limits, and it is likely that the recent introduction of a serum marker for this purpose, 1,5-anhydroglucitol, will help improve patient outcomes. By intensifying therapy early during the course of the disease process, using the most effective and acceptable therapies available, and maintaining the lowest and safest HbA1c levels for as long as possible, we will be serving our patients well and living up to our responsibilities as diabetes care physicians.

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The chronic progressive nature of diabetes mellitus, which affects nearly 21 million Americans,¹ and its devastating associated comorbid disease states, make diabetes management ubiquitous in primary care. Approximately 20% of all patients seen by family physicians have diabetes,² and >90% of individuals with diabetes in the United States are managed by primary care physicians (PCPs). PCPs refer <10% of patients with diabetes to endocrinologists, and 60% of these referrals are for insulin-replacement therapy. The majority of PCPs have had <4 hours of diabetes-related education while in medical school,³⁻⁵ highlighting the need for supplementary, continuous education focusing on diabetes pathophysiology and treatment options.

It is widely agreed that modern polypharmaceutical intervention increases longevity in individuals with diabetes, but finding ways to reduce the excess mortality related to long-term complications remains a priority. Evidence-based clinical trials have consistently demonstrated that early intervention and intensive management can improve long-term diabetes outcomes.⁶⁻⁹ However, 70% of patients with diabetes still die prematurely from heart disease.¹⁰ The cost of managing a patient with diabetes and coexisting coronary heart disease and hypertension over 3 years is 300% higher than for diabetes alone (US $46,000 versus $14,000).¹¹ An increase in glycosylated hemoglobin (HbA1c) from 6% to 10% results in an 11% increase in overall costs for each patient with diabetes.¹¹ If every PCP reduced HbA1c by 2% in 100 of their patients, a financial saving of $150,000 per physician could be realized over 3 years. The combined efforts of all 50,000 practicing members of the American Academy of Family Physicians (AAFP) to reduce the median HbA1c levels of their patient population with diabetes by 2% could save >$2.5 billion annually.¹²

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THE CHALLENGE OF ACHIEVING RECOMMENDED GLYCEMIC TARGETS

Most patients with diabetes in the United States have yet to attain the glycemic treatment goals established by expert consensus within various professional organizations. The recommendations for glycemic control established by the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) are shown in Figure 1.\(^\text{1-3}\) It is worth noting that the ADA recommends an HbA1c <7% in individual patients, provided that undue hypoglycemia does not occur.

Koro and colleagues\(^\text{14}\) compared epidemiologic data from adult patients with type 2 diabetes between 1988 to 1994 and 1999 to 2000. The mean HbA1c level increased from 7.7% to 7.9% in the National Health and Nutrition Examination Surveys (NHANES) 1999 to 2000 cohort despite the marketing of novel pharmacologic therapies and acknowledged importance of intensifying diabetes management. Surprisingly, the percentage of patients successfully treated to an HbA1c level <7% declined from 44.5% to 35.8% over 12 years.

Attainment of ADA-recommended HbA1c levels is far from optimal in the United States, and differs by age, race, duration of diabetes, and education. Public health resources should focus on empowering people with diabetes to improve their diabetes self-management skills and on identifying ways to improve the efficacy and efficiency of patient–physician partnerships aimed at achieving practice recommendations.

REALISTIC GOALS FOR DIABETES MANAGEMENT

To overcome deficiencies in diabetes management, we must become more proactive in minimizing long- and short-term exposure to hyperglycemia. The traditional approach to managing patients with type 2 diabetes includes prescribing a period of lifestyle intervention, followed by introduction of a single oral agent. As glycemic control deteriorates, a second oral agent is added, followed eventually by a third.\(^\text{16}\) In some cases, patients are inappropriately threatened with warnings suggesting that the use of insulin is “just around the corner” unless they become more diligent about their own care; if they return to their physician with a further increase in HbA1c, they may be labeled as “nonadherent.” Frustration, misunderstandings concerning the inevitability of certain complications such as painful peripheral neuropathy being inaccurately attributed to aging, and depression, all limit patients’ empowerment in diabetes self-management.\(^\text{17}\)

Newer treatment paradigms suggest that early intervention can profoundly improve prognosis: better glycemic control at the time of initial pharmacologic intervention is associated with lower HbA1c values over time and decreased long-term microvascular and macrovascular complications.\(^\text{18}\) During the Epidemiology of Diabetes Interventions and Complications Trial (EDIC)—a 10-year follow-up of 1,375 of the original 1,441 patients in the landmark Diabetes Control and Complications Trial (DCCT) in patients with type 1 diabetes—most patients were intensively managed by community-based physicians. Patients originally randomized to conventional treatment who entered EDIC to intensify their regimens reduced their mean HbA1c from 9.1% to 8.2%. However, because fewer community-based diabetes resources were available compared with those offered to intensively managed participants in the DCCT, glycemic control in the DCCT’s intensively managed cohort deteriorated during EDIC from an HbA1c level of 7.2% to 7.9%.

