

DIABETES UPDATE 2006: URGENCY FOR NEW APPROACHES

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INTRODUCTION

Type 2 diabetes mellitus already a substantial public health problem in most industrialized nations, is increasing in prevalence worldwide. According to the International Diabetes Federation, the global prevalence of diabetes is expected to increase from 194 million cases in 2003 to an estimated 333 million cases in 2025. Particularly hard hit will be developing countries, where type 2 diabetes is still an emerging disease. During the same period, prevalence is predicted to increase by 105% in the eastern Mediterranean region and the Middle East, by 108% in Southeast Asia, and by 111% in Africa.¹

RISK FACTORS AND COMORBIDITY

Type 2 diabetes is strongly correlated with overweight and obesity. In the United States, the prevalence of obesity increased by 61% between 1991 and 2000, and more than 60% of US adults are overweight.²⁻⁴ A substantial ethnic disparity exists in diabetes in the United States. Approximately 11% of Black adults (age ≥ 18 years) have diagnosed diabetes, compared to $\approx 9\%$ of Hispanic adults and $\approx 7\%$ of White adults.⁵⁻⁷

Diabetes is responsible for substantial morbidity and mortality in the United States. Since 1979, the age-adjusted rates for mortality from major cardiovascular disease (CVD), cancer mortality, and all-cause mortality have generally decreased. Mortality rates for diabetes, however, increased steadily over the same period.⁸ Diabetes is also one of the four "traditional" risk factors for coronary heart disease events (the other three are hyperlipidemia [total cholesterol ≥ 240 mg/dL], hypertension [blood pressure $\geq 140/90$ mm Hg], and cigarette smoking).⁹ In the third Na-

tional Health and Nutrition Examination Survey (NHANES III), comorbidities were prevalent among patients with type 2 diabetes: 7.6% had proteinuria, 28.2% had microalbuminuria, 45.3% were obese, 67.0% had dyslipidemia, and 63.0% had hypertension.¹⁰

MANAGEMENT

One treatment algorithm is shown in Figure 1. A primary care provider does not necessarily have to understand all the complexities of diabetes in order to treat it well, but he or she must understand that type 2 diabetes is a progressive disease that involves regulatory influences of multiple hormones, each of which has its own treatment requirements. In patients with normal glucose tolerance, insulin levels rise sharply in response to a carbohydrate meal; at the same time, glucagon levels drop sharply. Over the course of several hours, as blood glucose slowly returns to normal, insulin gradually falls to preprandial levels and glucagon gradually rises to preprandial levels. In patients with type 2 diabetes, the insulin response is blunted and glucagon is not adequately suppressed; in fact, glucagon levels may increase postprandially.

