This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

Initial Management of Glycemia in Type 2 Diabetes Mellitus

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After an overnight fast, an asymptomatic 45-year-old Hispanic man has a plasma glucose level of 142 mg per deciliter (7.9 mmol per liter) on initial evaluation and 139 mg per deciliter (7.7 mmol per liter) on reevaluation. Other than a steady gain in weight since college and borderline hypertension, his medical history is unremarkable. He is 175 cm (5 ft 9 in.) tall and weighs 95 kg (209 lb; body-mass index, 31.2), and his blood pressure is 138/88 mm Hg. Physical examination is notable only for abdominal obesity and absent ankle reflexes. How should this patient be treated?

THE CLINICAL PROBLEM

Type 2 diabetes mellitus has become epidemic in the past several decades owing to the advancing age of the population, a substantially increased prevalence of obesity, and decreased physical activity, all of which have been attributed to a Western lifestyle. In the United States, almost 8 percent of the adult population and 19 percent of the population older than the age of 65 years have diabetes.[1] There are 800,000 new cases of diabetes per year, almost all of which are type 2. In addition to the risk factors already mentioned, several racial and ethnic groups in the United States are at particularly high risk for diabetes, including blacks, Hispanics, Asians and Pacific Islanders, and Native Americans.[2] Given the high prevalence of environmental and genetic risk factors,[3] it should come as no surprise that type 2 diabetes is now being diagnosed in young people, including adolescents.[4] The clinical course and typical sequence of treatment of type 2 diabetes are outlined in Figure 1.

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Diabetes mellitus is associated with long-term complications, including retinopathy, nephropathy, and neuropathy.[5,6] In the past, type 2 diabetes was considered to be mild and not associated with the same spectrum of complications as type 1 diabetes. Longer survival of patients with type 2 diabetes and development of the disease at an earlier age have increased the risk of development of the duration-dependent complications. Type 2 diabetes is patently not mild; rather, in the United States, it currently contributes to more cases of adult-onset loss of vision, renal failure, and amputation than any other disease. The average delay of four to seven years in diagnosing type 2 diabetes[7] translates into approximately 20 percent of patients with type 2 diabetes having some evidence of microvascular or neurologic diabetic complications at the time of diagnosis.[8] These complications are influenced not only by the duration of diabetes, but also by the average level of chronic glycemia,[9,10] which is measured most reliably with the glycosylated hemoglobin assay. Unfortunately, the relatively high glycosylated hemoglobin values associated with usual care increase the risk of complications.[11]

As compared with patients without type 2 diabetes, patients with type 2 diabetes — the majority of whom are obese and have hypertension and dyslipidemia — have two to five times the risk of cardiovascular disease.[12] Seventy percent of patients with type 2 diabetes die of cardiovascular disease.[13] The development of cardiovascular disease appears to precede the development of diabetes itself, in association with subdiabetic levels of hyperglycemia.[14,15] In the United States, the estimated cost of providing care for diabetes and its complications is $100 billion per year, with half the cost attributable to direct care.[16]

