Abstract

The most common cause of mortality in diabetes is macrovascular disease, specifically coronary artery disease. The relationship between increasing mortality and rising glucose concentrations has been demonstrated in several studies, providing the rationale for tight metabolic control in these patients. Although lifestyle measures form the cornerstone of treatment for type 2 diabetes, most patients will ultimately require pharmacotherapy to achieve and maintain glycemic control. The traditional stepwise approach to therapy has neither been effective nor sufficiently aggressive; new treatment paradigms should therefore be considered in order to improve glycemic control and lower the risk of mortality. The choice of agent should be based primarily on the predominant underlying disease pathophysiology, side-effect profile of the agent, effects of the drug beyond glucose control, and whether the agent can prevent the progressive deterioration of beta cell function over time.


The majority of patients destined to develop type 2 diabetes become insulin resistant many years before diabetes develops. Initially, the beta cell compensates by enhancing insulin secretion and maintaining normal glucose levels; however, by the time frank diabetes occurs, the beta cell is no longer able to secrete adequate insulin to maintain normal glucose levels. As patients progress from normal glucose tolerance to diabetes, postprandial glucose levels rise, followed by a rise in fasting glucose concentrations. The rise in fasting glucose concentrations is caused by increased hepatic glucose production.

By the time type 2 diabetes is diagnosed, up to 20% of patients will already have developed microvascular complications. The risk for microvascular complications increases exponentially when fasting glucose levels exceed 126 mg/dL and postprandial glucose levels exceed 200 mg/dL. The most common cause of mortality in diabetes, however, is macrovascular disease, specifically coronary artery disease. The risk for macrovascular disease increases when glucose tolerance becomes impaired—before the criteria used to diagnose diabetes have been met.

The relationship between increasing mortality and rising glucose concentrations has been demonstrated in several studies. In the European Prospective Investigation of Cancer–Norfolk (EPIC–Norfolk) study, there was an increase in mortality while hemoglobin A\textsubscript{1c} (HbA\textsubscript{1c}) levels increased within the normal range (Figure 1). The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study provided further epidemi-
logic evidence supporting the relationship between increased mortality, including cardiovascular mortality, and impaired glucose tolerance. This study involved more than 25,000 people, 95% of whom did not have diabetes. Subjects were followed up for 10 years. All patients received standard 75-g glucose tolerance tests with measurements of fasting and 2-hour postprandial glucose concentrations. The primary outcomes were cardiovascular and all-cause mortality. Subjects with the lowest mortality were those whose fasting and 2-hour postchallenge glucose levels were below 110 mg/dL and 140 mg/dL, respectively (Figure 2). Postchallenge glucose concentrations between 140 mg/dL and 200 mg/dL, even in subjects whose fasting glucose levels were below 110 mg/dL, were associated with a significant increase in mortality. Mortality was further increased as postchallenge glucose levels exceeded 200 mg/dL.

**Rationale for Tight Metabolic Control**

Three well-designed studies—the Diabetes Control and Complications Trial (DCCT; type 1 diabetes), the Kumamoto study (insulin-treated type 2 diabetes), and the United Kingdom Prospective Diabetes Study (UKPDS; insulin, sulfonylureas, and/or metformin in newly diagnosed type 2 diabetics)—showed that any improvement in glycemic control was associated with a significant reduction in the risk for development or progression of microvascular complications (Table 1). In the UKPDS, a 1% difference in HbA1c between the intensively and conventionally treated patients resulted in an average 25% reduction in the risk of microvascular complications. A 2% difference in HbA1c between the treatment and control groups in both the DCCT and the Kumamoto studies was associated with a 50% to 60% reduction in risk for the onset or progression of microvascular complications. Epidemiologic review of data from the UKPDS showed that for every 1% reduction in HbA1c, there was a 12% reduction in the risk of stroke; 14% reduction in the risk of myocardial infarction; 16% reduction in the risk of heart failure; 19% reduction in the risk of cataract extraction; 21% reduction in the risk of any diabetes-related endpoint, including diabetes-related death; 37% reduction in the risk of microvascular endpoints; and a 43% reduction in the risk of amputation or death from peripheral vascular disease. There appeared to be no glycemically
threshold below which there was no development of the complications of diabetes.

Tight blood pressure control was also studied in the UKPDS. Subjects were randomized to more intensive blood pressure control using captopril or atenolol. More aggressive blood pressure control (144/82 mm Hg vs 155/87 mm Hg) was associated with a significant reduction in all endpoints measured (Figure 3). The relative effect of tight blood pressure control and tight glycemic control (HbA1c, 7% vs 7.9%) is also shown in Figure 3. Subjects who benefitted most in this study were those who achieved the best glycemic and blood pressure control.

**Choosing Drug Therapy**

The American Diabetes Association (ADA) and the American College of Endocrinologists (ACE) have different criteria for glycemic targets in the treatment of diabetes. The ADA has not addressed postprandial hyperglycemia but has determined that preprandial plasma glucose levels should be between 90 mg/dL and 130 mg/dL, bedtime glucose levels should be 100 mg/dL to 150 mg/dL, and HbA1c levels should be less than 7%. The ACE has become more aggressive in its latest recommendations, suggesting that fasting plasma glucose concentrations should be below 100 mg/dL, postprandial levels below 140 mg/dL, and HbA1c levels less than 6.5%.