Despite their gradual increase in HbA1c levels, patients originally managed with intensive therapy in the DCCT had a 57% reduction in first occurrence of stroke, myocardial infarction, or death from cardiovascular disease when compared with the previously conventionally treated patients during EDIC. In addition, intensive therapy resulted in a 52% reduction in retinopathy and urinary albumin excretion.\(^\text{19}\) Although only patients with type 1 diabetes participated in the DCCT and EDIC, most experts believe that similar results can be expected for patients with type 2 diabetes.

Based on the conclusions derived from these landmark trials, our approach to diabetes should become much more aggressive while minimizing the risk for hypoglycemia. Not only must we strive to intensify therapy early during the course of the disease process, we must also maintain the lowest and safest HbA1c level for as long as possible. Patients who are able to obtain HbA1c levels between 6.5% and 7% shortly after being diagnosed with diabetes, and who maintain this level of control for 4 to 6 years, are likely to induce metabolic memory, which protects them from long-term diabetes-related complications.\(^\text{6}\)

DIABETES THERAPIES AND THEIR ROLE IN THE TREATMENT OF TYPE 2 DIABETES

Modern principles of management for type 2 diabetes focus on disease prevention, screening high-risk individuals, and aggressive treatment of individuals in the prediabetic state. In all cases, the cornerstone of successful management is lifestyle intervention. In addition to the beneficial effects of modest weight loss (approximately 4 kg) on fasting glycemia, the additive effects of increased physical activity can improve other cardiovascular risk factors such as hypertension, atherogenic dyslipidemia, endothelial cell dysfunction, and high plasma viscosity.\(^\text{17,20}\)

When initiating pharmacotherapy it is important to consider the individual’s current glycemia. Patients with HbA1c levels >8.5% should be started on medications such as a sulfonylurea drug or metformin; in the absence of specific contraindications, metformin can improve glycemia and weight reduction, and it does not result in hypoglycemia. In addition, metformin is generally well tolerated, has broad formulary coverage, and is relatively inexpensive. The ADA has recommended that metformin be initiated alongside lifestyle intervention at the time of diagnosis of type 2 diabetes.\(^\text{21}\) Patients whose HbA1c level is <7.5% may be appropriately managed using a drug with a slower onset of action, such as a thiazolidinedione (TZD), although in-
creased weight gain and prohibitive cost may limit their suitability. Recently, concerns have been raised over the safety of rosiglitazone and pioglitazone; recent meta-analysis has shown that both of these TZDs are associated with an increased risk for heart failure.22-24 Combination oral antidiabetic drug therapy can be suitable first-line therapy for treatment-naive patients with type 2 diabetes because it addresses both insulin resistance and insulin deficiency; however, as HbA1c levels drift above 8.5%, combination therapy is unlikely to achieve HbA1c targets25 as oral agents, either alone or in combination, can lower HbA1c only 1% to 2%.26

In addition to these traditional agents, several novel classes of drug are currently being used to intensify diabetes management. Several of these achieve their therapeutic effect through activity on glucagon-like peptide–1 (GLP-1), a naturally occurring intestinal peptide hormone secreted by the L-cells of the small intestine. After a meal, release of GLP-1 results in pancreatic β-cell stimulation of insulin production and secretion. In addition to this “incretin effect,” defined as the difference in glucose-stimulated insulin secretion from an oral versus an intravenous glucose bolus, GLP-1 has several other important neuroendocrine effects, including suppression of α-cell glucagon secretion, maintenance of normal gastric emptying and subsequent stabilization of serum glucose concentrations, and suppression of appetite leading to weight loss of 2 to 3 kg over 6 months.27 Because patients with type 2 diabetes are GLP-1 deficient, they are unable to reduce glucagon secretion after eating or to minimize postprandial glucose excursions.

Clinical trials using exenatide (Byetta; Eli Lilly & Co., Indianapolis, IN), a synthetic form of exendin-4 that is approved in the United States for type 2 diabetes inadequately controlled with metformin and/or a sulfonylurea, indicate that injection of exenatide 10 μg twice daily for 6 months can reduce HbA1c by 1%, and body weight by ~2 kg28; long-term efficacy trials show sustained reduction in HbA1c of 1.1% after 18 months accompanied by progressive mean body weight reductions of 4.4 kg.29 Up to 45% of patients experience transient nausea, vomiting, or diarrhea. Exenatide appears most beneficial when used during the earliest stages of type 2 diabetes; because it lowers HbA1c by approximately 1%, a patient with an HbA1c level >8% on combination oral agents is unlikely to successfully achieve the ADA target of <7% when adding exenatide to this regimen. Most patients with HbA1c levels >8% still require insulin replacement to successfully achieve target goals.