Studies have identified several modifiable factors that prevent or slow the progression of the microvascular and neurologic complications.[17-20] The Diabetes Control and Complications Trial demonstrated the potent effects of intensive therapy, with the aim of achieving near-normal glycemia, in decreasing long-term complications in patients with type 1 diabetes.[17] Two studies have established the role of intensive therapy in reducing long-term complications in patients with type 2 diabetes.[18-20] These studies have helped to establish the metabolic goals in patients with type 2 diabetes as a glycosylated hemoglobin value of less than 7 percent, an average fasting plasma glucose level of 90 to 130 mg per deciliter (5.0 to 7.2 mmol per liter), and a postprandial plasma glucose level of less than 180 mg per deciliter (10.0 mmol per liter) (Table 1).[21]
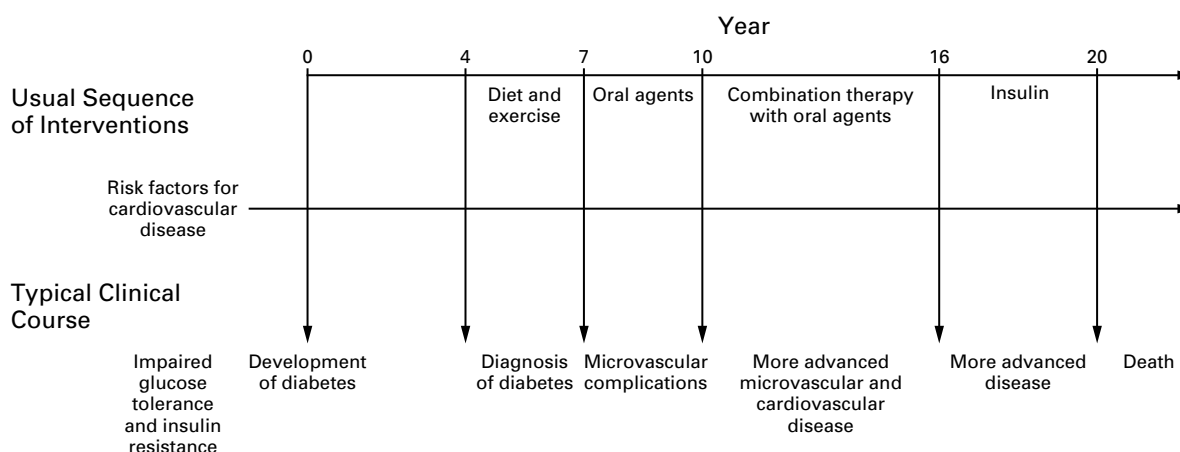
Figure 1. The Typical Clinical Course of Type 2 Diabetes, Including the Progression of Glycemia and the Development of Complications, and the Usual Sequence of Interventions.

The American Diabetes Association uses the following criteria for the diagnosis of diabetes in nonpregnant persons: a plasma glucose level of more than 126 mg per deciliter (7.0 mmol per liter) after a fast of at least eight hours, a plasma glucose level of more than 200 mg (11.1 mmol per liter) two hours after an oral glucose-tolerance test (dose, 75 g of glucose), or symptoms consistent with the presence of diabetes, such as polyuria and polydipsia, plus a plasma glucose level of more than 200 mg per deciliter, regardless of the time of day at which the measurement was obtained. The fasting plasma glucose level and results of the oral glucose-tolerance test should be confirmed by retesting on another day.

Aggressive treatment of hypertension also reduces the risk of retinopathy, nephropathy, and certain cardiovascular outcomes.[25] Reducing low-density lipoprotein cholesterol levels[26,27] and reducing triglyceride levels while raising high-density lipoprotein cholesterol levels[28] can decrease the risk of cardiovascular disease. The guidelines of the National Cholesterol Education Program[23] and the American Diabetes Association[24] acknowledge that the presence of diabetes is a risk factor equivalent to having preexisting coronary artery disease[29] and have therefore adjusted treatment goals accordingly (Table 1). Intensive glycemic control and aggressive treatment of hypertension and dyslipidemia are particularly demanding in patients with type 2 diabetes; currently, many patients take at least six medications to manage the panoply of risk factors.

STRATEGIES AND EVIDENCE

The data from clinical trials demonstrating the benefits of aggressive control of glycemic levels, blood pressure, and abnormal lipid levels call for a comprehensive approach to the treatment of type 2 diabetes that includes the treatment of all of the coexisting risk factors for cardiovascular disease, including smoking. A discussion of the treatment of all coexisting risk factors is beyond the scope of this article; in this regard, the recommendations of the American Diabetes Association,[24] National Cholesterol Education Program,[23] and the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[22] and recent reviews[30,31] are of value.

