Glycemic Management of Type 2 Diabetes Mellitus

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A 39-year-old man with a 2-year history of type 2 diabetes mellitus presents for care. He has no microvascular or macrovascular complications. His family history is positive for type 2 diabetes and cardiovascular disease in his mother and older brother. On examination, his weight is 99.8 kg (220 lb), with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 37, and his blood pressure is 125/85 mm Hg. His glycated hemoglobin level is 8.9%, serum creatinine level 1.0 mg per deciliter (88.4 μmol per liter), low-density lipoprotein (LDL) cholesterol 88 mg per deciliter (2.3 mmol per liter), high-density lipoprotein (HDL) cholesterol 45 mg per deciliter (1.2 mmol per liter), and triglyceride level 130 mg per deciliter (1.5 mmol per liter); he does not have microalbuminuria. His medications include metformin (500 mg twice daily), glipizide (5 mg twice daily), simvastatin (20 mg daily), and lisinopril (10 mg daily). What would you recommend to improve his glycemic control?
postprandial suppression of glucagon secretion also occurs. Beta-cell failure is mediated by genetic factors and exposure to chronically elevated levels of blood glucose (glucotoxicity) and free fatty acids (lipotoxicity). Older age, amyloid fibrils in islets, and chronically high rates of insulin secretion also play mechanistic roles. The majority of genetic abnormalities that have been identified in patients with type 2 diabetes are related to beta-cell function.\(^{11}\)

According to the American Diabetes Association, the diagnosis of type 2 diabetes is based on a glycated hemoglobin level of 6.5% or more, a fasting plasma glucose level of 126 mg per deciliter (7.0 mmol per liter) or more, or a 2-hour plasma glucose level of 200 mg per deciliter (11.1 mmol per liter) or more during an oral glucose-tolerance test.\(^{6}\) The diagnosis can also be established by classic symptoms of hyperglycemia and a random plasma glucose level of 200 mg per deciliter or more. Test results require confirmation with the use of the above criteria, unless the diagnosis is obvious on the basis of the symptoms.\(^{6}\)

### Key Clinical Points

**Glycemic Control in Type 2 Diabetes Mellitus**

- Intensive glycemic control reduces the risk of microvascular complications of type 2 diabetes, but the effect of strict glycemic control on the risk of macrovascular disease (especially in well-established type 2 diabetes) is less certain.
- Psychosocial factors (e.g., motivation and capacity for self-care) and clinical factors (e.g., age, presence or absence of coexisting conditions, and presence or absence of a tendency toward hypoglycemia) should be considered in setting a target range of glycated hemoglobin for an individual patient.
- A near-normal glycemic target range (6.0 to 6.5%), if implemented safely, could be considered for otherwise healthy patients with recently diagnosed type 2 diabetes and a long life expectancy; more relaxed goals for the glycated hemoglobin level may be preferable in older patients with long-standing type 2 diabetes and cardiovascular disease.
- Lifestyle modification and metformin are recommended as initial therapies for most patients with type 2 diabetes.
- Several therapeutic agents are available when therapy in addition to metformin is needed to control glycemia, but evidence is lacking to support the choice of any one agent over another. Decisions should take into account cost, side effects, and long-term safety and effects on complications of diabetes.

### Strategies and Evidence

This article focuses on glycemic management in type 2 diabetes. However, glycemic control is only one facet of the multifactorial approach required for attempted control of all known risk factors for the development of cardiovascular and microvascular disease.\(^{12}\)