Regardless of which targets are chosen, one should strive for the best possible glycemic control without increasing the risk for other complications, such as hypoglycemia. Treatment targets should be individualized and based on each patient's comorbid conditions and projected longevity.

Although lifestyle measures (diet and exercise) form the cornerstone of treatment for type 2 diabetes, the majority of patients will ultimately require pharmacotherapy to achieve and maintain glycemic control. Most pharmacologic agents will lower HbA1c between 1% and 2% with the exception of the alpha glucosidase inhibitors and nateglinide, which target postprandial hyperglycemia and lower HbA1c up to 1%

Addition of a second drug from a different class will further lower the HbA1c by another 1% to 2% (Table 2). The choice of agent should be based primarily on the predominant underlying pathophysiology, the side-effect profile of the agent, effects of the

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HbA1c = hemoglobin A1c.

Data from the DCCT Research Group; Ohkubo et al; and the UKPDS Study Group.

![Figure 3. UKPDS: Comparison Between Tight Blood Pressure Control and Glycemia on Risk of Diabetes Complications](image.png)

HbA1c = hemoglobin A1c.

Data from the UKPDS Study Group.

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**Table 1. Good Glycemic Control Reduces the Incidence of Microvascular Complications**

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drug beyond glucose control, and whether the agent can prevent the progressive deterioration of beta cell function over time.

Nateglinide and repaglinide restore the acute insulin response toward normal. Insulin secretion returns to baseline levels within 3 hours of ingestion of the drug. Glyburide, on the other hand, enhances insulin secretion, though not quite as rapidly as nateglinide; however, because this agent has a longer half-life, insulin levels are persistently higher between meals. The sulfonylurea glimepiride, which is taken once daily, demonstrates a pattern of insulin secretion that is more like nateglinide than glyburide. The thiazolidinediones enhance insulin sensitivity and lead to increased glucose uptake in muscle and adipose tissue. Metformin acts primarily by inhibiting hepatic gluconeogenesis, whereas alpha glucosidase inhibitors delay the absorption of carbohydrate from the gastrointestinal tract. When monotherapy fails, a second drug should be added rather than substituted.

**Side Effects**

Antidiabetic drugs are associated with a variety of side effects, including hypoglycemia, hyperinsulinemia, weight gain, edema, lactic acidosis, gastrointestinal disturbances, and liver function disturbances. All insulin secretagogues can cause hypoglycemia. Glyburide causes more hypoglycemia than glimepiride or short-acting insulin secretagogues. Metformin is not associated with weight gain. Acarbose causes gastrointestinal side effects, such as diarrhea and flatulence. Thiazolidinediones cause weight gain and edema, but lower circulating insulin concentrations. Weight gain also occurs with insulin secretagogues and insulin therapy. Lactic acidosis is an extremely rare complication of metformin therapy, but should not occur if the drug is avoided in patients with renal or hepatocellular dysfunction. Hepatotoxicity has not been noted to occur with increased prevalence with the newer-generation thiazolidinediones. Thiazolidinediones are contraindicated in patients with class 3 or 4 congestive heart failure. Echocardiographic studies in patients taking thiazolidinediones have shown no adverse effects on cardiac function or structure. A beneficial effect on blood pressure has been demonstrated with their use.\(^9\)\(^1\)\(^1\)

Insulin sensitizers affect some of the other biochemical parameters associated with atherogenic predisposition. The glitazones, while increasing
low-density lipoproteins (LDL), increase the amount of fluffy and buoyant LDL, and decrease the amount of the more atherogenic and dense LDL particles. High-density lipoprotein concentrations are increased with the glitazones. Glitazones and metformin reduce plasminogen activator inhibitor type 1 and have also been shown to reduce C-reactive protein concentrations.

No antidiabetic agents have been conclusively shown to protect the beta cell in humans. In one study, rosiglitazone restored pancreatic islet insulin content to normal in diabetic mice, whereas treatment with glyburide and metformin led to further loss of beta cell insulin.12

Type 2 diabetes is a progressive disease characterized by progressive beta cell dysfunction. With time, fewer people maintain adequate glycemic control with monotherapy, and multiple agents are required (Figure 4).13 Overall in the United States, only 45% of patients with type 2 diabetes mellitus have an HbA1c level less than 7%, and a high percentage of patients have HbA1c levels greater than 9%.14

SUMMARY

Type 2 diabetes mellitus is a progressive disease that traditionally has been managed by sequential addition of pharmacologic agents when monotherapy is not effective. This classic stepwise approach has neither been effectivenor sufficiently aggressive. New treatment paradigms should be considered in an attempt to improve glycemic control. Medical nutrition therapy, exercise, education, and blood glucose monitoring remain the cornerstone of therapy. If HbA1c levels are less than 7%, adding oral therapy that does not cause hypoglycemia should still be considered, so that the HbA1c levels drop as close as possible to 6%. If the HbA1c remains between 7% and 8%, an insulin sensitizer or a secretagogue should be added. If the HbA1c level is greater than 8%, combination therapy should be considered initially, and the dose of medications should be titrated as needed.

REFERENCES