The traditional approach to the treatment of diabetes has been a stepwise introduction of nonmedication approaches followed by oral agents (Fig. 1). Insulin therapy, despite being the most potent and durable hypoglycemic intervention available, has generally been saved for last, presumably because of the need to administer it by injection. The stepwise strategy has usually been applied at a slow pace with long delays between steps. By the time patients with type 2 diabetes are treated with insulin, they usually have had diabetes for more than 10 to 15 years and have established complications.

Glycemia appears to increase progressively the longer diabetes is present, presumably as a result of decreasing beta-cell function.[32] However, at least some beta-cell dysfunction is reversible and insulin secretion can be restored by lowering glycemia, either with diet and exercise or with hypoglycemic medications.[33] Restoration of endogenous insulin secretion, which is most likely to occur early in the course of diabetes, is key to improving glycemia. Remissions, characterized by normoglycemia and the absence of the need for hypoglycemic medications, can be achieved,[34] although their duration is unknown. Because the usual pace in introducing hypoglycemic therapies is slow, the opportunity to reverse beta-cell dysfunction may be missed.

VARIABLE	VALUE
Glucose	
Glycosylated hemoglobin (%)	<7
Fasting plasma glucose	
mg/dl	90–130
mmol/liter	5.0–7.2
Peak postprandial glucose	
mg/dl	<180
mmol/liter	<10.0
Blood pressure (mm Hg)	
Systolic	<130
Diastolic	<80
Lipids	
Low-density lipoprotein cholesterol	
mg/dl	<100
mmol/liter	<2.6
High-density lipoprotein cholesterol	
mg/dl	>45
mmol/liter	>1.2
Triglycerides	
mg/dl	<200
mmol/liter	<2.3

*Data on glycemia are from the American Diabetes Association.[21] Data on blood pressure are from the American Diabetes Association[21] and the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[22] Data on lipids are from the National Cholesterol Education Program[23] and the American Diabetes Association.[24]

Diet and Lifestyle Changes

Lifestyle changes, which attempt to reverse or counteract the environmental factors that initiate or exacerbate diabetes in susceptible persons, have great appeal given their low risk and potentially high benefit. Weight loss, achieved with hypocaloric diets, is the primary goal; increased activity has an ancillary role. Plasma glucose levels fall with hypocaloric diets, before weight loss occurs, and levels can decline into the near-normal range with a weight loss of even 2.3 to 4.5 kg (5 to 10 lb).[35] Unfortunately, many changes in lifestyle, like most dietary interventions for the treatment of obesity, are short-lived. The most dramatic and lasting reversals of the diabetic state have followed extensive, prolonged weight loss, as occurs after bariatric surgery.[36] Although most dietary programs do not result in sustained weight loss, efforts to lose weight and increase activity levels are critical for several reasons. The cost–benefit ratio is high for the small fraction of the population with type 2 diabetes who can lose weight and keep it off, hypoglycemic medications are more effective if the weight gain that commonly accompanies their use is limited, and such lifestyle changes are likely to have other benefits, including amelioration of risk factors for cardiovascular disease.

Oral Agents

For patients who are unable to change their lifestyle through weight loss and increased activity level and for those who make these changes but continue to have glycemia above the target range, a variety of oral agents are now available (Table 2). The sulfonylureas and the biguanide metformin are the oldest and most commonly used classes of oral hypoglycemic drugs.[37,38] They have different mechanisms of action (sulfonylureas stimulate insulin secretion and biguanides predominantly decrease hepatic glucose output), but have a similar hypoglycemic effect: they both lower the glycosylated hemoglobin value by approximately 1.5 percentage points. The glitinides are nonsulfonylurea drugs that stimulate insulin secretion in a manner similar to that of the sulfonylureas, but their onset of action is faster and their duration of action is briefer, so they must be given before each meal.[39] Sulfonylureas and metformin appear to have a limited duration of effectiveness, with most patients requiring a change or additional medications after five years of therapy.[40] Where sulfonylureas and metformin diverge is in their respective adverse effects (Table 2). In appropriately selected patients, metformin may be the oral hypoglycemic agent of first choice, since it achieves a level of glucose control similar to that of the sulfonylureas without the same risk of weight gain or hypoglycemia.