Once released, human GLP-1 is rapidly degraded by the ubiquitous intestinal cell–surface enzyme known as dipeptidyl peptidase–4 (DPP-4). Pharmacologic inhibitors of DPP-4 mimic many of the actions of GLP-1 agonists including stimulation of insulin, inhibition of glucagon secretion and preservation of β-cell mass through stimulation of cell proliferation, and inhibition of β-cell death (apoptosis).30 By contrast, DPP-4 inhibitors are generally not associated with a deceleration of gastric emptying or weight loss. Drugs that inhibit DPP-4 activity can reduce circulating plasma DPP-4 levels by up to 80% for up to 24 hours.31 DPP-IV inhibition is accompanied by a rise in postprandial levels of GLP-1. The only US Food and Drug Administration (FDA)–approved and currently marketed DPP-IV inhibitor is sitagliptin (Januvia; Merck & Co., Inc., Whitehouse Station, NJ). Vigitaptin (Galvus; Novartis International AG, Basel, Switzerland) is currently used in Europe and is awaiting a US license.
Sitagliptin is effective and well tolerated when used as a monotherapy: A randomized, double-blind, placebo-controlled trial showed that, in patients with type 2 diabetes inadequately controlled by exercise and diet, significant reductions in HbA1c were achieved (–0.77% at doses of 50 mg twice daily) with few side effects and no significant weight change.\(^{32}\) Sitagliptin is also well tolerated as part of combination therapy in type 2 diabetes treatment; in particular, use with high doses of metformin (~2,000 mg once daily) can lower HbA1c by as much as 2%.\(^{33}\) Other researchers have found that sitagliptin alone or in combination with metformin has a positive effect on parameters of β-cell function.\(^{34,35}\) Sitagliptin can also be used with gliptin or a combination of glimepiride and metformin.\(^{35}\) Evidence also exists to support use of vildagliptin: At a dose of 100 mg once daily, fasting and postprandial glucose concentrations were reduced after 4 weeks of vildagliptin treatment.\(^{31}\) Plasma glucagon concentrations were also suppressed, together with an increase in the ratio of insulin to glucose.\(^{31}\) In clinical studies of longer duration, the addition of vildagliptin to patients already given metformin reduced HbA1c levels by 0.7% after 12 weeks, compared with placebo.\(^{36}\) Indirect evidence from modeling experiments suggests that β-cell function is improved with vildagliptin treatment lasting >1 year in patients with type 2 diabetes.\(^{37}\) Vildagliptin monotherapy either 50 mg twice daily or 100 mg once daily has shown sustained efficacy, but noninferiority when compared with metformin after 1 year of therapy, although vildagliptin was better tolerated.\(^{38}\) Similarly, vildagliptin was as effective as rosiglitazone in a direct comparison monotherapy study.\(^{39}\)

A third modern oral agent, amylin, is cosecreted from pancreatic β-cells with insulin in response to a glucose challenge. Once released, amylin reduces glucagon secretion, inhibits gastric emptying, and reduces food intake. In animal models, continuous amylin infusion results in weight reduction by controlling satiety.\(^{40}\) Plasma levels of endogenous amylin in healthy individuals are lower in the fasting state and rise 4-fold after a meal.\(^{41}\) Type 1 diabetes is an amylin- and insulin-deficient disease, whereas amylin and insulin levels are often elevated in patients with impaired glucose tolerance and early type 2 diabetes.\(^{42}\) The use of exogenous amylin (pramlintide) (Symlin; Amylin Pharmaceuticals Inc., San Diego, CA) and GLP-1 hormones can improve glycemic fluctuations, lower HbA1c and postprandial glucose excursions, and enhance satiety while favoring weight reduction. Unlike exenatide, pramlintide’s effects are not glucose dependent. Therefore, patients using pramlintide with exogenous insulin are more likely to develop postprandial hypoglycemia, particularly when appropriate insulin dose adjustment is not made.

Unlike oral medications, which lower HbA1c by a mean of 1.5% to 2%, insulin is the most powerful and versatile antihyperglycemic drug available; its use is restricted only by the potential for hypoglycemia. Patients who are symptomatic feel improvement in nearly all core symptoms of hyperglycemia (fatigue, thirst, polyuria, impaired vision) shortly after beginning insulin therapy. No consensus has been reached regarding the ideal insulin regimen for patients with type 2 diabetes, and data exist to support initiating treatment with basal insulin with oral agents,\(^{42,43}\) premixed insulin analogues,\(^{44-46}\) and basal-bolus insulin.\(^{47}\) Although most patients would presumably prefer the convenience of a single injection of basal insulin daily (either glargine or detemir), practicality suggests that prandial insulin is often needed, and the continued utility of oral agents is questionable as HbA1c levels rise to >9.5%. The development of newer insulin delivery devices, such as pen injectors, insulin pumps, and, in the future, inhaled insulin, provides patients with many essentially painless options for improving chronic hyperglycemia. Discussing with patients shortly after the diagnosis of type 2 diabetes the likely need for insulin therapy at a future stage is appropriate and increases the later acceptability of insulin, while limiting the potential for using insulin therapy as a threat or to imply patient “failure” in managing their diabetes effectively. Key data on currently available insulins are reviewed in other articles in this supplement.\(^{48-50}\)