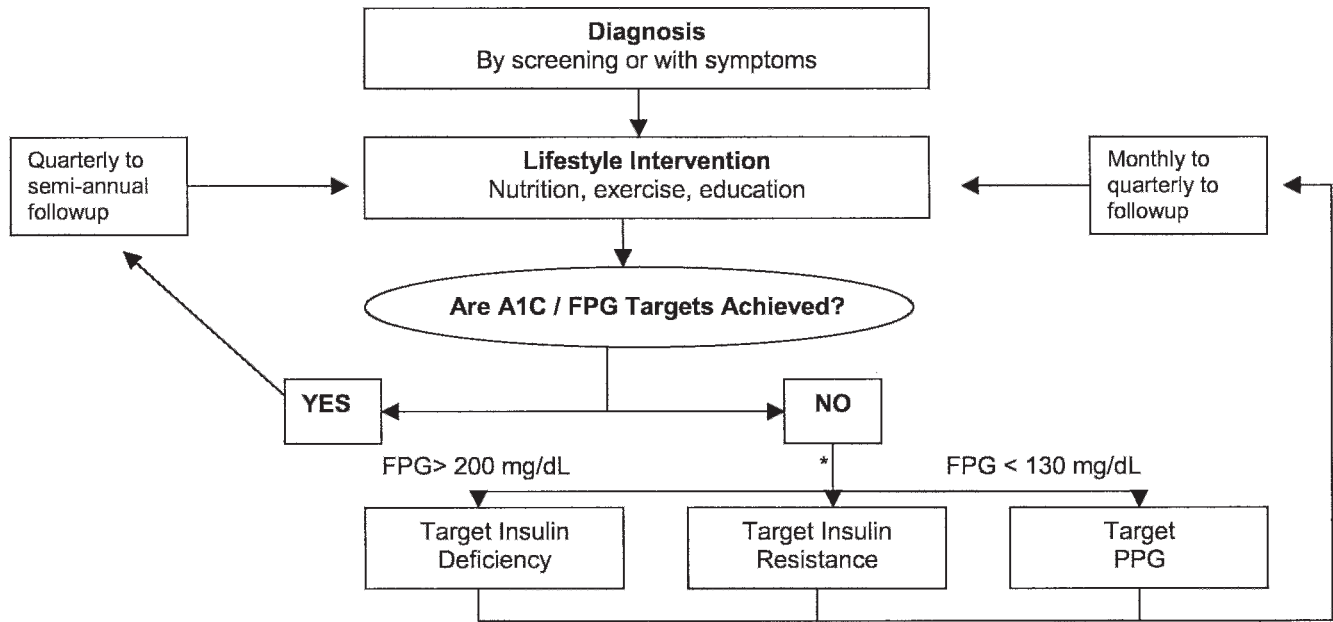
Therapeutic Goals

Diabetes management is often presented as an ABC approach—"A" for hemoglobin (Hgb) A1C, "B" for blood pressure, and "C" for cholesterol. More specifically, the American Diabetes Association (ADA) recommends that all diabetes patients should maintain tight glycemic control (HbA1C $< 7.0\%$, preprandial plasma glucose 90–130 mg/dL, postprandial plasma glucose < 180 mg/dL), healthy blood pressure ($< 130/80$ mm Hg), and beneficial lipid levels (low-density lipoprotein [LDL]

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*Keep adding agents until target is reached. Self-titration at home when possible.

Fig 1. Treatment algorithm - glucose

cholesterol <100 mg/dL, triglycerides <150 mg/dL, high-density lipoprotein [HDL] cholesterol >40 mg/dL).¹¹ In addition, patients >40 years of age or those with other risk factors should receive antiplatelet therapy, and all patients who smoke should stop.

Of diabetes patients who participated in the interview and examination portions of the 1999–2000 NHANES ($n=404$), 63% were not at the ADA HbA1C goal of <7%. In fact, only 7% had attained the goals of HbA1C, <7% blood pressure <130/80 mmHg, and total cholesterol <200 mg/dL.¹² A number of difficulties can interfere with achieving target HbA1C goals: lack of knowledge of the appropriate HbA1C target, late diagnosis and initiation of therapy, therapeutic “inertia,” absent or ineffective lifestyle intervention, non-compliance with therapies because of adverse events, and general complexity of care.

Guidelines may differ in therapeutic goals. In contrast to the ADA goals, the

American Association of Clinical Endocrinologists recommends goals of fasting glucose <100 mg/dL, 2-hour postprandial glucose <140 mg/dL, and HbA1C <6.5%.¹³ The ADA further notes that lower HbA1C goals (eg, <6%) can reduce the risk of diabetes complications at the risk of hypoglycemic events; they also suggest that postprandial glucose can be a specific target of therapy in patients for whom postprandial hyperglycemia is a problem.¹⁴

Early Detection and Disease Progression

Early detection can be key to diabetes management. Early in the course of disease, fasting plasma glucose and HbA1C levels are modestly elevated, and lifestyle changes or pharmacologic monotherapy are often sufficient to achieve goals. In early diabetes, preserving β -cell function is essential. Later in the course of disease, fasting glucose and HbA1C elevations are more signif-

icant, signs of microvascular disease may be present, and atherosclerosis will have almost certainly progressed. For later stage diabetes, combination therapy is usually needed to prevent further β -cell deterioration and control blood glucose and other risk factors.