Other oral hypoglycemic medications have become available in the past five years, but they largely have a supporting role rather than a primary role as monotherapy. The α-glycosidase inhibitors work by inhibiting the absorption of carbohydrates in the small intestine, resulting in lower glycemic profiles postprandially. For patients who can tolerate the common gastrointestinal side effects, these agents lower glycosylated hemoglobin values by 0.5 to 1.0 percentage points.[41] The thiazolidinediones are peroxisome-proliferator–activated receptor agonists that increase peripheral glucose uptake and lower glycosylated hemoglobin values moderately when they are used as monotherapy.[42,43] The main role of these agents may be as part of combination therapy, as described below.

Insulin

Insulin is the oldest of the hypoglycemic agents. It is also the only one that occurs naturally in humans and has no upper dose limit. Higher doses of insulin virtually always result in lower glucose levels, and numerous studies have demonstrated that glycemic levels are nearly normal when adequate doses of insulin are used.[44-48] Although insulin is theoretically the most

TABLE 2. SUMMARY OF AVAILABLE ANTIDIABETIC THERAPIES.

VARIABLE	DIET AND EXERCISE	SULFONYLUREAS AND GLITINIDES	METFORMIN	α-GLYCOSIDASE INHIBITORS	THIAZOLIDINEDIONES	INSULIN
Primary mechanism*	Decrease insulin resistance	Increase insulin secretion	Decrease hepatic glucose output	Delay gastrointestinal absorption of carbohydrates	Increase insulin sensitivity	Increase insulin levels
Typical resulting decrease in glycosylated hemoglobin values (percentage points)	0.5–2.0	1.0–2.0	1.0–2.0	0.5–1.0	0.5–1.0	1.5–2.5
Typical starting dose	Caloric restriction to reduce weight by 1–2 kg/mo	Glyburide, 1.25 mg/day; Glipizide, 2.5 mg/day; Nateglinide, 60 mg before meals; Repaglinide, 0.5 mg before meals	500 mg before breakfast and dinner†	Acarbose, 25 mg with meals; Miglitol, 50 mg with meals	Rosiglitazone, 4 mg/day; Pioglitazone, 7.5 mg/day	Depends on insulin regimen and patient's characteristics; 10–20 U/day usually a safe starting dose
Maximal dose	Can use meal substitutes and add orlistat or sibutramine	Glyburide, 20 mg/day; Glipizide, 40 mg/day; Nateglinide, 120 mg before meals; Repaglinide, 4 mg before meals	2550 mg/day (850 mg with each meal)	Acarbose, 100 mg with meals; Miglitol, 100 mg with meals	Rosiglitazone, 8 mg in 1 or 2 daily doses; Pioglitazone, 45 mg/day	None
Most common or severe adverse effects	Injury	Hypoglycemia, weight gain	Gastrointestinal symptoms,† lactic acidosis‡	Flatulence,† gastrointestinal discomfort,† weight gain	Edema,§ weight gain	Hypoglycemia,¶ weight gain
Agents used in combination with this therapy||	Sulfonylureas, glitinides, metformin, α-glycosidase inhibitors, thiazolidinediones, insulin	Metformin, α-glycosidase inhibitors, thiazolidinediones	Sulfonylureas, glitinides, α-glycosidase inhibitors, thiazolidinediones, insulin	Sulfonylureas, glitinides, metformin, thiazolidinediones, insulin	Sulfonylureas, glitinides, metformin, α-glycosidase inhibitors, insulin	Metformin, α-glycosidase inhibitors, thiazolidinediones

*Although the primary mechanism of action of each intervention is listed, any intervention that decreases the plasma glucose level usually results in a secondary improvement in insulin resistance and secretion.