### Goals of Glycemic Control and Target Range for Glycated Hemoglobin

The overall aim of glycemic management is to minimize long-term complications while avoiding severe hypoglycemic events. Results of large randomized trials involving patients with type 1 diabetes or newly recognized or established type 2 diabetes show that control of glycemia delays the onset and slows the progression of microvascular complications, including nephropathy, retinopathy, and neuropathy.\(^{13-18}\) Long-term follow-up of patients with newly diagnosed type 2 diabetes enrolled in the U.K. Prospective Diabetes Study (Current Controlled Trials number, ISRCTN75451837) showed a reduced risk of cardiovascular disease events 10 years after the end of the trial among patients who were initially randomly assigned to intensive glycemic management, as compared with conventional therapy (average glycated hemoglobin level, 7.0% vs. 7.9%).\(^{19}\) Results of three trials involving older patients with established type 2 diabetes and a history of or risk factors for cardiovascular disease showed no reduction in total mortality or cardiovascular disease–related mortality associated with intensive glycemic control compared with standard glycemic control\(^{15,16,20}\); one of the studies showed increased mortality.\(^{20}\) Moreover, intensive glycemic control was associated with higher rates of hypoglycemia and weight gain. Thus, the microvascular benefits that are derived from intensive glycemic control must be balanced against the risks.
The first step in glycemic management is setting an appropriate glycemic target in each individual patient. Current guidelines specify glycated hemoglobin targets of less than 7.0% or less than 6.5%. However, the appropriateness of these goals varies according to clinical characteristics and psychosocial factors, including the patient’s capacity for self-care and home support systems. Intensive glycemic control often requires a greater number and larger dosages of medications, resulting in an increase in adverse events and costs. Figure 2 shows the influence of various patient-specific features on the selection of glycated hemoglobin targets.

In general, in patients with recently recognized type 2 diabetes and few or no complications (especially younger patients), a near-normal glycemic target aimed at prevention of complications over many years of life can be suggested. In contrast, in older persons with cardiovascular disease or multiple risk factors for cardiovascular diseases, higher targets are often appropriate.

GENERAL TREATMENT CONSIDERATIONS
Whenever possible, patients should be involved in decision making regarding glycemic targets and should be informed that the targets may require adjustment over time with changes in clinical or personal factors, such as the patient’s experience with and acceptance of frequent self-monitoring of blood glucose levels and his or her ability to identify and prevent hypoglycemic events. In general, the glycated hemoglobin level should be checked at least twice yearly.

Long-term maintenance of glycemic control ideally should involve a multidisciplinary approach, including nutrition counseling and visits with a diabetes nurse, certified diabetes educator, or both. Educational programs that empower patients to become involved in their day-to-day glycemic management and education of health care providers are helpful. Successful glycemic control at a reasonable cost has been reported with the use of telecommunication and computer-based information-transfer systems.

LIFESTYLE APPROACHES
Weight loss and exercise are important nonpharmacologic approaches to improving glycemic control (Fig. 1). The American Diabetes Association recommends a balanced diet that is rich in fiber, whole grains, and legumes; contains less than 7% saturated fat and reduced trans fats; and is limited in calories and foods with a high glycemic index. Exercise has an additive effect when combined with caloric restriction for glycemic control.
control. Patients should be encouraged to engage in at least 150 minutes of moderate-intensity aerobic exercise per week.6

PHARMACOTHERAPY

Medications that are available for glycemic management of type 2 diabetes4,5,21,34-46 their usual effects on the glycated hemoglobin level, and their major advantages and disadvantages are summarized in Table 1. Treatment options have greatly expanded in the past two decades. Available agents reduce glucose levels, often through a variety of mechanisms (Fig. 1).

Agents That Improve Insulin Sensitivity

Metformin is the cornerstone of type 2 diabetes treatment.4,21,34,40 By stimulating AMP-activated protein kinase, metformin reduces hepatic glucose production. It does not cause weight gain and may result in a slight weight loss, and it rarely causes hypoglycemia; gastrointestinal side effects may occur, especially if therapy is initiated at higher doses.

Thiazolidinediones (pioglitazone and rosiglitazone) are peroxisome proliferator–activated receptor γ activators that enhance insulin sensitivity in peripheral tissues and reduce hepatic glucose production.5,21 Although a randomized trial showed that rosiglitazone, as compared with metformin or a sulfonylurea as the only initial therapy, maintained glycemic control for a longer period,35 the use of rosiglitazone is highly restricted in the United States (and was discontinued in Europe) owing to concern about an increased risk of myocardial infarction. This concern was based mostly on a meta-analysis of observational studies.44 In a randomized study, pioglitazone was associated with a reduction in the secondary composite cardiovascular disease outcome but also with increased risks of edema and heart failure.43

Agents That Increase Circulating Insulin Levels

Insulin is the most potent agent for reducing glycemia. By activating plasma-membrane receptors, it stimulates glucose uptake by responsive tissues and decreases hepatic glucose production. The use of insulin causes weight gain and may cause severe hypoglycemia.21 Long-acting (basal) and short-and rapid-acting insulin formulations and combined formulations are available.