In the longitudinal United Kingdom Prospective Diabetes Study (UKPDS), treatments with insulin, a sulfonylurea, and metformin all produced an initial decrease in HbA1C, but during 10 years of followup, levels steadily increased, showing progression of hyperglycemia despite pharmacologic monotherapy.¹⁵ Similarly, both metformin and a sulfonylurea used as monotherapy failed to maintain β -cell function over time in both obese and nonobese patients.¹⁶

Pharmacologic Therapy Options

A number of agents are available to treat type 2 diabetes; several of these are shown in Table 1. In general, current treatments for type 2 diabetes are

Table 1. Agents available for diabetes treatment

Agent	Mechanism of Action	Advantages	Disadvantages
Insulin	Replace or supplement endogenous insulin	Long history of efficacious use, easily titrated	Must be injected, associated with weight gain, risk of hypoglycemia
Sulfonylureas	Increase insulin secretion from β cells	Long history of safe and efficacious use, inexpensive, titratable	Risk of hypoglycemia, associated with weight gain
Meglitinides	Increase insulin secretion from β cells	Flexible—rapid onset and short duration of action	Expensive, dosed three times daily
Biguanides	Increase glucose uptake and utilization in muscle, decrease hepatic glucose output	Not associated with weight gain, may have beneficial cardiovascular effects	Associated with gastrointestinal complaints, contraindications
Thiazolidinediones	Increase glucose uptake and utilization in muscle, decrease hepatic glucose output, decrease lipolysis in fat cells	Preserve β -cell function, may reduce cardiovascular events	Expensive, slow onset of action, associated with fluid retention and weight gain
α -Glucosidase inhibitors	Inhibit carbohydrate absorption from intestines	Not associated with weight gain or hypoglycemia	Expensive and frequently cause gastrointestinal complaints

limited by the durability of their effect, potential for hypoglycemia, gastrointestinal side effects, poor responder rates, and their potential to cause weight gain and edema. Additionally, use of many agents is limited in elderly patients or patients with renal impairment or coronary heart disease.

Inadequacy of therapies for diabetes may be partially explained by their poor alignment with the underlying pathophysiology of the disease. Insulins do not normalize the glucagon response (decrease hepatic glucose output). Secretagogues do not preserve β -cell function, although thiazolidinediones and biguanides decrease insulin resistance and may enhance β -cell function.

Patients and providers must recognize that pharmacologic monotherapy is rarely a long-term treatment option. In a retrospective Kaiser Permanente database analysis, Brown et al found that 354 patients on metformin monotherapy remained on monotherapy for an average of 14 months after their first HbA1C reading $>8.0\%$ before changing or adding medications. For 2517 patients on sulfonylurea monotherapy, the average was 20 months.¹⁷

A limitation of current oral therapies is that they do not address all the

metabolic needs of type 2 diabetes. Acute β -cell dysfunction is targeted by sulfonylureas and meglitinides, insulin resistance is targeted by thiazolidinediones and biguanides, and glucose influx from the gastrointestinal tract is targeted by α -glucosidase inhibitors. Still, no agents are available to address inadequate glucagon suppression (α -cell dysfunction) or chronic β -cell dysfunction.

Newer Agents

Several promising new agents target the incretin system. Incretins are a family of gastrointestinal hormones that are produced in response to a carbohydrate meal. They stimulate β cells to produce insulin even before serum glucose levels increase. Incretins also inhibit glucagon release and slows gastric emptying; it may also directly affect appetite centers in the central nervous system to reduce food intake.

The primary candidate incretin is a molecule known as glucagon-like peptide-1 (GLP-1). Because GLP-1 is rapidly degraded by an enzyme known as dipeptidyl peptidase IV (DPP-IV), exogenous GLP-1 must be administered by continuous subcutaneous infusion in order to be effective. However, several agents are under investigation that

agonize GLP-1 receptors; the first such agent to receive approval from the US Food and Drug Administration for the treatment of type 2 diabetes is exenatide.

Exenatide has multiple sites of action: it slows gastric emptying, stimulates glucose-dependent insulin secretion, increases β -cell mass, inhibits glucagon secretion from α cells, reduces hepatic glucose output, promotes satiety, and reduces appetite. In a placebo-controlled study of 25 patients with type 2 diabetes, exenatide normalized the blunted glucose-dependent insulin response.¹⁸ Postprandial glucose “excursions” are now known to contribute to the increase risk for cardiovascular disease seen in diabetes patients. While secretagogues acutely increase β -cell sensitivity to glucose, the effect may not be sustainable, and they do not similarly restore sensitivity to α cells, which leaves a key feature of the underlying pathophysiology unattended.

At higher HbA1C levels, fasting glucose is the primary contributor to diabetes severity. As HbA1C approaches the 7% target, however, postprandial glucose plays an increasingly important role. Unfortunately, postprandial glucose elevations are often overlooked in diabetes therapy.