†Slowly increasing the dose over a period of several weeks may limit the gastrointestinal side effects.

‡Although very rare (<3 cases per 100,000 patients treated), lactic acidosis may be fatal. The risk of lactic acidosis can be decreased by not giving metformin to patients with decreased glomerular filtration rates, abnormal liver function, congestive heart failure, or binge alcoholism and by stopping metformin therapy shortly before surgical procedures or radiologic studies involving the use of dye that may affect renal function.

§Edema and fluid retention may cause or exacerbate congestive heart failure. The relatively rare but potentially fatal liver dysfunction that occurred with troglitazone does not appear to be associated with the currently approved thiazolidinediones; nevertheless, periodic assessment of liver function is required.

¶Severe hypoglycemia (defined as episodes that require assistance to treat) in patients receiving intensive therapy is rare among those with type 2 diabetes (≤3 episodes per 100 patient-years), as compared with those with type 1 diabetes (approximately 60 episodes per 100 patient-years).

||The principle that guides combination therapy is to combine agents with different primary modes of action. Although combination therapy with sulfonylurea (or glitinides) and insulin has been approved for use, I do not recommend it.

potent of the drugs, it is often not used in the doses necessary to achieve recommended glycemic goals. The risks of insulin therapy include weight gain (like all of the hypoglycemic agents, except metformin), hypoglycemia, and in very rare cases, allergic and cutaneous reactions. The chief barrier to its use, especially early in the course of diabetes treatment, appears to be the reluctance to use an injectable drug; fear of weight gain and hypoglycemia may also be disincentives. However, severe hypoglycemia is extremely rare,[18,19,44-48] as compared with its frequency during intensive treatment in patients with type 1 diabetes.[17] Moreover, insulin injections are generally painless and considerably less uncomfortable than finger-stick testing of glucose levels, whose use has been widely promulgated and adopted. Regardless of the reason, insulin therapy is often reserved as a last resort.

Since relatively few studies have compared the various insulin regimens (Fig. 2), there are insufficient data to help determine the best one. The most common theme of successful insulin therapy is the use of a sufficiently large dose of insulin (typical range, 0.6 to more than 1.0 U per kilogram of body weight per day) to achieve or approach normoglycemia, rather than any specific pattern of insulin administration. Once-daily injections of intermediate-acting or long-acting insulins at bedtime[19,44] or before breakfast,[45] daily or twice-daily combinations of intermediate- and rapid-acting insulins,[46] and more complex regimens[18,48] have been used to good effect. Although insulin therapy has not traditionally been implemented early in the course of type 2 diabetes, there is no reason why it should not be. Early initiation of insulin therapy has resulted in remissions in patients with type 2 diabetes.[34]

Combination Therapy

The disappointing results with monotherapy, especially the worsening metabolic control often seen within five years after the initiation of an oral hypoglycemic agent,[49] have led to the use of combination therapy. The principle behind combination therapy should be to use drugs with different mechanisms of action. The first commonly used combination regimen — insulin at bedtime and sulfonylurea during the day — combined two drugs that increased insulin levels. Predictably, this combination was not synergistic; similar results could usually be obtained, at a lower cost, solely by increasing the dose of insulin.[50] Myriad other combinations have proved to be more effective than the use of either drug alone. Sulfonylurea and metformin,[51] insulin and metformin,[52] thiazolidinediones and either metformin[53] or insulin,[54] and any of the drugs plus acarbose[41] are among the combinations that can improve glycemic control. In general, when such drugs are combined, the adverse-event profile resembles that of the more problematic drugs.

Other Potential Approaches

Potential additions to the armamentarium include inhaled insulin,[55] new insulin secretagogues, and better weight-loss agents. All of these agents face substantial delays before they become available.