Once patients begin insulin therapy, they must become more involved with diabetes self-management, such as with home blood glucose monitoring, medical nutritional therapy, and increased physical activity. When possible, patients should be referred to certified diabetes educators to learn the skills required for diabetes intensification. Diabetic education delivered in a group setting is a cost-effective and time-efficient way to improve glycemic control in patients with the disease.\(^{51}\)

Regardless of the initial choice of drug therapy, physicians must be vigilant in monitoring patients’ glycemic control. Diabetes remains a progressive disease, and physicians should revisit their management decisions regularly, keeping mindful of the need to maintain glycemic control while minimizing short-term complications such as weight gain and hypoglycemia. Decisions about which drugs to use should be guided by the patient’s current HbA1c levels and symptoms.

**THE CONTRIBUTION OF GLYCEMIC VARIABILITY AND POSTPRANDIAL HYPERGLYCEMIA TO DIABETIC COMPLICATIONS**

Results from the seminal DCCT trial suggested that the improvement in mean glycemia (from an HbA1c level of 9% to 7%) was responsible for the 60% reduction in microvascular complications observed in the intensively treated cohort.\(^{5}\) However, the risk of progression of diabetic retinopathy was markedly reduced for the intensive therapy group at each level of HbA1c when compared with the conventionally treated group, prompting the questions of why the intensively treated patients who ended the study with an HbA1c of 9% did not experience the same risk for retinopathy progression as the conventionally treated patients with identical HbA1c levels, and whether etiologies other than mean glycemia could be responsible for the development of...
microvascular complications. One hypothesis is that patients who do not monitor blood glucose levels and who are minimally treated (such as those in the DCCT conventional cohort) experience an increase in glycemic variability, in which wide swings in daily glucose control generate reactive oxygen species (ROS), which can lead to diabetes complications.

Although levels cannot be measured directly, ROS interact with various other macromolecules to generate oxidative byproducts and result in glucose-mediated endothelial damage. The molecules nitrotyrosine and 8-hydroxydeoxyguanosine (8-OHdG) have been evaluated to determine the extent of vascular damage induced by periodic versus continuous exposure to high levels of glucose. In their study, Risso and associates investigated the effect of intermittent low- or high-flow glucose concentration on human umbilical vein endothelial cell death, a downstream marker of ROS, and concluded that “variability in glycemic control could be more deleterious to endothelial cells than a constant high concentration of glucose.”

Patients who tend toward significant postprandial hyperglycemic spikes may be at particular risk for the consequences of glycemic variability. Novel markers of postprandial glucose excursions could therefore help reduce glycemic variability, the extent of ROS, and overall risk for macrovascular complications. One such compound, serum 1,5-anhydroglucitol (1,5-AG) (GlycoMark; Biomarker Group, Kannapolis, NC) has been approved in the United States as a short-term marker for glycemic control. 1,5-AG is filtered and completely reabsorbed by the kidneys during periods of euglycemia. If glucose levels exceed 180 mg/dL (the average renal threshold for glucose), serum 1,5-AG levels decrease in direct correlation to the severity of glycosuria. If glucose levels exceed 180 mg/dL (the average renal threshold for glucose), serum 1,5-AG levels decrease in direct correlation to the severity of glycosuria. In their study, Risso and associates investigated the effect of intermittent low- or high-flow glucose concentration on human umbilical vein endothelial cell death, a downstream marker of ROS, and concluded that “variability in glycemic control could be more deleterious to endothelial cells than a constant high concentration of glucose.”

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SUMMARY

Although lifestyle interventions remain the cornerstone for the management of hyperglycemia, physicians should intensify pharmacologic therapy early during the course of the disease, aiming for the lowest Hba1c level safely achieved without unacceptable frequency of hypoglycemia. Patients who are unable to successfully reach an Hba1c level of <7% on combination oral therapy, with or without the addition of exenatide, should be considered candidates for insulin replacement therapy. Advances in insulin therapy and insulin-delivery devices along with patient education can improve quality of life and reduce the potential for complications and other adverse effects in patients requiring insulin therapy.

AUTHOR DISCLOSURES

The author of this article has disclosed the following industry relationships:

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