In a 30-week study of 77 patients on sulfonylurea-metformin combination therapy, injection of 5 µg or 10 µg exenatide before a meal significantly decreased postprandial glucose, compared to elevations seen in patients who injected a placebo.¹⁹

In a 2-year study of 146 patients with type 2 diabetes randomized to placebo or exenatide, patients in the exenatide group experienced an average reduction in HbA1C of 1.2 percentage points, and they lost an average of 5.5 kg body weight. Compared to insulin glargine, exenatide more potently reduced postprandial glucose elevations and smoothed the peaks and troughs in plasma glucose during the course of the day.²⁰ Over the course of the 26-week study, exenatide and glargine produced similar reductions in HbA1C, but glargine patients gained ≈4 pounds while exenatide patients lost ≈5 pounds.

Liraglutide is, like exenatide, a GLP-1 agonist that is currently in phase III clinical trials. Liraglutide is absorbed into the bloodstream more slowly and is highly bound to serum albumin, which results in reduced renal clearance and slower degradation by DPP-IV. Consequently, it is expected to receive an indication for once-daily dosing. In clinical trials, liraglutide reduced patients' body weight, both as monotherapy and in combination therapy with metformin.²¹

Other agents that target the incretin system are DPP-IV inhibitors. By blocking the enzyme responsible for degrading endogenous GLP-1, these drugs potentiate the body's naturally occurring incretins. The DPP-IV inhibitor vildagliptin, in combination with glimepiride, reduced HbA1C more than glimepiride alone.²² DPP-IV inhibition offers a number of therapeutic advantages. These agents are dosed orally, which can increase patient compliance. Because they increase exposure to endogenous GLP-1, they have most of the same beneficial effects of GLP-1

agonists, but they are not associated with the same tolerability issues as exogenous GLP-1 agonists.²³

Intensive Therapy and CVD Risk Reduction

In an algorithm for intensive diabetes management, patients should receive oral insulin sensitizers in combination with a secretagogue. Insulin glargine or neutral protamine Hagedorn (NPH) insulin should be added and titrated to normalize fasting glucose. As needed, add a monomeric insulin analog to normalize postprandial glucose and discontinue secretagogue.

Diabetes treatment begins with glucose control, but it must continue with global treatment of CVD risk factors. In addition to maintaining HbA1C <7%, patients should receive antithrombotic therapy (acetylsalicylic acid) and a statin or other drug to control lipids (LDL cholesterol <100 mg/dL, HDL cholesterol >40 mg/dL, triglycerides <150 mg/dL); blood pressure should be maintained at <130/80 mm Hg. Patients should follow the Dietary Approaches to Stop Hypertension (DASH) Diet, increase aerobic exercise, and stop smoking.

Failure to reach treatment goals is associated with increased disease burden. As blood pressure increases, so do healthcare costs; patients with systolic blood pressure ≥120 mm Hg have more than twice as many physician visits per year as do those with systolic blood pressure <120 mm Hg.²⁴ In the Steno-2 study, type 2 diabetes patients who received multifactorial intensive therapy reached an endpoint (CVD death, myocardial infarction, stroke, revascularization, or amputation) at only about half the rate as did patients who received conventional therapy.²⁵ In the Hypertension Optimal Treatment (HOT) trial, type 2 diabetes patients who maintained a target diastolic blood pressure <80 mm Hg benefited from a 48% reduction in risk of a CVD event.²⁶

CONCLUSIONS

Diabetes is a serious problem in the industrialized world and is increasing in prevalence globally. Diabetes must be acknowledged as a progressive disorder, and therapy must be established and adjusted accordingly. Deviations from treatment goals while on monotherapy should be addressed early; avoid delays in treatment progression. Combination therapy with synergistic oral antihyperglycemic agents can be used to treat patients to goal, but transition to injection-based therapies should be pursued when necessary. Precise strategies for diabetes management are more "art" than science, and treatment paradigms will continue to evolve as new agents become available. A multifaceted approach is needed to treat diabetes and reduce risk of CVD events. Disease must be diagnosed early and managed with a team approach. Lifestyle interventions are essential, but pharmacologic therapy will be needed to lower blood glucose, decrease insulin resistance, preserve β-cell function, and decrease inflammation. Glycemic control can be improved by achieving and maintaining target HbA1C levels and paying special attention to postprandial glycemic control.

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