Even with improved therapies, the magnitude of the diabetes epidemic makes prevention a critical goal. The Diabetes Prevention Program investigators and other groups of researchers have recently demonstrated that lifestyle changes and metformin or acarbose therapy can prevent or delay the development of diabetes by 25 to 58 percent in high-risk patients with impaired glucose tolerance.[56-58]

AREAS OF UNCERTAINTY

The progressive worsening of the metabolic state and the seeming resistance to beta-cell salvage that occur over time suggest that more aggressive treatment of type 2 diabetes may be warranted early in its course. Whether the earlier application of combination therapy, insulin, or both will be effective in maintaining near-normal glycemia over the long term is unknown. The cost effectiveness of this approach, as compared with waiting to implement more intensive therapy, requires careful examination. Similarly, the practicality and cost effectiveness of even earlier intervention to prevent diabetes must be determined. Finally, studies to determine the effects of earlier and more aggressive management or prevention of diabetes on the risk of cardiovascular disease, the long-term complication with the greatest human cost, will be necessary to understand the influence of these interventions on public health. Only with answers to these questions in hand will we be able to select the most effective course.

GUIDELINES

Therapeutic goals and guidelines for the management of type 2 diabetes have been advanced by the American Diabetes Association,[24] National Cholesterol Education Program,[23] and the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[22] (Table 1). Some of these guidelines are supported by excellent-quality data from clinical trials, whereas others are based on extrapolation from studies in persons without diabetes or epidemiologic data. Their implementation should not be delayed, even though the data to support them remain incomplete.

CONCLUSIONS AND RECOMMENDATIONS

Type 2 diabetes, a chronic degenerative disease of epidemic proportions, is one of the major challenges to public health in the United States and elsewhere. Although effective interventions to reduce the long-term complications are available, the complex interven-
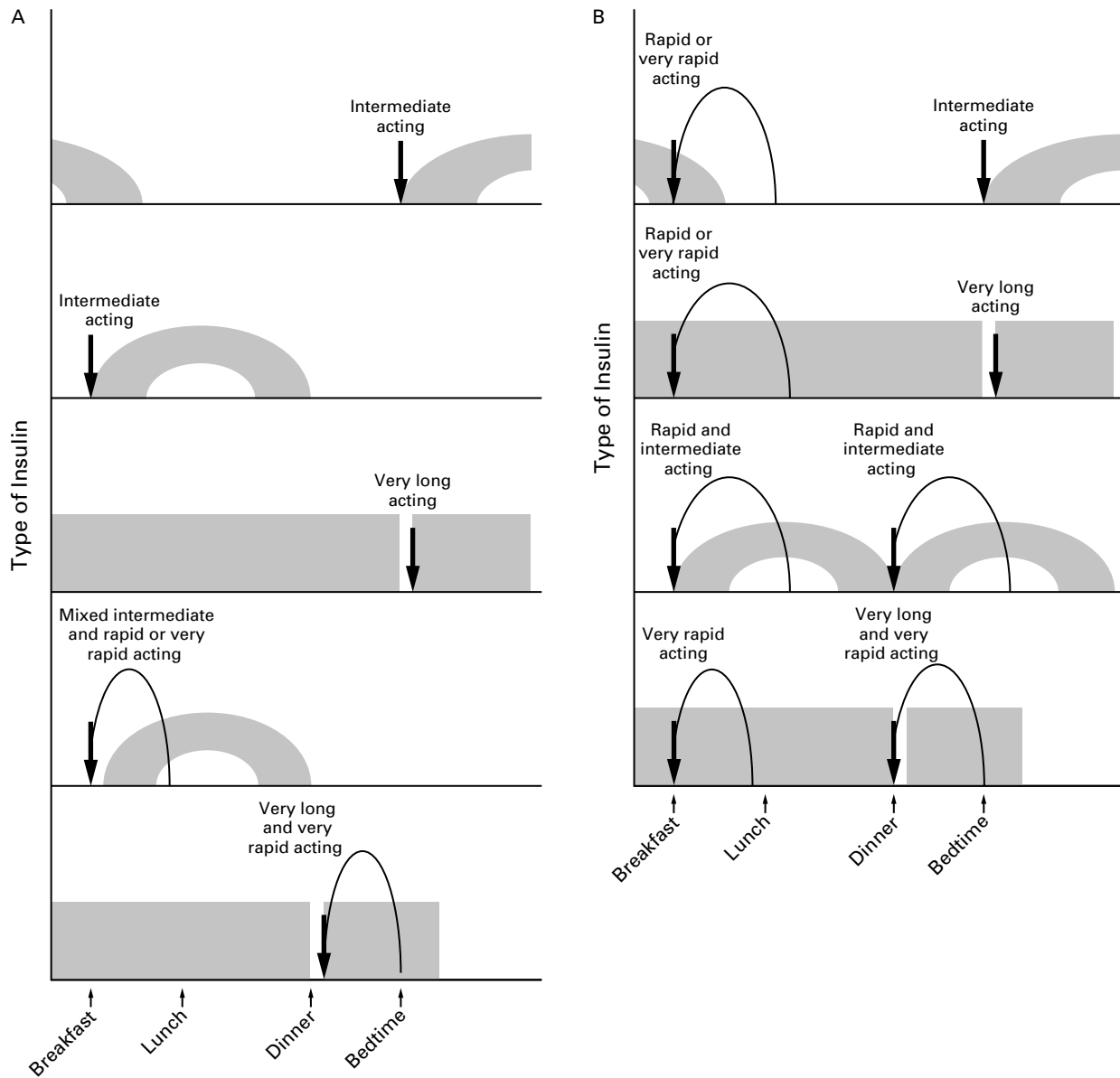
Figure 2. Commonly Used Once-Daily (Panel A) and Twice-Daily (Panel B) Insulin Regimens for the Treatment of Type 2 Diabetes.