Sulfonylureas (e.g., glipizide) stimulate insulin release by closure of specific potassium channels on beta cells. Their use is associated with modest weight gain and hypoglycemia. Meglitinides (e.g., repaglinide) have actions similar to those of sulfonylureas but have a short duration of action (hours) and are most effective preprandially.

The Food and Drug Administration (FDA) has approved agents that increase blood glucagon-like peptide 1 (GLP-1) activity or levels and stimulate insulin secretion (in a glucose-dependent manner)
while inhibiting glucagon secretion. GLP-1–receptor agonists (e.g., exenatide and liraglutide) are injectable agents that are structurally similar to endogenous GLP-1 and activate GLP-1 receptors in many tissues. Other effects include delayed gastric emptying and appetite suppression, typically resulting in a weight loss of approximately 2 to 4 kg (4.4 to 8.8 lb).21 Dipeptidyl peptidase IV (DPP-IV) inhibitors (e.g., sitagliptin) are oral agents that inhibit the degradation of GLP-1 and result in modest elevations of circulating GLP-1 levels; they do not affect weight. Either class of agent may cause hypoglycemia if used with insulin or sulfonylureas. The long-term safety of these agents (including their potential for causing pancreatitis), as well as their effects on the risk of cardiovascular disease, are unknown.

Other Agents
Other FDA-approved agents are used less frequently because of the smaller reductions in glycated hemoglobin levels (typically, approximately 0.6%) and, in some cases, side effects (Table 1).21 Alpha-glucosidase inhibitors (e.g., acarbose) interfere with the digestion of glucose polymers, thereby decreasing carbohydrate absorption; a high frequency of gastrointestinal side effects limits their use. The bile acid sequestrant colesevelam reduces hepatic glucose production and increases incretin levels by unknown mechanisms; it also reduces LDL cholesterol levels. The dopamine agonist bromocriptine activates D2 dopamine receptors and increases insulin sensitivity by unknown mechanisms; a rapid-release form was approved by the FDA for this indication. Pramlintide, an amylin mimetic, is an injectable agent that stimulates receptors for amylin. It suppresses glucagon secretion, delays gastric emptying, and decreases appetite.

STRATEGIES FOR IMPLEMENTATION
Of the various strategies for glycemic control, lifestyle modification and metformin are preferred and are cost-effective.21,34,38,40 Patients with chronically high levels of glycated hemoglobin (approximately 9.0%) are unlikely to have adequate glycemic control with metformin alone, and in patients with clinically significant hyperglycemia (blood glucose level, >300 mg per deciliter [>16.7 mmol per liter]; glycated hemoglobin level, >10%), initial insulin therapy should be considered. If metformin monotherapy cannot be used, other oral agents (e.g., a sulfonylurea, a DPP-IV inhibitor, or pioglitazone) or a GLP-1–receptor agonist can be administered. Over time, additional medications become necessary for glycemic control. A logical strategy is to consider agents with complementary mechanisms of action (Fig. 1).5,21 Combinations that are effective in reducing glycemia include metformin plus another oral agent, a GLP-1–receptor agonist, or long-acting insulin.21,34,38,46 However, strong evidence is lacking to support any one particular second agent over another. Perhaps because of the reluctance of patients and providers, insulin is generally added much later than medically indicated.21 The recent introduction of disposable pen devices may make insulin therapy more acceptable to patients.42 Initiation of insulin therapy with the use of a single dose of basal (long-acting) insulin, preferably at bedtime (starting with approximately 10 units and increasing by 2 to 3 units every several days) can reduce the glycated hemoglobin level by 1.5 to 2.0% or more.21,30 If glycemia is not controlled, a dose of rapid-acting insulin can be added at the largest meal. Premixed “biphasic insulin” preparations, typically administered before breakfast and dinner, or basal insulin plus rapid-acting insulin (“basal-bolus”) therapy before a meal can also be considered. Lower glycated hemoglobin levels are obtained with the use of biphasic or basal-bolus regimens but at the expense of a greater likelihood of hypoglycemia and weight gain.36,39

SURGICAL APPROACHES TO GLYCEMIC CONTROL
Long-term observational studies have shown considerable improvements in glycemic control, as well as improvements in associated cardiovascular risk factors and a reduced risk of cardiovascular disease,47 among patients who have undergone bariatric surgery (laparoscopic adjustable gastric banding or Roux-en-Y gastric bypass), as compared with obese patients who have not undergone surgery. Benefits have been noted particularly among very obese persons with a shorter duration of type 2 diabetes and in association with procedures that limit the absorptive surface (by-pass surgery).48 Bariatric surgery is increasingly used in patients with type 2 diabetes who are obese but not morbidly obese. The results of two recently published randomized trials of bariatric surgery involving patients with type 2 diabetes (one of which included patients with a BMI of <35) showed significant improvement in glycemic control.
<table>
<thead>
<tr>
<th>Class</th>
<th>Agent (Brand Name)</th>
<th>Expected Reduction in Glycated Hemoglobin Level (%)</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Biguanide Metformin (Glucophage)</td>
<td>1.0–2.0</td>
<td>Extensive clinical experience; hypoglycemia rare; improved lipid profile; decreased cardiovascular disease events; some weight loss in most patients</td>
<td>Gastrointestinal intolerance; lactic acidosis rare (avoid in patients at increased risk, such as men with a serum creatinine level of ≥1.5 mg/dl and women with a serum creatinine level of ≥1.4 mg/dl); vitamin B₁₂ deficiency</td>
<td>Low (generic)</td>
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<td></td>
<td>Sulfonylurea Glyburide (Diabeta), glipizide (Glucotrol), gliclazide (Diamicron), glimepiride (Amaryl)</td>
<td>1.0–1.5</td>
<td>Extensive clinical experience</td>
<td>Hypoglycemia; less durability; weight gain</td>
<td>Low (generic)</td>
</tr>
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<td></td>
<td>Meglitinide Nateglinide (Starlix), repaglinide (Prandin)</td>
<td>0.5–1.0</td>
<td>Short duration of action, hepatic clearance, glucose-dependent postprandial action</td>
<td>Low efficacy, hypoglycemia in some patients, weight gain</td>
<td>High</td>
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<td></td>
<td>Thiazolidinedione Rosiglitazone (Avandia), pioglitazone (Actos)</td>
<td>0.5–1.4</td>
<td>Hypoglycemia rare, more durable effect than that of metformin or sulfonylurea, improved lipid profile, some evidence of beneficial effect on coronary atherosclerosis (with pioglitazone)</td>
<td>Edema, heart failure, weight gain, increased risk of long-bone fractures and potential risk of bladder cancer and cardiovascular events (with rosiglitazone); use of rosiglitazone highly restricted</td>
<td>High</td>
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<td></td>
<td>DPP-IV inhibitor Saxagliptin (Onglyza), linagliptin (Tradjenta), vildagliptin (Galvus), sitagliptin (Januvia)</td>
<td>0.5–0.8</td>
<td>Hypoglycemia rare, infrequent side effects</td>
<td>Less efficacy than GLP-1–receptor agonists, angioedema, unknown long-term safety, risk of pancreatitis</td>
<td>High</td>
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<td>Alpha-glucosidase inhibitor Miglitol (Glycet), voglibose (Volix), acarbose (Precose)</td>
<td>0.5–0.9</td>
<td>Decreased level of postprandial glucose, hypoglycemia rare, possible decrease in risk of cardiovascular disease events**</td>
<td>Flatulence, diarrhea</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Bile acid sequestrant Colesevelam (Welchol)</td>
<td>0.5</td>
<td>Lowering of LDL cholesterol level; hypoglycemia rare</td>
<td>Gastrointestinal side effects, including constipation; low efficacy; only approved agent in class</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>D2 dopamine–receptor agonist Bromocriptine, rapid release (Cyloset)</td>
<td>0.5</td>
<td>Hypoglycemia rare</td>
<td>Low efficacy; gastrointestinal side effects, including nausea; fatigue; dizziness; rhinitis; only rapid-release agent approved</td>
<td>High</td>
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<tr>
<td>Injectable</td>
<td>GLP-1–receptor agonist Exenatide (Byetta), exenatide once weekly (Bydureon), liraglutide (Victoza)</td>
<td>0.5–1.5</td>
<td>Hypoglycemia rare, weight loss in most patients; possible protective cardiovascular effects</td>
<td>Nausea and vomiting; risks of pancreatitis, thyroid C-cell hyperplasia, and tumors (with liraglutide and weekly exenatide); unknown long-term safety</td>
<td>High</td>
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Clinical Practice