The arrows indicate the timing of the injections. The duration of the glucose-lowering effect of the intermediate-acting insulins (isophane insulin and extended insulin zinc) and very-long-acting insulin (insulin glargine) is indicated by shaded areas, whereas that of the rapid-acting insulin (prompt insulin zinc) and very-rapid-acting insulin (insulin lispro and aspart) is indicated by the black lines. Combinations of intermediate-acting and rapid-acting or very-rapid-acting insulins are available in premixed, fixed-ratio mixtures such as 70:30 and 50:50 (isophane insulin and regular insulin, respectively) and 75:25 (isophane insulin and insulin lispro, respectively). The very-long-acting insulin glargine cannot be mixed with other insulins. When given before meals, most insulins and combinations of insulins are usually administered 30 minutes before the meal; however, the very-rapid-acting insulins and combinations that include them should be administered 5 to 10 minutes before meals.

tions required and the size of the diabetic population have made the application of such therapies problematic. The treatment of patients with type 2 diabetes of relatively recent onset — especially young people with a long projected life span such as the patient described in the case vignette — should include lifestyle interventions to address hyperglycemia, hypertension, and dyslipidemia. If such interventions do not achieve the goals established by controlled clinical trials, I recommend accelerated implementation of the known effective treatments. For example, if after a three-to-six-month program of diet and increased exercise, glycosylated hemoglobin values are not less than 7 percent, medications should be added. One could consider using metformin as a first agent, since it is less likely to cause weight gain. If the treatment goals continue to be elusive, the addition of insulin or other medications should be considered. Whatever the choice of medications, the usual slow transition from one treatment to the next should be avoided. Similarly, aggressive treatment of hypertension and dyslipidemia is warranted. Renewed or continued attention to lifestyle modification should be encouraged at every step of diabetes intervention to try to limit the weight gain that accompanies treatment with most of the medications. With the prospect of 800,000 new cases of type 2 diabetes per year, primary prevention is an obvious strategy that has recently been recommended.[59]

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