Areas of Uncertainty

The underlying cause or causes of accelerated cardiovascular disease in type 2 diabetes and the effects of glycemic control on this process remain incompletely understood. Whereas intensive glycemic control clearly reduces the risk of microvascular complications, its effect (measured as the glycated hemoglobin level, a surrogate marker) on outcomes of cardiovascular disease is less certain. A better understanding of the factors underlying the large variations in insulin resistance and beta-cell number and function in healthy persons is needed for the development of strategies to prevent and treat type 2 diabetes; data are lacking on treatments that preserve beta-cell function. Although there is general agreement on the first-line use of metformin in most patients with type 2 diabetes, evidence is lacking to inform the most appropriate choice of second-line agents. Devices such as continuous glucose-monitoring systems (to ascertain glycemic patterns over a period of a few days) and insulin pumps are increasingly used in patients with type 2 diabetes who require insulin, but data on the benefits and risks of these devices are lacking. Mechanisms underlying the impressive effects of bariatric surgery on glycemic control warrant further exploration. Finally, the long-term safety of GLP-1–receptor agonists, DPP-IV inhibitors, and other newer agents and their effects on diabetic complications, including cardiovascular disease, need to be determined.

Guidelines

The American Diabetes Association, the European Association for the Study of Diabetes, and other organizations have published guidelines for glycemic control in patients with type 2 diabetes. All these guidelines specify that glycemic goals should be individualized (with some placing particular emphasis on psychosocial factors in setting goals), and all advocate lifestyle modifications and metformin as first-line therapy, though they differ in their subsequent recommendations. A joint statement by the American Diabetes Association and the European Association
for the Study of Diabetes recommends that for patients with glycemia that is not adequately controlled with lifestyle changes and metformin, “well-validated” therapies, including sulfonylureas or basal insulin, should be used, followed by more intensive insulin therapy, as needed21; pioglitazone, GLP-1 agonists, and other medications discussed above are considered “less-well-validated” options. The recommendations in this article are generally concordant with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient in the vignette is relatively young and has a recent diagnosis of type 2 diabetes with inadequately controlled glycemia and a family history of type 2 diabetes and cardiovascular disease. The major goals of treatment should be to prevent microvascular and macrovascular complications over a period of many years, given his long life expectancy. His blood pressure and lipid levels are well controlled. I would discuss with him the risks associated with hyperglycemia and the benefits of glycemic control, and I would assess his capacity and willingness to self-monitor his blood glucose levels. In the absence of any apparent contraindications to targeting a normal or near-normal glycemic range, I would recommend a target glycated hemoglobin level of 6.0 to 6.5% (if it can be implemented safely). I would also recommend an exercise program (preferably at least 150 minutes per week) and encourage him to follow a diet that is low in fat, carbohydrates, and salt and high in grains and fiber, with the aim of gradual weight loss (perhaps 4.5 to 6.8 kg [10 to 15 lb] over the next year). I would increase the dose of metformin to 2000 mg daily while diet and exercise are actively pursued.

If these approaches are effective, it may be possible to decrease or discontinue glipizide. If the glycated hemoglobin level remains high, it is unlikely that the addition of another oral agent would reduce the glycated hemoglobin level from approximately 9% to near-normal levels. Although data are currently insufficient to guide the most appropriate choice among additional therapies, I would recommend adding long-acting insulin at bedtime or a GLP-1–receptor agonist to his regimen. Although some clinicians would consider the discontinuation of glipizide, I favor its continuation, at least initially. Basal insulin is effective and less expensive, but it is associated with hypoglycemia and weight gain. GLP-1–receptor agonists have the advantage of causing weight loss in most patients. They rarely cause hypoglycemia but are more costly than basal insulin, and data are lacking on their long-term safety.

Dr. Ismail-Beigi reports receiving consulting fees from Eli Lilly and owning stock in Thermalin Diabetes. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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